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Multimodality Imaging in Cardiomyopathies

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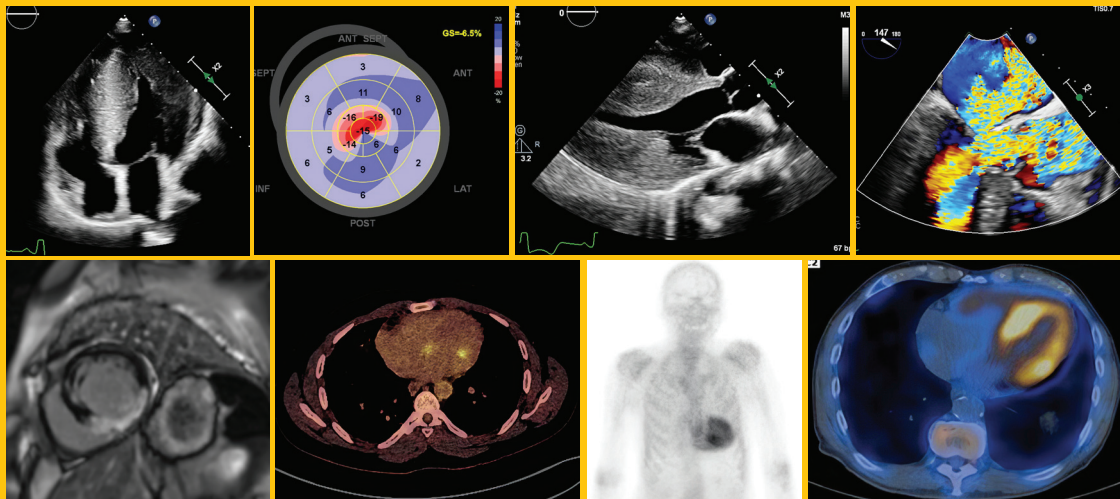
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Dear colleagues,

Cardiomyopathy is a broad term that encompasses various diagnoses. It includes pathologies with similar clinical and laboratory findings which could actually be quite distinct in etiology. General cardiologists are not necessarily obliged to diagnose every subgroup of specific cardiomyopathy, but its their responsibility to suspect the possible diagnoses, perform initial tests, and guide patients. With this work, our aim is to provide diagnostic algorithms and precise definitions that would lead to the final subgroup of cardiomyopathy identification. However, this is often not feasible to do only with initial symptoms or findings. There is a worldwide need for a "cardiomyopathy mindset," which emphasizes a holistic perspective. We present you a Turkish resource on cardiomyopathies enriched with up to date information and images. We are grateful to the esteemed colleagues who contributed to this work by sharing their experience. It has been an intense preparation process for all of us. We extend our heartfelt thanks to Prof. Dr. Muzaffer Değertekin, President of the Turkish Society of Cardiology, and the Executive Board for their moral and financial support, as well as to Prof. Dr. Dilek Ural, the Chief Editor of the Turkish Society of Cardiology Archives.

Yours sincerely,

On behalf of the Cardiac Imaging Working Group of the Turkish Society of Cardiology,
Prof. Dr. Gamze Babur Güler

MULTIMODALITY IMAGING IN CARDIOMYOPATHIES

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ABSTRACT

Cardiomyopathy, which is shortly defined as a disease of the myocardium, has a broad definition that includes many different diagnoses. Recent advances in cardiac imaging techniques, including basic and advanced echocardiography, computed tomography, nuclear medicine, and cardiac magnetic resonance, allow for a more accurate evaluation of volumes and thickness of cardiac chambers, systolic and diastolic function of the ventricles, and tissue structure. Multimodality imaging often provides the first clinical suspicion for specific etiologies, especially when the medical and family history is unclear, by identification of red flags of underlying systemic diseases. In this review, we aimed to evaluate the role of multimodality imaging in diagnosis of cardiomyopathies with key images and discussed the effects of genetics on the diagnostic, prognostic, and therapeutic guidance of cardiomyopathies.

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Echocardiographic Evaluation Focused on Cardiomyopathy

Cardiomyopathy refers to structural and functional abnormalities in the heart muscle (myocardium) that occur independently of conditions like coronary artery disease, hypertension, valvular disease, or congenital heart defects that could explain these abnormalities.¹

According to the latest European Society of Cardiology (ESC) guideline on cardiomyopathies, there are five distinct phenotypes of cardiomyopathy: dilated cardiomyopathy, non-dilated left ventricular cardiomyopathy, hypertrophic cardiomyopathy, restrictive cardiomyopathy, and arrhythmogenic right ventricular cardiomyopathy.¹

Describing cardiomyopathy phenotypes involves identifying abnormalities in myocardial structure and function through morphological and functional evaluations. Morphological assessments include left and/or right ventricular hypertrophy, left and/or right ventricular dilatation, and left and/or right atrial dilatation. Functional evaluation, particularly using strain imaging, is crucial. Echocardiography, being non-invasive and widely accessible, serves as the primary imaging modality from initial diagnosis to follow-up.

This article will focus on discussing basal echocardiographic measurements for diagnosing cardiomyopathy. It will cover how to measure ventricular and atrial dilatation, ventricular hypertrophy, the role of strain imaging, and normal values. Please note that the diagnosis of cardiomyopathies is beyond the scope of this article and will be addressed in separate articles.

Measurement of Left Ventricular Size and Volumes

To assess the size of the left ventricular (LV) cavity, we use internal linear dimensions and volumes. Measurements of the interventricular septum and LV posterior wall should be taken simultaneously and at the same level as the LV end-diastolic dimension. These internal dimensions are typically obtained using a 2-dimensional (2D) echocardiography M-mode approach (Figure 1A). The parasternal long-axis view is used to obtain internal linear LV measurements and assess LV wall thickness. It's important to measure these values carefully at or just below the level of the mitral valve leaflet tips and perpendicular to the LV long axis. Linear measurements from 2D echocardiographic images are preferred to avoid oblique sections of the ventricle (Figure 1B).^{2,3}

Left ventricular volumes can be assessed using either 2-dimensional (2D) or 3-dimensional (3D) echocardiography. It's important to emphasize that calculating LV volumes and ejection fraction from linear measurements is not advisable. Instead, the biplane summation-of-disks method is recommended for volume calculations using 2D echocardiography. This method involves acquiring apical views with a reduced sector size that specifically shows the LV. Measurements are taken in the apical four- and two-chamber views at both end-diastole and end-systole (Figure 2).

Volumetric measurements typically involve tracing the interface between the compacted myocardium and the LV cavity. Papillary muscles and trabeculae are excluded from the tracing and are considered part of the chamber. At the level of the mitral valve, the contour is closed with a straight line connecting opposite points of the mitral ring. From the midpoint of this line, a vertical line is extended to the farthest point of the apex to determine the height of the disks. It is recommended to use the longer LV length obtained from either the apical two- or four-chamber views. The difference

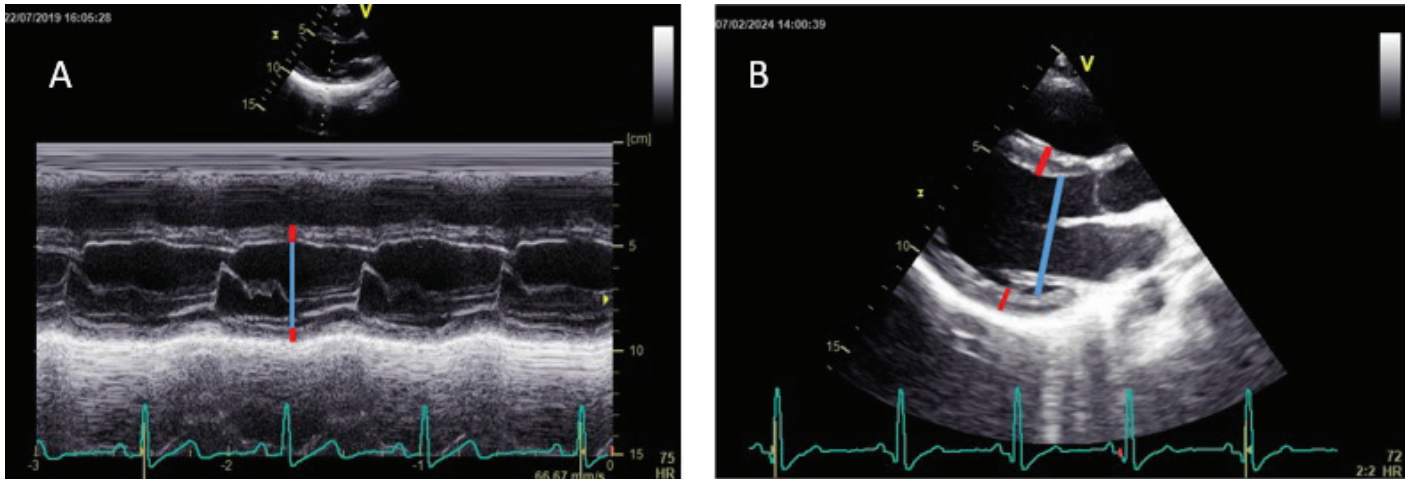


Figure 1. Left Ventricular Linear Measurement using M-mode (A) and 2D echocardiographic (B) approach.

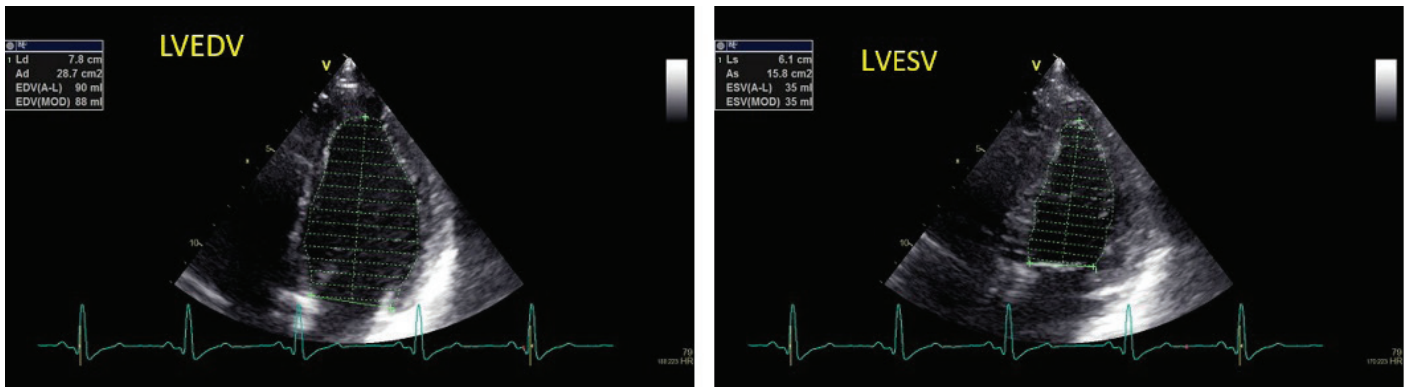


Figure 2. Left ventricle volumetric measurement by modified Simpson's method. LVEDV, Left ventricular end-diastolic volume; LVESV, Left ventricular end-systolic volume.

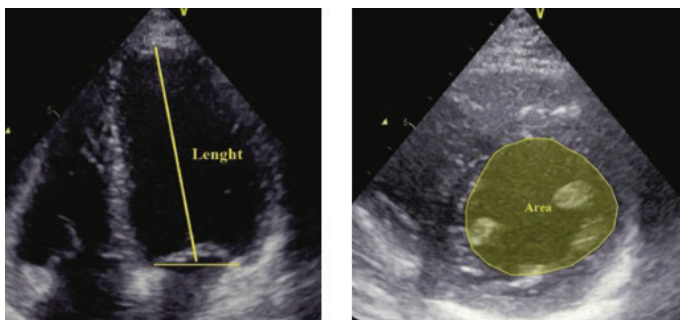


Figure 3. Left ventricular area-length volumetric approach.

in LV lengths measured between the four- and two-chamber views should ideally be less than 10%.^{3,4}

The area-length method is an alternative volumetric technique used when the LV apex is not well visualized. This method assumes the LV has a bullet-shaped structure. In this approach, the mid-LV area is traced in a short-axis view, while the length is measured in the apical four-chamber view (Figure 3).

Routine assessment of LV systolic function should include the use of 2D or 3D echocardiography to calculate ejection

fraction (EF) from end-diastolic and end-systolic volumes. Baseline EFs for LV systolic function are typically defined as LV EFs of less than 52% for men and less than 54% for women (Table 1).²

When available, 3D echocardiographic algorithms are preferred over the summation-of-disks method for assessing LV volume and function (Figure 4). Unlike the summation-of-disks method, 3D echocardiography doesn't rely on geometric assumptions, making it more accurate and reproducible, especially with good image quality. Labs experienced with 3D echocardiography are encouraged to adopt it for LV volume measurement and reporting, depending on image quality.⁵⁻⁷

3D echocardiographic LV volumes tend to be larger than 2D echocardiographic values, with upper limits of normal defined as end-diastolic volumes of 79 mL/m² for men and 71 mL/m² for women, and end-systolic volumes of 32 mL/m² for men and 28 mL/m² for women (Table 2).^{6,7}

Dilated cardiomyopathy is characterized by LV dilatation and systolic dysfunction not solely explained by abnormal loading or coronary artery disease. LV dilatation is defined by LV end-diastolic dimensions or volumes more than 2 z-scores above mean values adjusted for body size, sex, and age. In adults, this

Table 1. Normal values for 2D echocardiographic parameters of LV size and function according to gender

Parameter	Male		Female	
	Mean±SD	2-SD range	Mean±SD	2-SD range
LV Internal Diameter				
Diastolic Diameter (mm)	50.2±4.1	42.0±58.4	45.0±3.6	37.8±52.2
Systolic Diameter (mm)	32.4±3.7	25.0±39.8	28.2±3.3	21.6±34.8
LV Volume (biplane)				
LV EDV (ml)	106±22	62±150	76±15	46±106
LV ESV (ml)	41±10	21±61	28±7	14±42
LV Volumes/BSA				
LV EDV (ml/m ²)	54±10	43±74	45±8	29±61
LV ESV (ml/m ²)	21±5	11±31	16±4	8±24
LV EF (biplane)	62±5	52±72	64±5	54±74

Lang RM, Badano LP, Mor-Avi V, et al. Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. *Eur Heart J Cardiovasc Imaging*. 2015;16(3):233-270. Erratum in: *Eur Heart J Cardiovasc Imaging*. 2016;17(4):412. Erratum in: *Eur Heart J Cardiovasc Imaging*. 2016;17(9):969.

BSA, Body surface area; EDV, End-diastolic volume; ESV, End-systolic volume; EF, Ejection fraction; LV, Left ventricular; SD, Standard deviation.

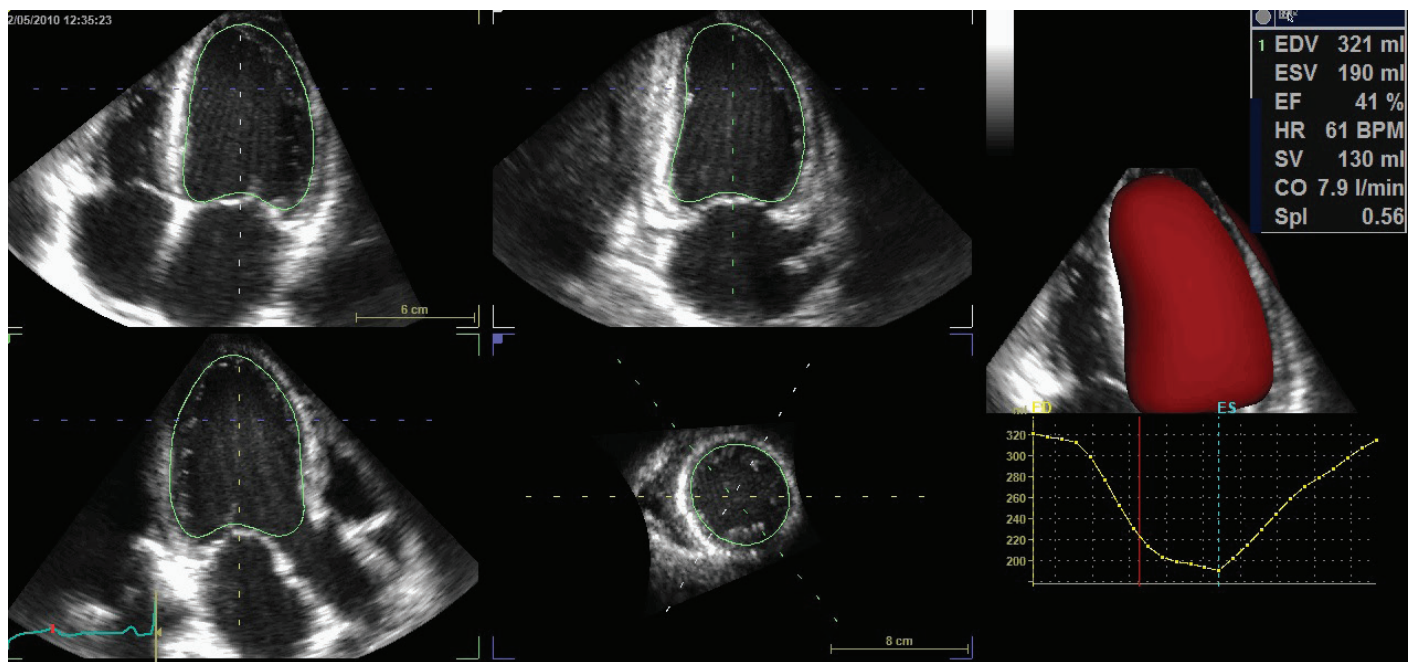


Figure 4. Left ventricular end-diastolic volume, end-systolic volume and global systolic function assessment using 3D echocardiography.

means an LV end-diastolic diameter over 58 mm in males and 52 mm in females, and an LV end-diastolic volume index of 75 mL/m² or higher in males and 62 mL/m² or higher in females, as assessed by echocardiography. LV global systolic dysfunction is an EF below 50%.^{1,8}

Non-dilated LV cardiomyopathy is marked by non-ischemic LV scarring or fatty replacement without LV dilatation. It may include global or regional wall motion abnormalities, or isolated global LV hypokinesia without scarring, assessed by the absence of late gadolinium enhancement on cardiac magnetic resonance (CMR). These findings aren't solely explained by hypertension,

valve disease, or coronary artery disease. Global LV systolic dysfunction is an abnormal LVEF below 50%.^{1,8}

Detection of Left Ventricular Hypertrophy

Transthoracic echocardiography is the main method for detecting left ventricular hypertrophy. It's especially important in apical hypertrophy to avoid foreshortening in apical views. If these views aren't clear, using ultrasound enhancing agents is advised. These agents improve the detection of apical aneurysms, ventricular thrombi, and myocardial non-compaction for better imaging.²

Table 2. Normal values for LV parameters obtained with 3D echocardiography		
	Chahal et al. ⁶	Muraru et al. ⁷
EDVI (ml/m ²)		
Male, mean (LLN, ULN)	49 (31,67)	63 (41,85)
Female, mean (LLN, ULN)	42 (26,58)	56 (40,78)
ESVI (ml/m ²)		
Men, mean (LLN, ULN)	19 (9,29)	24 (14,34)
Women, mean (LLN, ULN)	16 (8,24)	20 (12,28)
EF (%)		
Men, mean (LLN, ULN)	61 (49,73)	62 (54,70)
Women, mean (LLN, ULN)	62 (52,72)	65 (57,73)
Bhave NM, Lang RM. Evaluation of left ventricular structure and function by three-dimensional echocardiography. <i>Curr Opin Crit Care</i> . 2013;19(5):387-396. EDVI, End-diastolic volume index; ESVI, End-sistolic volume index; LLN, Lower limit of normal; ULN, Upper limit of normal.		

Long-axis views aren't reliable because they can cause tangential cuts and overestimate wall thickness. Only the compacted septal tissue should be measured, excluding right ventricular trabeculae, the moderator band insertion, or the tricuspid valve apparatus.

When measuring the interventricular septum, position the caliper where the right ventricular cavity meets the compacted interventricular septum, and then move it to where the interventricular septum meets the left ventricular cavity. Similarly, for measuring the left ventricular posterior wall, place the caliper at the interface of the compacted posterior wall and the left ventricular cavity, and then move it to the left ventricular posterior wall-pericardial interface. Care should be taken to exclude the mitral valve apparatus from these measurements. Advancing the cine loop frame by frame can help distinguish the posterior wall from the leaflets and chordae tendineae.

Avoid including trabeculations or papillary muscles in measurements. Integrating and cross-referencing short- and long-axis views ensures optimal alignment.³

Various methods, like M-mode, 2D, and 3D echocardiography, accurately calculate left ventricular mass. Measurements should be taken at end-diastole, usually before mitral valve closure or when the ventricular dimension is largest.^{9,10}

Linear measurements should be obtained perpendicularly via the parasternal approach, at the mitral valve leaflet tips, using short-axis or parasternal long-axis views. M-mode measurements should be obtained either from a targeted short-axis view or a parasternal long-axis view (Figure 5).²

For large population screenings, the M-mode method is advantageous because it's simple, fast, and has low variability. However, 2D echocardiography offers benefits over linear techniques. When measuring the entire ventricle using 2D images, the area-length or truncated ellipsoid methods are typically used.¹⁰

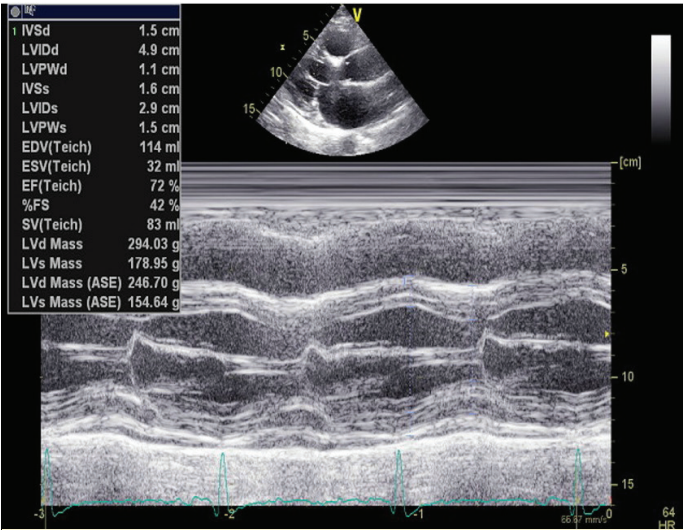


Figure 5. Left ventricular mass measurement with linear method M-mode echocardiography.

Table 3. Normal ranges of LV mass and wall thickness		
	Women	Men
Linear Method		
LV mass (gr)	67-162	88-224
LV mass/BSA (g/m ²)	43-95	49-115
Relative wall thickness (cm)	0.22-0.42	0.24-0.42
Septal thickness (cm)	0.6-0.9	0.6-1.0
Posterior wall thickness (cm)	0.6-0.9	0.6-1.0
2D method		
LV mass (gr)	66-150	96-200
LV mass/BSA (g/m ²)	44-88	50-102
Lang RM, Badano LP, Mor-Avi V, et al. Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. <i>Eur Heart J Cardiovasc Imaging</i> . 2015;16(3):233-270. Erratum in: <i>Eur Heart J Cardiovasc Imaging</i> . 2016;17(4):412. Erratum in: <i>Eur Heart J Cardiovasc Imaging</i> . 2016;17(9):969. LV, Left ventricle; BSA, Body surface area.		

Upper limits of normal left ventricular mass reference by linear measurements are 95 g/m² and 115 g/m² for women and men. When using 2D methods, upper limits of normal left ventricular mass reference are 88 g/m² and 102 g/m² for women and men (Table 3).²

3D echocardiography is distinguished as the only echocardiographic technique capable of directly measuring myocardial volume without relying on geometric assumptions regarding the pattern of left ventricular dilatation or the distribution of wall thickening. This approach shows promise and may be particularly advantageous in cases of abnormally dilated or hypertrophied ventricles, such as those with asymmetric or localized hypertrophy. High-quality 3D echocardiography surpasses 2D echocardiography in assessing LV mass and exhibits a closer correlation with CMR evaluations (Figure 6).

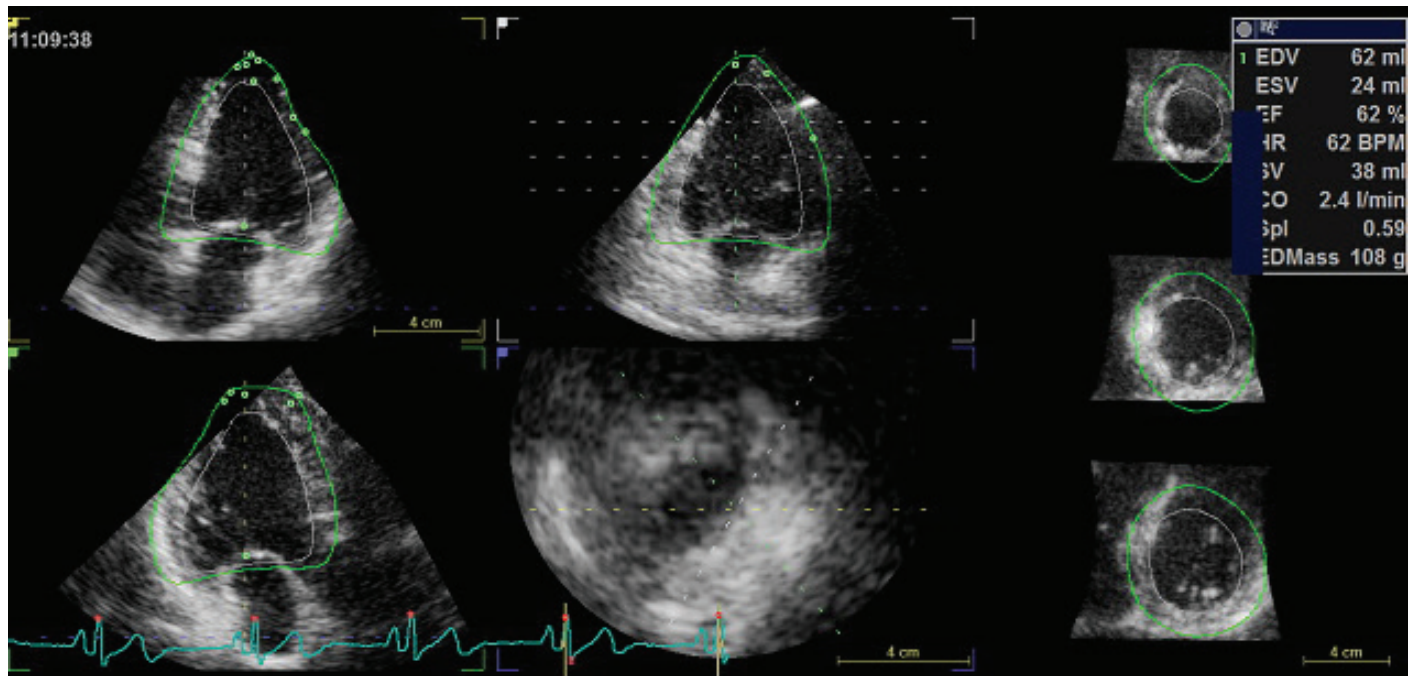


Figure 6. Left ventricular mass detection with 3D echocardiography.

Presently, in the literature available data for on upper normal limits of 3D echocardiographic LV mass are limited, and to support recommendations for reference values, these data are insufficient.^{11,12}

Finally, relative wall thickness (RWT) is calculated using the formula $(2 \times \text{posterior wall thickness}) / \text{left ventricular (LV) internal diameter at end-diastole}$. This calculation categorizes an increase in LV mass as either concentric hypertrophy ($\text{RWT} > 0.42$) or eccentric hypertrophy ($\text{RWT} \leq 0.42$). These measurements of LV mass are derived from linear assessments.²

Hypertrophic cardiomyopathy is identified by the presence of an end-diastolic wall thickness of 15 mm in any segment of the left ventricle, without abnormal loading conditions. However, a wall thickness of 13 mm is considered diagnostic in cases involving a family history of hypertrophic cardiomyopathy or in individuals known to carry disease-causing genes. Increased wall thickness can be observed in any location of the left ventricle, including the right ventricle. It's essential to examine all segments of the left ventricle, from base to apex, during end-diastole. This is preferably done in the 2D short-axis view, ensuring that wall thickness measurements are taken at the mitral, mid-LV, and apical levels.^{1,3}

Left Atrial Volume Measurement

The most common linear measurement for the left atrium is the anteroposterior (AP) dimension in the parasternal long-axis view using M-mode or preferably 2D echocardiography. However, during left atrial remodeling, the atrium may not expand evenly in all directions, so relying only on AP measurements may not give a full picture. It is recommended to measure left atrial volume for a more comprehensive assessment.²

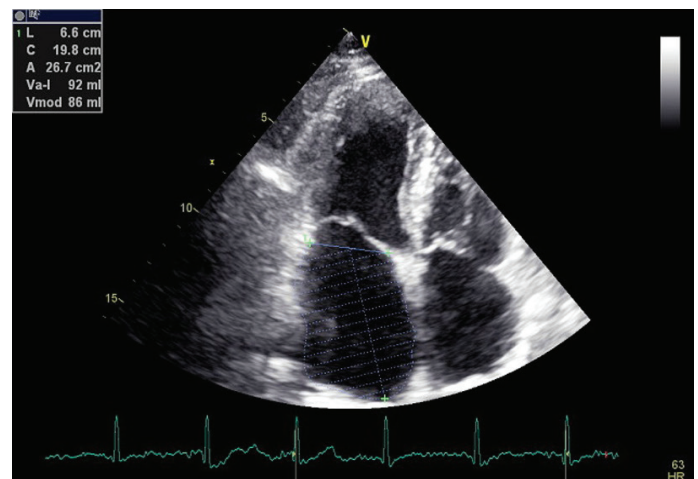


Figure 7. Left atrial volume measurement.

Two methods for measuring left atrial volume are the area-length method and the biplane method of discs. The biplane method, like Simpson's method for left ventricular volume, involves identifying the maximum volume at end-systole. The endocardial borders in the apical four-chamber and two-chamber views are traced, excluding the atrial appendage and pulmonary veins. The tracing is completed by drawing a line across the annulus. The length is measured from the center of the mitral annulus to the farthest edge of the superior left atrial wall in both views (Figure 7).

The upper normal value for left atrial volume is 34 mL/m², as per diastolic function guidelines from the American Society of Echocardiography and the European Association of Echocardiography.^{14,15}

Right Ventricular and Right Atrial Measurements

The structure, function, and deformation of the right ventricle (RV) are crucial for predicting cardiovascular outcomes in conditions like heart failure, pulmonary hypertension, congenital heart disease, and arrhythmogenic RV cardiomyopathy. In clinical practice, 2-D echocardiography is the primary tool for assessing the RV.

In the RV-focused apical four-chamber view, the end-diastolic dimension is measured from the middle of the tricuspid annulus to the compacted apex. The diameter includes the widest part of the basal third at end-diastole, and the mid-cavity dimension is taken halfway between the basal diameter and apex, at the papillary muscles level (Figure 8).¹⁶⁻¹⁸

To measure the RV area, trace the blood-endocardial border from the tricuspid annulus to the apex at end-diastole and end-systole to calculate the fractional area change, including papillary muscles, trabeculations, and the moderator band. The RV free wall is measured in subcostal views, avoiding epicardial fat.¹⁸

For the right atrium (RA), trace from the tricuspid annulus along the interatrial septum and RA walls. An RA area over 18 cm², length over 53 mm (major dimension), or diameter over 44 mm (minor dimension) indicates enlargement at end-diastole (Table 4). Cardiac magnetic resonance remains the gold standard for RV assessment.^{18,19}

Arrhythmogenic right ventricular cardiomyopathy (ARVC) is marked by the replacement of right ventricular muscle with fibrous and fatty tissue, leading to myocardial atrophy. On 2D echocardiography, significant right ventricular dilatation is a crucial diagnostic indicator. Key features for diagnosing ARVC include wall motion abnormalities like dyskinesia, akinesia, or bulging. The diagnosis largely depends on the extent of RV dilatation or dysfunction.^{1,20}

Strain Imaging

Various types of strain imaging exist, but the most clinically valuable data come from global longitudinal strain (GLS) using 2D speckle imaging. Peak GLS measures the relative change in the left ventricular (LV) myocardium length during end-diastole and end-systole. It's typically assessed in the end-systolic frame by tracing endocardial borders from the standard apical views, averaging the strain across all cardiac segments.

Two-dimensional GLS is reliable and practical for clinical use, offering prognostic insights beyond LV ejection fraction in various heart conditions. However, measurements can differ between vendors and software versions. In healthy individuals, a peak GLS around -20% is expected. A lower absolute value suggests abnormality (Figure 9).²¹

RV longitudinal strain is a valuable noninvasive measure of RV contractility, less influenced by geometric changes and load compared to traditional indices (Figure 10). It accurately reflects RV systolic function, detecting mild abnormalities and predicting prognosis. An RV free wall strain below -20% typically indicates abnormal function.^{2,23}

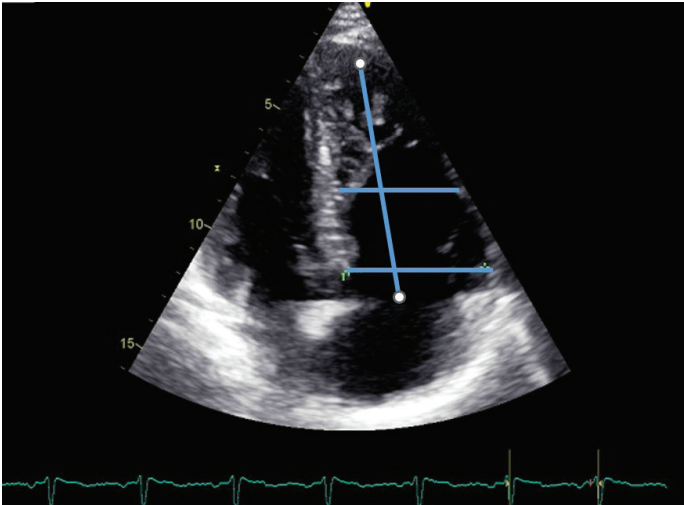


Figure 8. Measurement of right ventricular dimensions (basal, mid and longitudinal).

Table 4. Normal values for RV chamber size		
Parameter	Mean±SD	Normal Range
RV basal diameter (mm)	33±4	25-41
RV mid diameter (mm)	27±4	19-35
RV longitudinal diameter (mm)	71±6	59-83
RVOT PLAX diameter (mm)	25±2.5	2-30
RVOT proximal diameter (mm)	28±3.5	21-35
RVOT distal diameter (mm)	22±2.5	17-27
RV wall thickness (mm)	3±1	1-5
RV EDA/BSA (cm ² /m ²)		
Men	8.8±1.9	5-12.6
Women	8.0±1.75	4.5-11.5
RV ESA/BSA (cm ² /m ²)		
Men	4.7±1.35	2.0-7.4
Women	4.0±1.2	1.6-6.4
RV EDV/BSA (cm ³ /m ²)		
Men	61±13	35-87
Women	53±10.5	32-74
RV EDV/BSA (cm ³ /m ²)		
Men	27±8.5	10-44
Women	22±7	8-36

Lang RM, Badano LP, Mor-Avi V, et al. Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. *Eur Heart J Cardiovasc Imaging*. 2015;16(3):233-270. Erratum in: *Eur Heart J Cardiovasc Imaging*. 2016;17(4):412. Erratum in: *Eur Heart J Cardiovasc Imaging*. 2016;17(9):969.

EDA, end-diastolic area; ESA, end-systolic area; PLAX, parasternal long-axis view; RVOT, RV outflow tract.

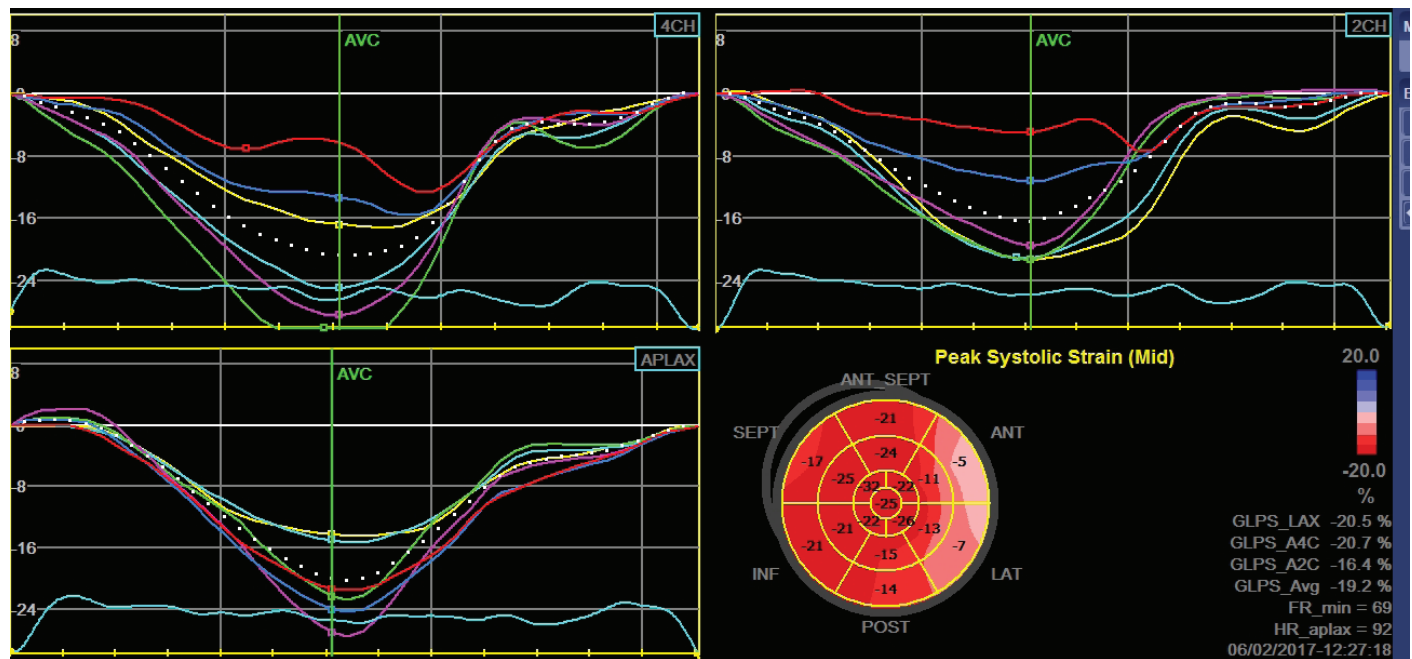


Figure 9. Left ventricular myocardial strain measurement with 2-D speckle-tracking echocardiography from each apical view with bull's eye plot.

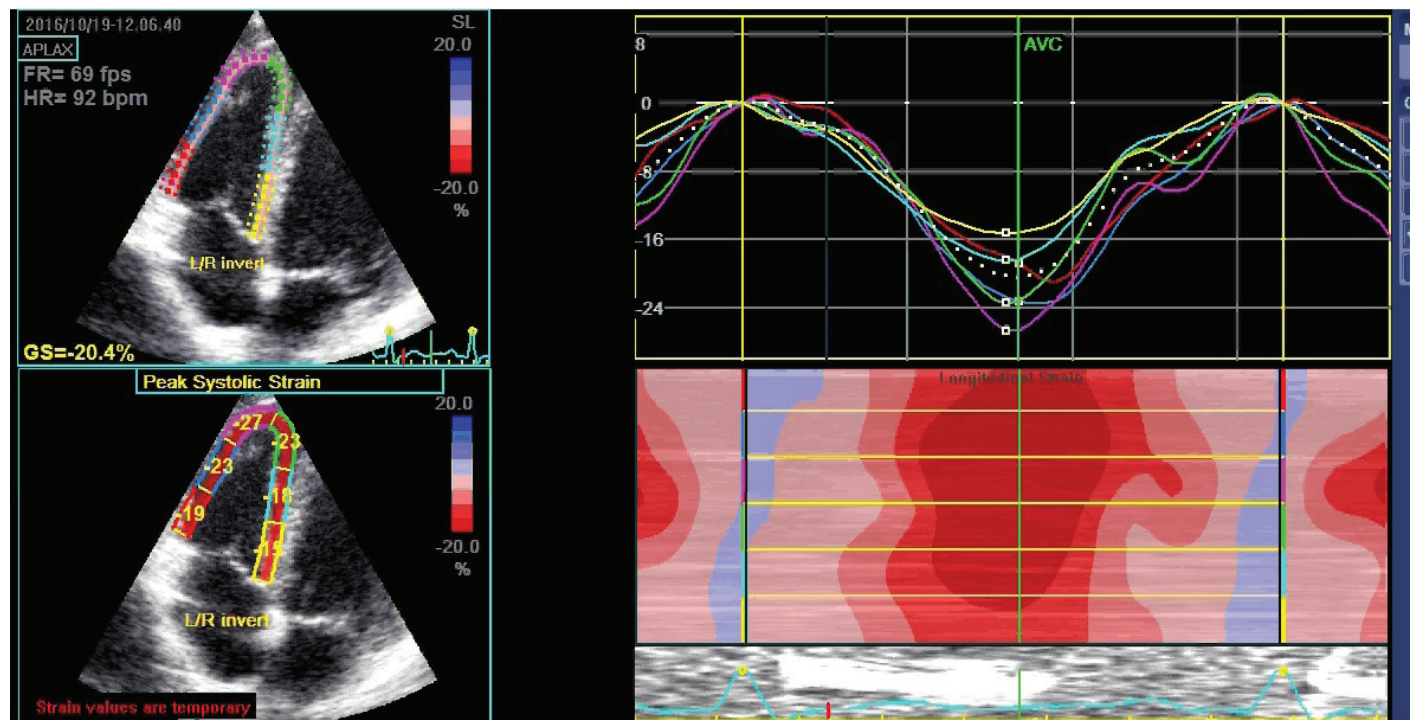


Figure 10. Right ventricular myocardial strain measurement with 2-D speckle-tracking echocardiography.

Cardiac Magnetic Resonance Methods Used in the Evaluation of Cardiomyopathies

Cardiomyopathies can be shortly defined as muscular diseases of the myocardium. Historically, the definition and classification of cardiomyopathies have mainly been based on the morphology of the ventricles, and although knowledge about the underlying genetic factors has increased considerably today, cardiac morphology is still essential in the definition of cardiomyopathies.²⁴ From this point of view, cardiac imaging modalities are primary in the diagnosis of cardiomyopathies as a disease group. Although there is a wide range of genetic and environmental causes in the etiology of cardiomyopathies, their effects occur with changes and deterioration in the structure (ventricular morphology, myocardial structure) and function (systolic/diastolic function) of the heart (Figure 11). Therefore, a satisfactory definition of the morphology and function of the ventricles (wall thickness, regional wall motion abnormalities, ventricular volumes and ejection fraction, deformation) and myocardial structure (fibrosis/scar, fatty infiltration, iron deposition) is valuable in the diagnosis of cardiomyopathies and cardiac MR is important in the diagnosis of cardiomyopathies in this respect.^{1,25}

In many patients, it is possible to obtain valuable information required for the evaluation of cardiomyopathy with a very basic and short cardiac MR protocol. Such a protocol includes static anatomical images, short- and long-axis cines and late contrast images, and can be completed in approximately half an hour; it does not require special software and can be performed with a routine MR scanner machine in a non-dedicated centre (Figure 12). If necessary, other and some more advanced sequences can be added to this basic protocol (e.g., right ventricle-specific cine planes, T1 and T2 mapping, perfusion and flow mapping).

Assessment of Cardiac Morphology

Cardiac MR studies routinely start with static anatomical images that cover the entire thorax. These may be white blood sequences in which the vessels and cardiac cavities appear white, or black blood sequences in which they are suppressed and appear black. The anatomical images are valuable to show the heart, great vessels, and the pericardium and to gain a general idea of the thorax (Figure 13). For example, such static anatomical images are valuable for assessing whether the ventricles are

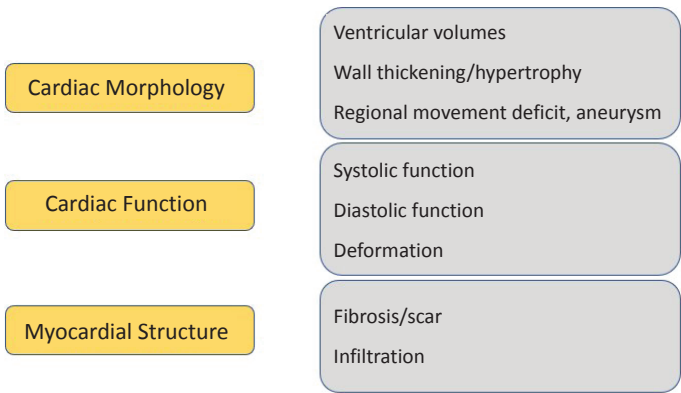


Figure 11. Changes seen in cardiomyopathies.

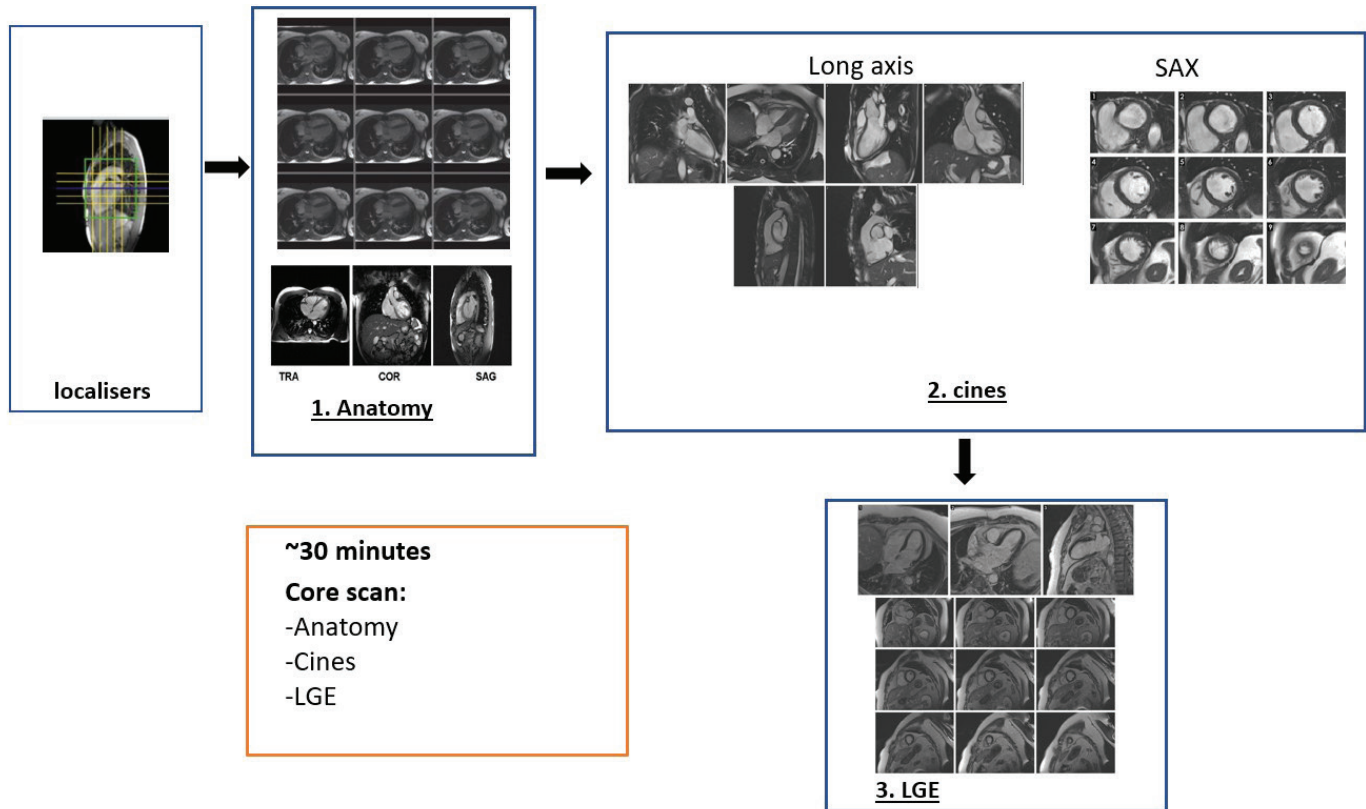


Figure 12. Basic CMR protocol for the evaluation of cardiomyopathies.

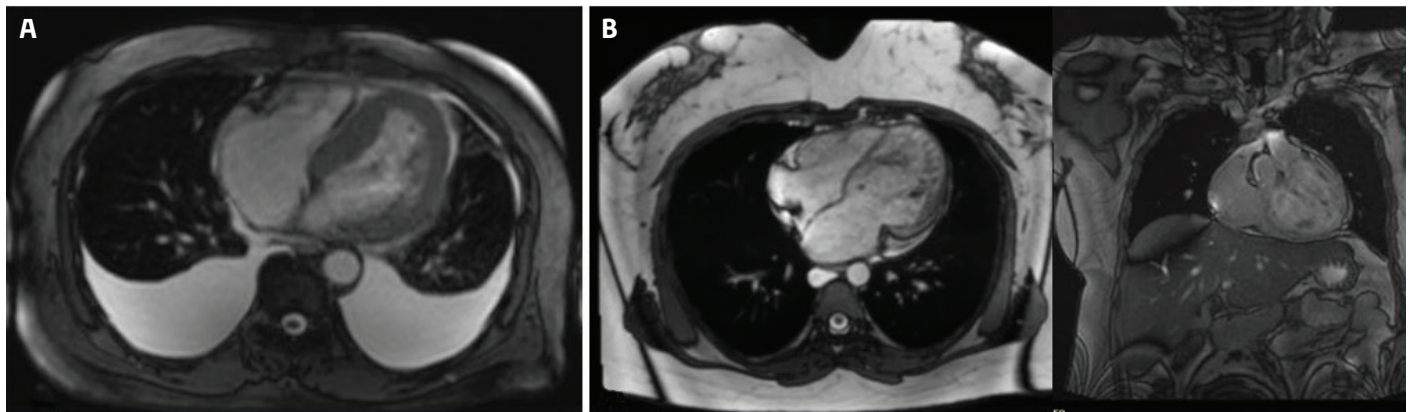


Figure 13. Anatomical images provide a global view of the heart and thorax. On the left (A), in a patient referred with a working diagnosis of cardiac amyloidosis, it is possible to see left ventricular hypertrophy and bilateral pleural effusions consistent with amyloidosis on the anatomical images taken at the beginning of study. On the right (B), in a patient who was thought to have non-compaction cardiomyopathy due to prominent "left" ventricular trabeculation, the anatomical image taken in the coronal section shows parallel course of the great arteries, and the left ventricle, which appears significantly trabeculated and thought to be non-compaction, could actually be the systemic right ventricle in a patient with congenitally corrected transposition of the great arteries.

enlarged at first glance, whether there is a pulmonary venous return anomaly that may cause enlargement of the right heart chambers in a patient with right ventricular enlargement and suspected arrhythmogenic cardiomyopathy, or inferior vena cava enlargement in a patient with restrictive cardiomyopathy.

Cine images follow the anatomical images. Cine images include long axis slices equivalent to echo and short axis slices covering

the entire ventricle. Cine images in other planes can be added to study protocol if needed. Since cine image quality is superb and short axis images cover the entire ventricle, ventricular volumes and ejection fraction can be calculated with high accuracy and reproducibility without any geometric assumption.^{26,27} Many studies have shown that left and right ventricular volume measurement with cardiac MR is more precise and reproducible

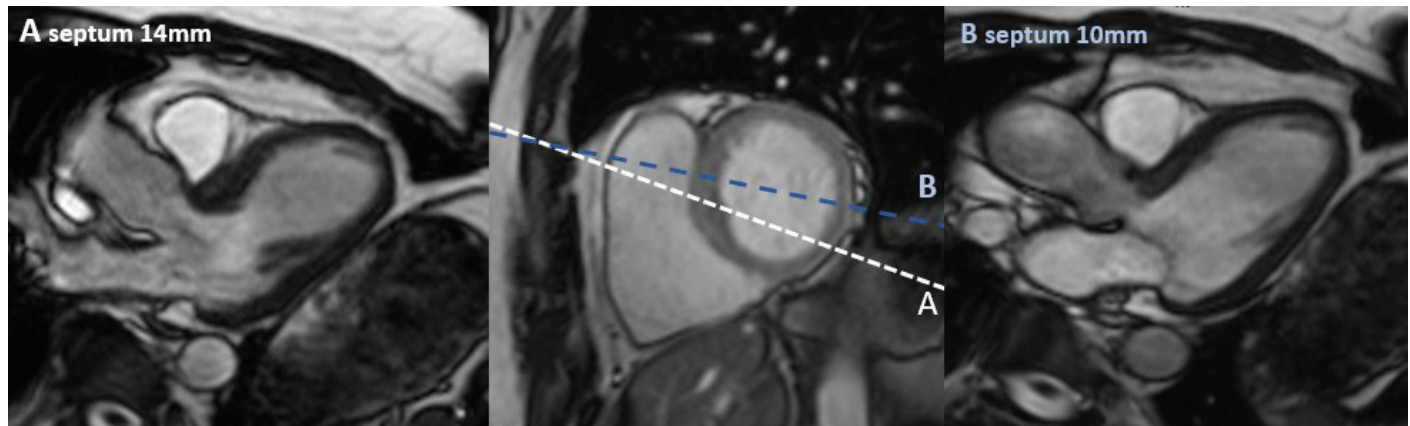


Figure 14. CMR was requested in an asymptomatic young patient because of mild basal septal hypertrophy seen on echocardiography. Indeed, the basal septum appeared hypertrophic on the first 3-chamber image (A), but later short-axis sections showed normal wall thickness. When the short axis plane of the first 3-chamber image is analysed, it can be tracked that the septum is cut obliquely and longitudinally (white dashed line). It is seen that the basal septum thickness is normal and there is no hypertrophy in the 3-chamber view taken again by planning the plane optimally so that the septum is not cut obliquely (blue dashed line).

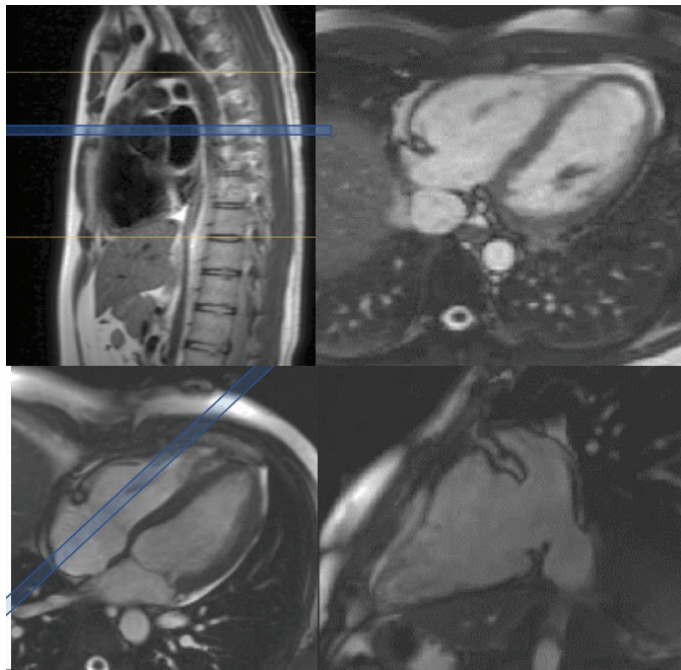


Figure 15. In patients with arrhythmogenic cardiomyopathy, where the right ventricle is to be specifically evaluated, cine planes for the right ventricle should be added to the acquisition protocol. The top row shows the planning of axial cine slices and an example of axial cine, and the bottom row shows the planning of the right ventricular long axis two chamber image and the cine image acquired.

than echo. This provides reliable data both for the initial diagnosis during the evaluation of cardiomyopathies and for the determination of changes in ventricular volume and ejection fraction during follow-up. Another advantage of images obtained with CMR is that the sections can be planned easily and precisely and foreshortening images or measurements from oblique sections, which may be misleading in echo, can be avoided

(Figure 14). Once again, the superior quality of cine images makes the assessment of ventricular myocardial thickness and left or right ventricular wall motion abnormalities more reliable.

In addition to routine long- and short-axis cine slices, cine images of the right ventricle and cine images in the axial plane should particularly be included in the protocol for evaluation of arrhythmogenic cardiomyopathy. These extra sections are necessary to detect wall motion abnormalities of the right ventricle, which contracts mainly in the longitudinal direction (Figure 15).

To complement the traditional parameters of ventricular volumes and ejection fraction, strain analyses can be easily performed from cine images; nevertheless, despite all the advances in the evaluation of cardiac mechanics, the determination of ventricular volumes and ejection fraction is still essential for the diagnosis of cardiomyopathies. Diastolic dysfunction is a typical finding for the diagnosis of restrictive cardiomyopathies, but it is also an important factor in other cardiomyopathies. Diastolic function can be evaluated with cardiac MR by obtaining mitral and pulmonary vein flow profiles with flow mapping, however diastolic function can be easily evaluated with echo and therefore it is not commonly performed with cardiac MR.

Assessment of Myocardial Structure (Tissue Characterisation)

In addition to morphological and functional impairment of the ventricles, alterations of myocardial structure are one of the main markers of cardiomyopathies. Cardiac MR provides important information in the diagnosis of cardiomyopathies, especially with late contrast imaging (late gadolinium enhancement – LGE) and myocardial fibrosis determination.²⁵

Late Contrast Imaging

The ability to demonstrate myocardial fibrosis and scar regions in late images obtained after gadolinium contrast agent injection is one of the most important advantages of cardiac MR in current cardiological practice.²⁶ LGE imaging was first used to demonstrate infarction scars and then gradually gained an important place in

the diagnosis of non-ischemic cardiac pathologies as well.^{28,29} Localisation and pattern as well as the presence and extent of scarring provide information about the underlying cardiac pathology. Essentially the fibrosis pattern detected by LGE can be classified according to whether it involves the subendocardium or not. Fibrosis and scar of infarction, i.e., ischaemic aetiology, always involve the subendocardium; in other words, LGE patterns without subendocardial involvement suggest non-ischemic and cardiomyopathic processes (Figure 16). Beyond this basic ischaemic/non-ischemic distinction based on the presence or absence of subendocardial involvement, patterns such as mid-wall or subepicardial are more suggestive of certain pathologies but do not provide a definitive distinction. For example, although myocarditis is classically known with subepicardial enhancement, it may show mid-wall contrast uptake to the same extent, and this is also true for other non-ischemic aetiologies and cardiomyopathies. As our knowledge of the genetic and environmental aetiology of cardiomyopathies has increased, it has become possible to match certain gene defects and cardiomyopathy subtypes with certain LGE patterns, but it is important to emphasise that no LGE pattern is completely specific to an aetiology. As an example, while subepicardial LGE classically suggests myocarditis, subepicardial LGE in the lateral wall has also been frequently observed in most of the left dominant arrhythmogenic cardiomyopathy patients in

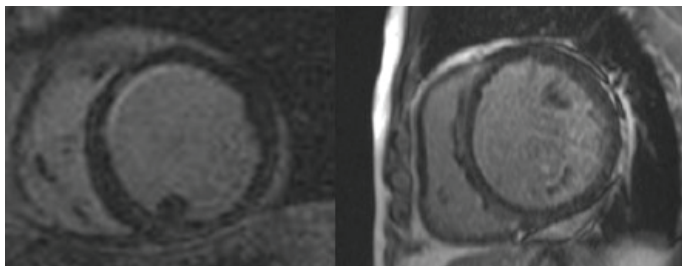


Figure 16. On the left, LGE in the subendocardium in the anteroseptal region typically indicates infarction, whereas on the right, mid-wall LGE in the septum is a typical example of a non-ischemic fibrosis pattern.

a similar pattern. Furthermore, from an aetiological perspective, it is possible that some arrhythmogenic cardiomyopathies may be triggered by myocarditis attacks in the presence of underlying gene defects, or conversely endomyocardial biopsies of some patients with typical ARVC phenotype show typical myocarditis and not cardiomyopathy as the underlying pathologic process.³⁰ Even more confusingly, it is possible that two different pathologies may happen simultaneously in a patient and more than a single pattern of LGE is seen. It should be kept in mind that myocardial fibrosis determined by LGE is never normal with our current knowledge and is considered pathological; the exception is mild late contrast uptake in the septum at the sites of right ventricular insertion which can occasionally be seen in normal individuals (Figure 17).

Although cardiac MR provides important information in addition to echocardiography in defining the phenotypic features of cardiomyopathies, it should be kept in mind that many cardiomyopathies of different etiologies will have similar phenotypes and may not be differentiated by echo or CMR imaging alone. For example, it is not possible to differentiate a tachycardia-related dilated cardiomyopathy from a genetically based familial dilated cardiomyopathy by imaging alone. Furthermore, some dilated cardiomyopathy gene mutations such as LMNA may be the primary underlying cause of both the arrhythmic tachycardia and cardiomyopathy.³¹ Similarly, although some mutations may directly cause dilated cardiomyopathy, they may also predispose to development of dilated cardiomyopathy when exposed to an environmental factor. For example, in dilated cardiomyopathy secondary to chemotherapy, the chemotherapy appears as the obvious etiological factor, however a titin gene truncation mutation which is associated with familial dilated cardiomyopathy may also be present and play an underlying predisposing role.³² It is not possible to demonstrate these differences with imaging alone at the time being.

The presence of LGE has prognostic importance as well as diagnostic value. Myocardial fibrosis is detected by LGE in approximately one third of dilated cardiomyopathy and two thirds of hypertrophic cardiomyopathy patients.^{29,33} In these patients,

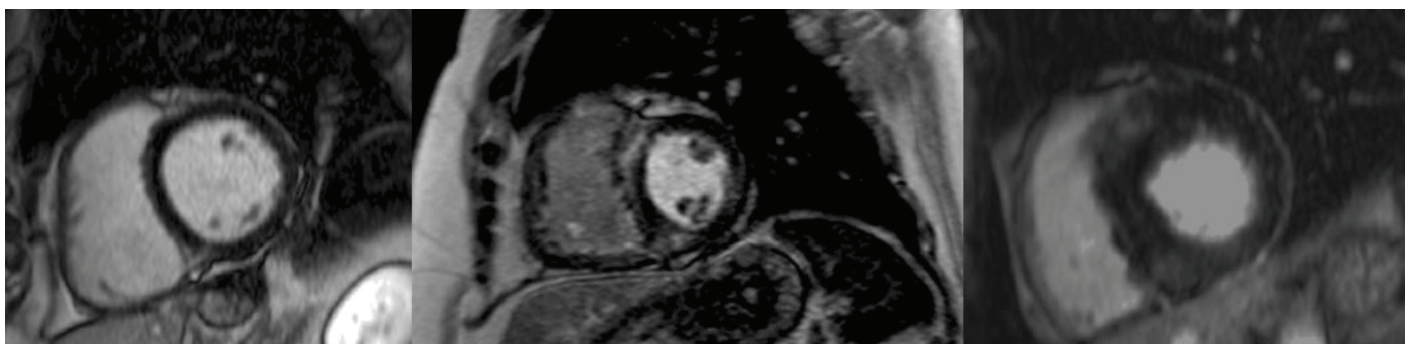


Figure 17. A mild LGE at the right ventricular attachment sites of the septum can be seen in normal individuals and is not considered to indicate any pathology on its own with current knowledge. In cases of either right or the left ventricular hypertrophy, LGE at the attachment sites may become more prominent and compatible with the underlying pathology. In a healthy person on the left, a mild LGE is seen at the right ventricular attachment site on the septum which is normal. In the centre, a patient with pulmonary hypertension and right ventricular hypertrophy, and on the right a patient with hypertrophic cardiomyopathy and left ventricular hypertrophy have prominent LGE at the ventricular attachment points in the septum, which are pathological late contrast enhancement at the attachment sites reflective of the underlying primary disease.

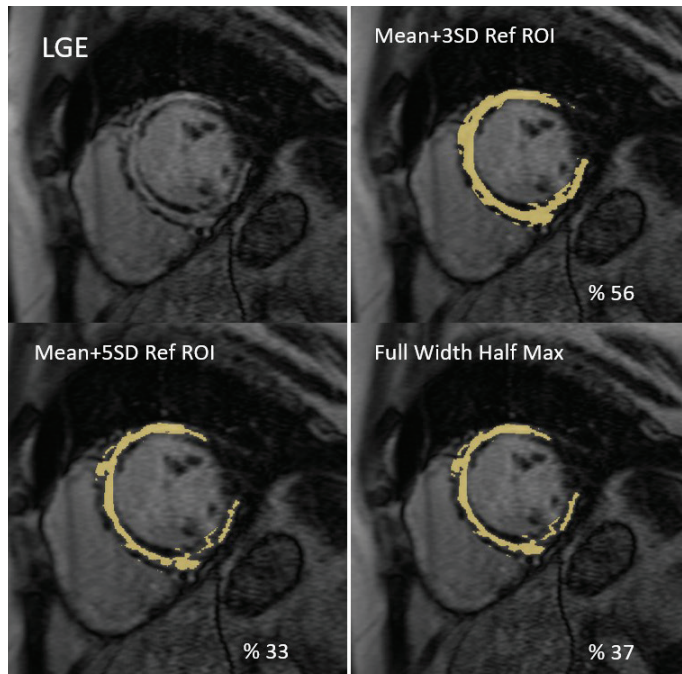


Figure 18. LGE quantification. In the upper left, a non-ischemic pattern extensive mid-wall LGE is seen. Quantification of the area of LGE in this patient using different methods and criteria yields significantly different LGE percentages.

the risk of cardiac mortality and heart failure is correlated with the increasing amount of fibrosis, but the most important risk increase is primarily determined by the presence or absence of fibrosis rather than its amount, and the presence of LGE is associated with increased risk regardless of its amount.²⁹ To give an example, in a patient with dilated cardiomyopathy, the risk of sudden cardiac death is higher when the left ventricular ejection fraction is 40% and LGE is present than when the ejection fraction is 25% and LGE is absent.²⁹

LGE Quantification

Myocardial fibrosis detected by LGE has been shown to be associated with increased cardiovascular risk in almost all cardiomyopathies and this relationship is proportional to the amount of fibrosis.²⁵ LGE quantification methods are used to determine the amount of fibrosis. However, LGE quantification may be a tedious method in non-ischemic cardiomyopathies. In addition, the presence of LGE is more critical than the amount of LGE in dilated cardiomyopathy²⁹, and in hypertrophic cardiomyopathy it is controversial whether the presence of LGE carries an additional risk independent of the conventional risk factors since LGE is present in most of the patients.³³ It should be kept in mind about the quantification of LGE is that these quantification methods were originally developed to quantify infarction scars in which fibrosis is much more intense and the borders are sharp, and then applied in non-ischemic cardiomyopathies. However, fibrosis in non-ischemic cardiomyopathies is generally more diffuse and less dense than in infarction scars. Also, although the LGE quantification methods in general correlate with each other well, the 2, 5 or 6 standard deviation methods in which normal myocardium is taken as the

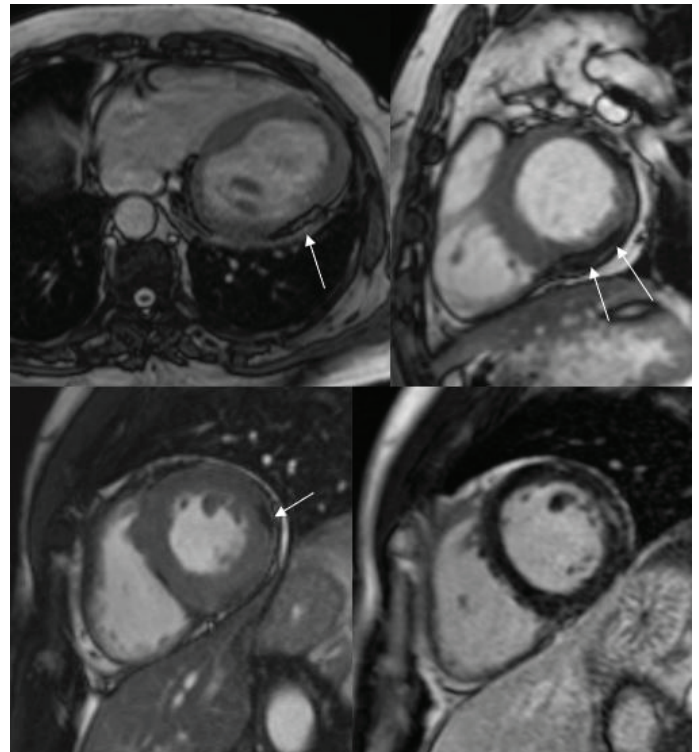


Figure 19. Myocardial fat infiltration may be an important finding for the diagnosis of cardiomyopathy. It is not easy to distinguish in the right ventricle due to the thin wall of the right ventricle, but it can be distinguished much more easily in the left ventricle. In the upper row, anatomical images taken in a patient with arrhythmogenic cardiomyopathy show significant fatty infiltration in the lateral and inferior walls of the left ventricle, which can be recognized by the "Indian ink" artifact (arrows). In another patient in the bottom row, fatty infiltration is seen on the anterolateral wall of the left ventricle in the section taken from the cine images (arrow), and late contrast enhancement is also seen in the LGE sections of the same region (bottom right image), indicating a possible fibrofatty change area.

reference or the "full-width-half maximum" method in which the fibrosis core is taken as the reference may give different absolute values in a single patient (Figure 18).³⁴ Therefore, these factors should be taken into consideration when using the LGE $\geq$ 15% criterion recommended in the guideline in the evaluation of the risk of sudden cardiac death.^{1,35}

Other Tissue Characterisation Sequences

Apart from myocardial fibrosis detection with LGE, there are other sequences and methods used in tissue characterisation. Macroscopic lipid in tissues can be determined by using sequences that suppress adipose tissue. We use these sequences especially in the detection of tumours such as lipomas and liposarcomas, and contrary to the general belief, we do not use them routinely in arrhythmogenic cardiomyopathy protocols in the current practice. In the Task Force diagnostic criteria for arrhythmogenic cardiomyopathy myocardial fat imaging with CMR is not included among the imaging markers.³⁶ The reasons for this are the thin structure of the right ventricular wall and the impossibility

to distinguish epicardial adipose tissue from right ventricular myocardium. On the other hand, adipose tissue can sometimes be seen within the left ventricular myocardium in left dominant arrhythmogenic and dilated cardiomyopathies (Figure 19).

Another tissue characterisation sequence is T2-weighted STIR (short tau inversion) imaging, which allows the detection of oedema in the myocardium. This sequence is especially important in the diagnosis of cardiac pathologies accompanied

by acute myocardial oedema and inflammation of any etiology, such as acute myocarditis or acute infarction. Since active myocardial oedema is not expected in primary cardiomyopathies, STIR T2 sequence is not routinely included in cardiomyopathy CMR protocols, although subclinical myocarditis attacks may even rarely occur during the course of genetic cardiomyopathies (Figure 20).³⁷ Moreover, the first clinical presentation of an arrhythmogenic cardiomyopathy, especially those related to some particular genetic mutations, may be as an acute myocarditis clinical picture.³⁸

T1 and T2 Mapping

Magnetic resonance imaging utilises the spin effect of protons in tissues. The signal formation from protons in the tissues for image acquisition following a radiofrequency impulse simply show two features. The first is the decay of the signal generated by the stimulation, which is determined by the T2 time, and the other is the return of the excited protons in the tissues to their initial excitable position, which is determined by T1 time.³⁹ In magnetic resonance imaging, this property of different T1 and T2 times of different tissues is exploited to create contrast in the images. For example, the T2 time of water, i.e., oedematous tissue, is long, which means it takes longer time for the signal to decay, therefore, in a T2-weighted image, the signal of the oedematous tissue is higher than the surrounding tissues because it is retained longer. In T1 and T2 mapping, instead of acquiring images in a way to exploit the relative differences in these properties of tissues, images are created in which each pixel directly reflects the T1 or T2 time.⁴⁰ For example, to show myocardial oedema, colour-coded T2 maps are obtained instead of the previously mentioned T2-weighted oedema images (Figures 21 and 22). The clinical use of T2 mapping is mainly for oedema imaging and in cardiac MR practice, oedema is the only explanation for an increased myocardial T2 on T2 maps. When the T1 properties of the myocardium are considered, there are multiple factors that prolong the T1 duration; for the perspective of practical clinical use oedema, fibrosis and amyloid deposition prolong the T1 duration of the myocardium; while lipid and iron deposition

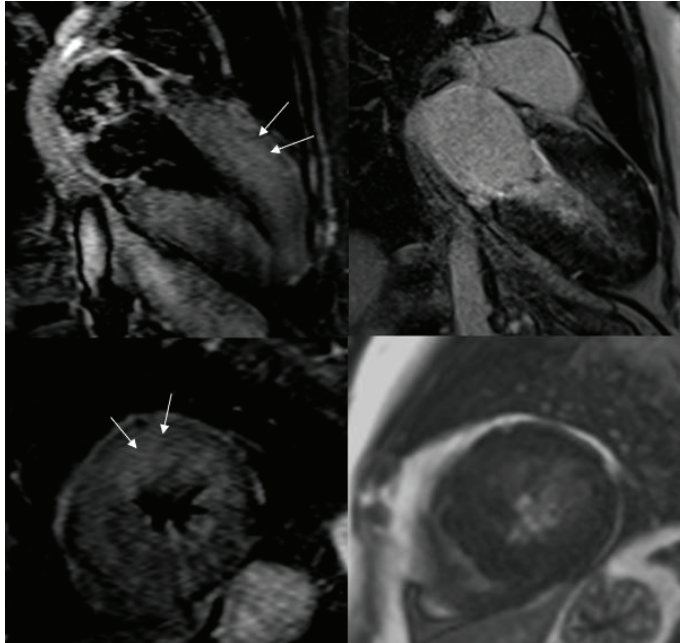


Figure 20. In a patient with hypertrophic cardiomyopathy and mildly elevated troponin levels, there is slightly increased myocardial signal on T2-weighted STIR images matching areas of fibrosis in the left ventricular anterior wall, suggesting mild oedema/inflammation in these areas. The left column shows STIR T2 images, the right column shows LGE images of the same sections.

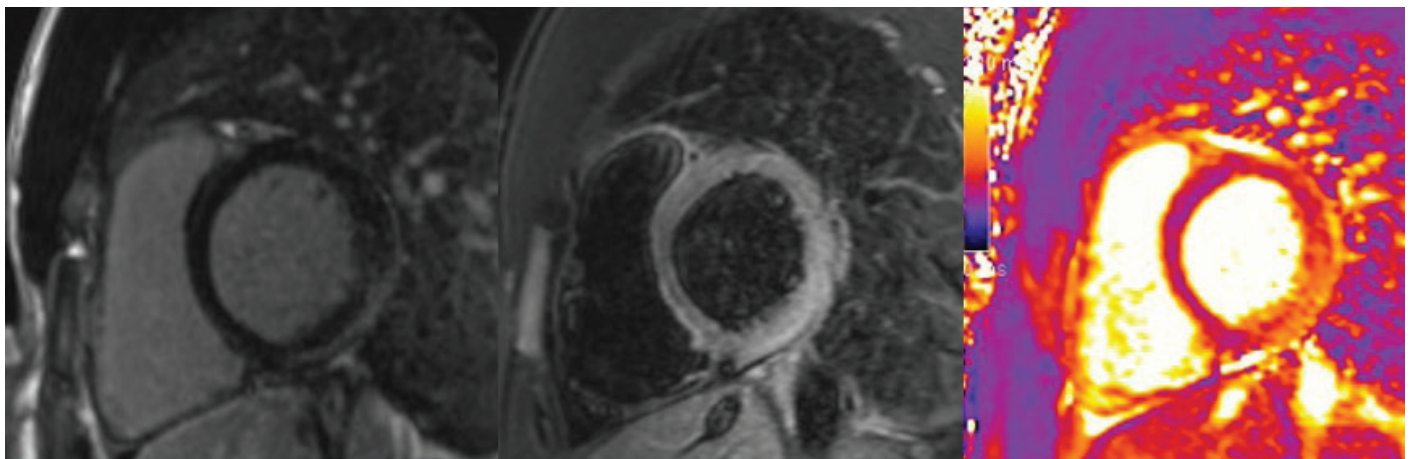


Figure 21. Myocardial oedema in acute myocarditis can be seen as areas of relatively increased myocardial signal on STIR T2 images, or it can be shown directly on T2 maps with increased T2 values which can be coded in a color scale. Late contrast image on the left, STIR T2 in the middle and T2 map images on the right show signs of myocarditis in the subepicardial region of the left ventricle inferolateral wall.

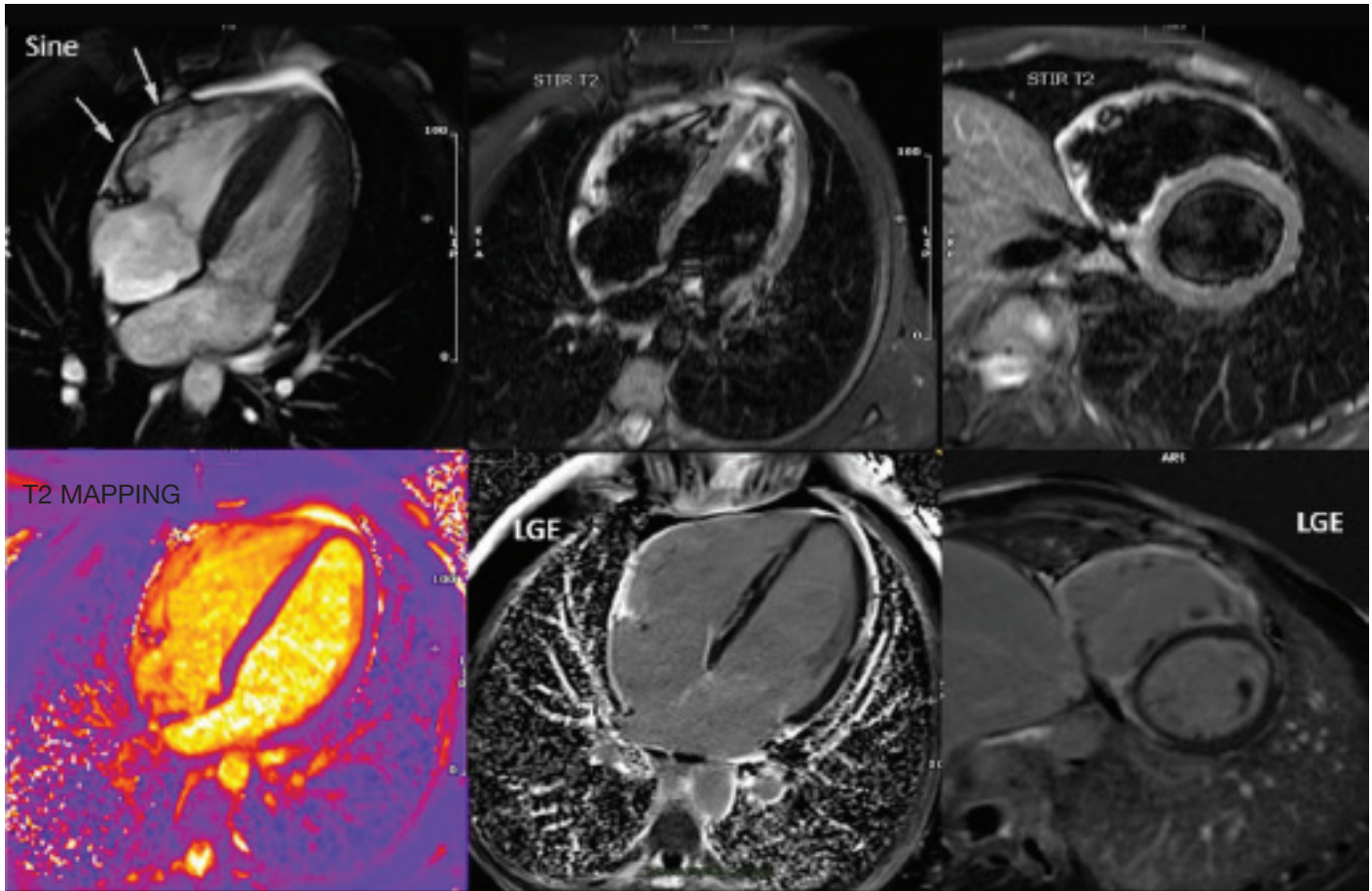


Figure 22. In a patient with arrhythmia, chest pain and elevated troponin, the CMR images showed hypokinetic areas (white arrows) on the free wall of the right ventricle along with right ventricular dilatation and decreased ejection fraction. While the findings initially suggested arrhythmogenic right ventricular cardiomyopathy, STIR T2 images and T2 map also show presence of active myocardial oedema in the right ventricular free wall consistent with myocarditis. There is also very significant fibrosis in the right ventricular free wall on late contrast images. Such patients who meet the diagnostic criteria for both arrhythmogenic right ventricular cardiomyopathy and acute myocarditis are increasingly being recognized. It may not always be possible to distinguish the underlying pathology in patients with such overlapping findings, but the reason for this lies in the complex nature of the underlying mechanisms rather than the inadequacy of imaging methods. Indeed, the underlying pathology in this patient may be a typical myocarditis or arrhythmogenic right ventricular cardiomyopathy, or both may occur simultaneously, or a typical myocarditis attack may have triggered the manifestation of arrhythmogenic right ventricular cardiomyopathy in a patient with a genetic background.

in the myocardium causes short T1 values on T1 maps.⁴¹ With this approach, it was thought that myocardial T1 time will be prolonged (increased) in the presence of myocardial interstitial fibrosis at a level not visible on LGE images, and this may provide important information in the evaluation of cardiomyopathies. Indeed, it has been shown in many studies that the increase in T1 values detected by CMR correlates with histologically determined interstitial fibrosis in myocardial tissue samples.⁴² However, since interstitial fibrosis is the common mechanism of many different etiologies of myocardial insult, it does not seem to be practically possible to use T1 mapping to recognize different types of cardiomyopathies for a diagnostic purpose. For example, myocardial T1 (native) values derived from T1 mapping are increased in all cases of left ventricular hypertrophy secondary to hypertension, aortic stenosis or hypertrophic cardiomyopathy. Although the increase in hypertrophic cardiomyopathy is

generally higher than the others, it is not practically possible to use T1 values to differentiate the underlying pathology since the T1 value ranges seen in these pathologies overlap.⁴³ Two important pathologies in which the T1 value may be valuable in practice are cardiac amyloidosis in which myocardial T1 is considerably increased and Fabry disease in which myocardial T1 is decreased due to fat accumulation. Therefore, Fabry disease should be considered in a patient with left ventricular hypertrophy and low myocardial T1 value and cardiac amyloidosis should be considered in a patient with markedly elevated myocardial T1 value. However, considering that both diseases are infiltrative diseases requiring accumulation in the myocardium, these T1 features may not be seen in the early stages of the disease when the accumulation is in the initial stages and has not reached a critical threshold. For cardiac amyloidosis, it will not be difficult to make the diagnosis when other typical CMR features (left

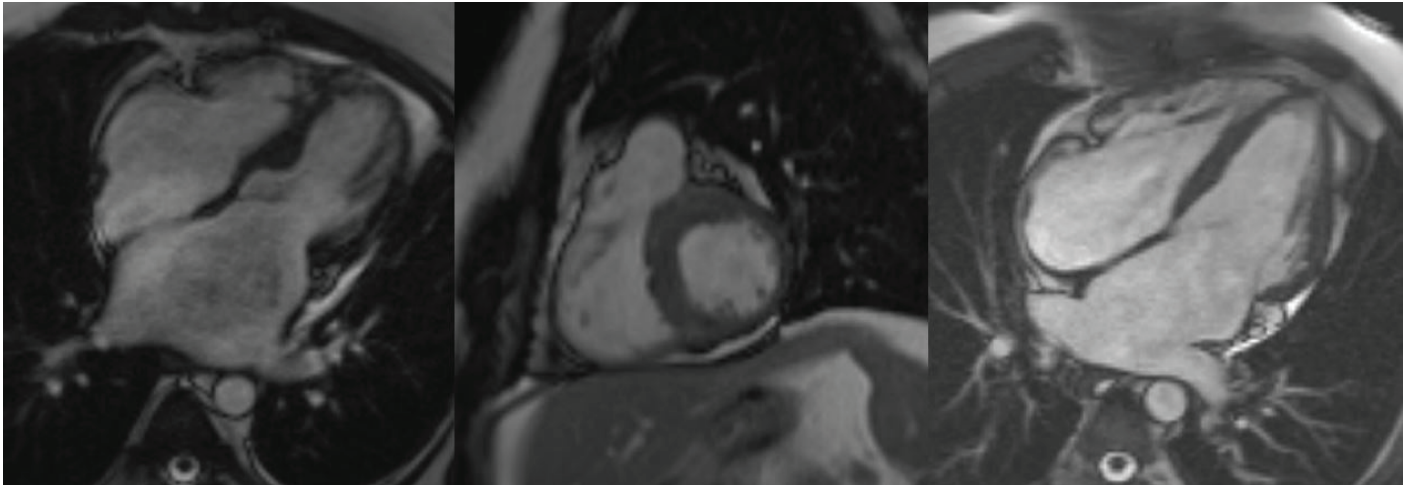


Figure 23. Two examples of patients with clinical findings of restrictive cardiomyopathy. In both patients, a greatly enlarged left atrium is noted as one of the main imaging findings. The first patient (left and middle image) had an underlying myosin heavy chain mutation and asymmetric septal hypertrophy is also seen in the images. The second patient (left picture) had familial restrictive cardiomyopathy, but an underlying genetic defect could not be detected. It is noteworthy that this patient also had the typical restrictive cardiomyopathy morphology, but the wall thickness was normal.

ventricular hypertrophy and typical LGE) are also present in a patient with significantly elevated myocardial T1 value on the maps. On the other hand, since the cause of a mildly increased T1 may be amyloidosis as well as any other pathology with interstitial fibrosis, consideration of cardiac amyloidosis based only on a mildly increased myocardial T1 value will considerably decrease the specificity. In addition, it should be kept in mind that T1 and T2 maps are reconstructed images derived from a set of images and may be inaccurate due to any artefact or technical inadequacy in any of these source images, as such the raw source image series from which the maps are produced should be checked for artefacts that may cause such errors.

The T1 and T2 mapping described above are from images acquired before contrast agent administration. T1 maps can be repeated after contrast agent administration, and the circulating volume of gadolinium contrast agent and thus the myocardial extracellular volume (ECV) fraction can be calculated with a formula including the haematocrit value. Both ECV fraction and myocardial native T1 increase in the presence of interstitial fibrosis and are generally closely correlated to each other.⁴¹ The main difference is that native myocardial T1 is determined by the properties of both the myocyte cells and the interstitial space in the myocardial tissue, whereas the ECV fraction is determined only by the interstitial space. In the presence of interstitial fibrosis, both myocardial T1 and ECV fraction are increased. The normal myocardial ECV fraction is about 28 +/- 2%. Slight increases (1-3%) can be seen in any pathology with interstitial fibrosis and does not provide much differential diagnostic value, but in cardiac amyloidosis, extracellular volume increases considerably due to amyloid deposition and ECV fraction is generally expected to be above 40%.⁴⁴

CMR in the Diagnosis of Restrictive and/or Infiltrative Cardiomyopathies

This group includes relatively rare cardiomyopathies that may differ considerably from other cardiomyopathies. While diastolic

dysfunction is the typical derangement that comes to mind when restrictive cardiomyopathies are considered, the primary manifestation in some of the infiltrative etiologies may be systolic dysfunction or the main presentation may be a hypertrophic cardiomyopathy phenotype. Primary restrictive cardiomyopathy is not related to any infiltrative disease and may be familial with a genetic basis, mainly presents with severe diastolic dysfunction and may not have cardiac hypertrophy in contrast to the typical restrictive cardiomyopathy definition (Figure 23). CMR is particularly valuable in the work-up of this group of patients when it is necessary to rule out constrictive pericarditis, hence should be included in the initial evaluation.

There are many metabolic, genetic, systemic aetiologies under the heading of infiltrative cardiomyopathies, some of which are rare and others relatively more common. Some of them present with a hypertrophic cardiomyopathy phenotype (such as cardiac amyloidosis, Fabry disease, endomyocardial fibrosis, Danon's disease, mitochondrial cardiomyopathies) and others present with a dilated cardiomyopathy phenotype (such as iron overload cardiomyopathy, sarcoidosis, radiation, cardiac involvement secondary to rheumatological diseases).⁴⁵ Although some of them have typical distinctive CMR findings, others do not have such findings; to give an example, it is only possible to identify a cardiomyopathy secondary to radiation on the basis of previous radiotherapy history. Infiltrative diseases with typical CMR findings can be summarised as follows:

Cardiac Amyloidosis (Figure 24): Left ventricular hypertrophy, diffuse subendocardial/mid-wall LGE, difficulty in myocardial "nulling" on LGE images, high native myocardial T1 and ECV fraction (usually >40%)

Fabry Disease: Left ventricular hypertrophy, low native myocardial T1 and mid-wall LGE in the inferolateral wall

Endomyocardial fibrosis (Figure 25): restrictive cardiomyopathy phenotype, left ventricular hypertrophy may be present, LGE in

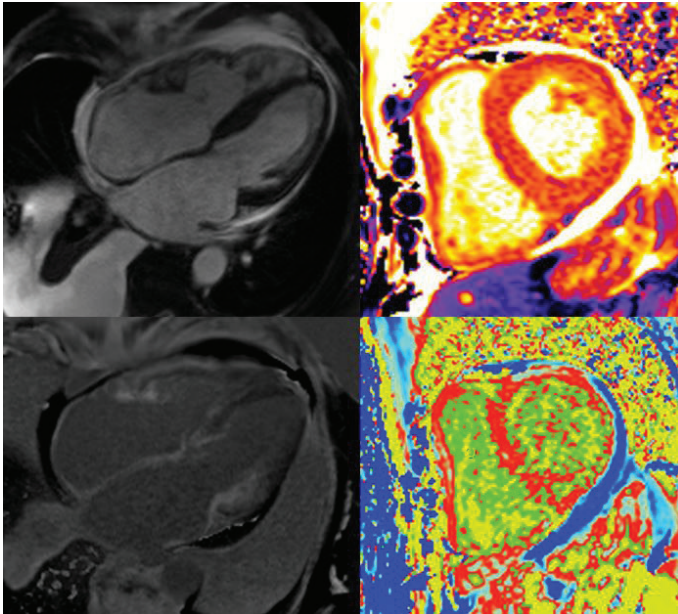


Figure 24. Typical findings of cardiac amyloidosis with CMR. Although left ventricular hypertrophy is commonly seen in the cine images, the hypertrophy may not always be very obvious, as in this example (upper left image). Native myocardial T1 value is increased significantly due to amyloid infiltration (upper right image T1 map, myocardial T1 is around 1150 ms., the upper limit of the normal range is 1065 ms). In late contrast images, there is late contrast enhancement, especially in the basal cavity level which starts from the subendocardium and extends to the mid-wall and is sometimes transmural (lower left image). The ECV fraction is increased significantly (bottom right image - ECV map, red color shows regions where the ECV fraction is greater than 50%).

the left and/or right ventricular endocardium, thrombus at the apex

Danon Disease: Left ventricular hypertrophy, mid-wall LGE sparing the septum

Iron overload: dilated cardiomyopathy phenotype, demonstration of myocardial iron overload by T2 star method (<20 ms at 1.5

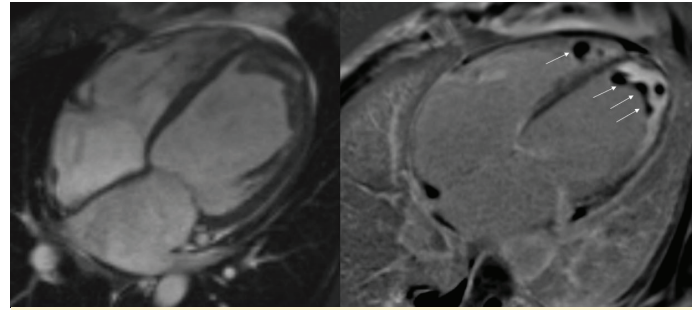


Figure 25. Endomyocardial fibrosis. In EMF, one of the restrictive cardiomyopathy phenotypes, there is typically widespread late contrast enhancement in the left and/or right ventricular endocardium on CMR. Thrombus is common in the left and right ventricular apex (the image on the right is cine image, the image on the left is LGE image; LGE of the left ventricular endocardium and thrombus -white arrows- in the left and right ventricular apex is seen).

T; <10 ms indicates severe iron loading), absence of myocardial LGE.

Other CMR Sequences and Artificial Intelligence Applications in the Evaluation of Cardiomyopathies

Apart from the sequences described above, other routine cardiac MR sequences can also be used as needed according to the clinical question in cardiomyopathy patients. For example, when co-existent coronary artery disease is suspected with a non-ischemic cardiomyopathy stress perfusion study can be performed, or valvular flow sequences can be added to the study protocols when valvular disease evaluation is required. Beyond these, there are sequences that are in the research stage and may have a role in the diagnosis of cardiomyopathies. For example, determination of myofibril orientation characteristics and impaired myocardial microstructure with diffusion tensor imaging may provide additional information in the diagnosis of cardiomyopathies.⁴⁶ Also studies on automated delineation of cardiac morphology and diagnosis of cardiomyopathies with artificial intelligence algorithms developed with large data sets obtained with CMR or by tissue characterisation without using contrast agent are ongoing.^{47,48}

Nuclear Imaging in Cardiomyopathy Management According to ESC 2023 Guidelines

In the latest updated 2023 ESC guidelines, cardiomyopathies (CMPs) were divided into five main categories according to a new phenotype-based approach: hypertrophic, dilated, non-dilated left ventricular, arrhythmogenic right ventricular, and restrictive CMP.¹ This condition manifests without the presence of coronary artery disease (CAD), hypertension, valvular disease, or congenital heart disease that would typically account for the observed myocardial abnormalities.¹ As a result, the terms "ischemic CMP" and "non-ischemic CMP," long utilized in nuclear medicine, are no longer applicable. Overall, cardiac imaging techniques in nuclear medicine offer a well-validated and versatile set of modalities for accurate diagnosis of pathophysiology and guidance for optimal therapy. To identify or rule out ischemic origins of left ventricular (LV) dysfunction and differentiate ischemia from myocardial infarction, myocardial perfusion imaging with SPECT (Tl-201, Tc-99m MIBI) or PET radiopharmaceuticals with better spatial resolution (Rb-82, N-13 ammonia, F-18 flurpiridaz, etc.), combined with ECG-gated SPECT to assess LV geometry and function, plays a key role. In dilated CMPs, perfusion distribution is typically homogeneous, with occasional mild heterogeneity that does not correspond to the distribution of coronary arteries.⁴⁹ Perfusion/metabolism mismatch, where glucose metabolism is preserved with F-18 FDG in areas of fixed perfusion defects, is a hallmark of hibernating myocardium. It helps clinicians predict which patients will experience improved LV function after revascularization based on the percentage of viable segments in the so-called myocardial territory.⁵⁰ Another radionuclide method, independent of ischemic or non-ischemic origin, is the assessment of absolute myocardial blood flow. This can indicate the severity of global microvascular dysfunction as a prognostic marker, particularly important in the detection of balanced three-vessel disease and microvascular diseases such as diabetes and hypertension.⁵¹ Coronary microvascular dysfunction, particularly in hypertrophic CMP (HCM), dilated CMP (DCMP), or infiltrative CMPs such as amyloidosis, can be found at varying levels and is frequent.⁵² Although its connection to the underlying cardiomyopathic process is uncertain, it is associated with worsening systolic and diastolic function, heart failure, sudden death, and poor clinical outcomes. Global coronary flow reserve, which can be truly quantified with PET perfusion agents like O-15 H₂O, N-13 ammonia, and Rb-82, is decreased in patients with CMP and indicates an increased risk of cardiac events.^{53,54} The most distinctive feature of HCM is asymmetric LV hypertrophy. Resting global myocardial blood flow is generally well-preserved, but regional perfusion demonstrates heterogeneity, with values decreasing mainly in hypertrophic segments.⁵⁵ The function of myocardial sympathetic nerve endings in CMPs, which causes sympathetic denervation such as in cardiac amyloidosis, can be visualized in vivo with the norepinephrine analog I-123 MIBG or PET radiopharmaceuticals like C-11 hydroxyephedrine. New agents of cardiac sympathetic innervation, such as F-18-labeled F-18 LMI1195, are now in research.⁵⁶ PET tracers allow for more accurate regional analysis and quantification of the denervated area. The larger the denervated area, the higher the risk of sudden death.⁵⁷ In patients with severely impaired cardiac sympathetic innervation, very low I-123 MIBG uptake is observed, which is an independent predictor of heart failure progression and mortality.^{58,59}

In this review, based on the new 2023 ESC guidelines, we primarily focus on nuclear imaging techniques utilized for amyloidosis and sarcoidosis, both of which are specifically highlighted as

recommendations. The pathogenesis of these restrictive CMPs is variable. Myocytes and the extracellular matrix structure (hypertrophy, atrophy, apoptosis, fibrosis, or a combination) and composition (edema and amyloid fibril deposits) are altered by infiltration. With complex metabolic transitions (glucose, fatty acid, and oxidative metabolism), the heart adapts to the pathology.⁶⁰ These structural and metabolic changes, depending on the degree and extent of infiltration, serve as a substrate for atrioventricular blocks and embolic phenomena, causing electrical heterogeneity in the atria and ventricles and leading to cardiac rhythm abnormalities.⁶¹ Thus, unchecked infiltration results in heart failure, morbidity, and death. Myocardial adaptation to this infiltration can be assessed by non-invasive radionuclide imaging, eliminating the need for endomyocardial biopsy.

Amyloidosis

Recent advances, especially in the treatment of transthyretin (ATTR) amyloidosis, have increased clinical awareness for the early and accurate diagnosis of cardiac amyloidosis. As a result, previously overlooked cases, despite not being rare, have been brought back into the spotlight. Cardiac amyloidosis is a CMP that develops due to the extracellular deposition of misfolded amyloid fibrils. These fibrils directly or indirectly trigger various structural and functional processes in the heart and may share hypertrophic and restrictive phenotypes.⁶² However, this is not true hypertrophy, as LV wall thickening results from the infiltration of fibrils into the extracellular matrix. The treatment, management, and prognosis of light chain amyloidosis (AL) and ATTR types, which account for 99% of cardiac amyloidosis cases, are quite different. Therefore, the diagnostic algorithm is of critical importance. In the ESC 2023 guidelines, cardiac amyloidosis scintigraphy using bone scintigraphy agents is recommended as a class I, level of evidence B, procedure in the diagnostic work-up of suspected cardiac amyloidosis cases.^{1,63} This non-invasive nuclear cardiac imaging modality has significantly reduced the need for endomyocardial biopsy, an invasive and risky procedure traditionally considered the gold standard for diagnosis. Among other non-invasive imaging modalities, echocardiography, despite being the first-step diagnostic tool, cannot differentiate between amyloid and non-amyloid causes of LV wall thickening, nor between AL and ATTR subtypes of cardiac amyloidosis. Similarly, MRI findings are non-specific for cardiac amyloidosis, and its use is limited by factors such as the possible presence of a cardiac device or renal insufficiency.⁶⁴

The analogous bone scintigraphy agents used for diagnosing ATTR cardiac amyloidosis include Tc-99m pyrophosphate (PYP), widely used in Türkiye and the USA, and Tc-99m 3,3-diphosphono-1,2-propanodicarboxylate (DPD) and Tc-99m hydroxymethylene diphosphonate (HMDP or HDP), both used in Europe. The use of Tc-99m methylene diphosphonate (MDP), a radiopharmaceutical routinely used for bone scintigraphy, is not recommended for imaging cardiac amyloidosis due to its low diagnostic sensitivity.⁶⁵ The radiopharmaceutical uptake mechanism is unclear, but hypotheses linked to high calcium content (especially predominant in ATTR and low in AL), microcalcifications, and C-terminal fragments of amyloid fibrils have been proposed.^{66,67}

Pearls and Pitfalls in the Evaluation of Images⁶⁸

Current national and international guidelines and consensus reports recommend scintigraphic imaging for diagnosing ATTR-CMP.^{68,69} To ensure precise diagnosis, every stage—from the preparation of the radiopharmaceutical to the evaluation of the images—should undergo rigorous quality control. Imaging technique and timing are crucial, with the evaluation proceeding step-by-step through visual, semi-quantitative, and quantitative assessments. Visual interpretation is considered fundamental, and relying solely on planar imaging is never recommended. The primary criterion is to identify diffuse and intense radiopharmaceutical uptake precisely corresponding to the LV wall, as seen visually on three-dimensional SPECT or SPECT/CT slices. SPECT or, ideally, SPECT/CT sectional images are superior to planar imaging because they allow differentiation between myocardial activity and blood pool activity, which is the most common cause of false positives (Figure 26). Early imaging at one hour is optional, but the main evaluation typically depends on the images acquired at three hours.

For standardization of the visual assessment, myocardial uptake is graded on a scale of 0–3 using the semiquantitative scoring system proposed by Perugini et al.⁷⁰ The presence of cardiac uptake equal to (Grade 2) or greater than (Grade 3) the bone activity (reference: costae) is considered positive for cardiac amyloidosis.

If there is blood pool activity in the cardiac chambers and vascular structures and no uptake is observed in the LV myocardium, cases are reported as Grade 0. In this scenario, quantitative imaging is not necessary. If myocardial activity is visually confirmed, one can proceed with the quantitative step. An H/CL ratio of >1.5 at 1 hour and >1.3 at 3 hours with Tc-99m-PYP strongly supports the diagnosis of ATTR-CMP.^{71,72} However, due to the subjective nature of the method and the potential for errors associated with the placement and delineation of regions of interest for quantification, more reliable and less variable quantitative data obtained via SPECT/CT have started to emerge in the literature. The role of standard parameters such as SUVmax, SUVmean, and SUVpeak, as well as measures like percent injected dose and cardiac amyloid burden derived from SPECT/CT images, is currently being investigated.^{73,74}

Results interpreted as Grade 2 and Grade 3 cannot distinguish between the two subtypes of ATTR, wild-type or hereditary/mutant type. Therefore, genetic testing should be performed to identify the subtype.

A diffuse pattern of involvement is characteristic of ATTR. If focal involvement is present, it may be due to a recent infarction. Focal involvement of the septum may represent early ATTR. Some mutant types of hereditary ATTR, early ATTR, early imaging, or errors in radiopharmaceutical labeling can contribute to false negatives.

According to current diagnostic algorithms, in cases with clinical and image-based (echocardiography and MRI) red-flag features for cardiac amyloidosis, diffuse uptake with a Grade 2–3 visual/semiquantitative assessment in the LV wall on SPECT or SPECT/CT is diagnostic for ATTR amyloidosis, provided that AL amyloidosis is excluded (Figure 27). In all cases of suspected ATTR amyloidosis,

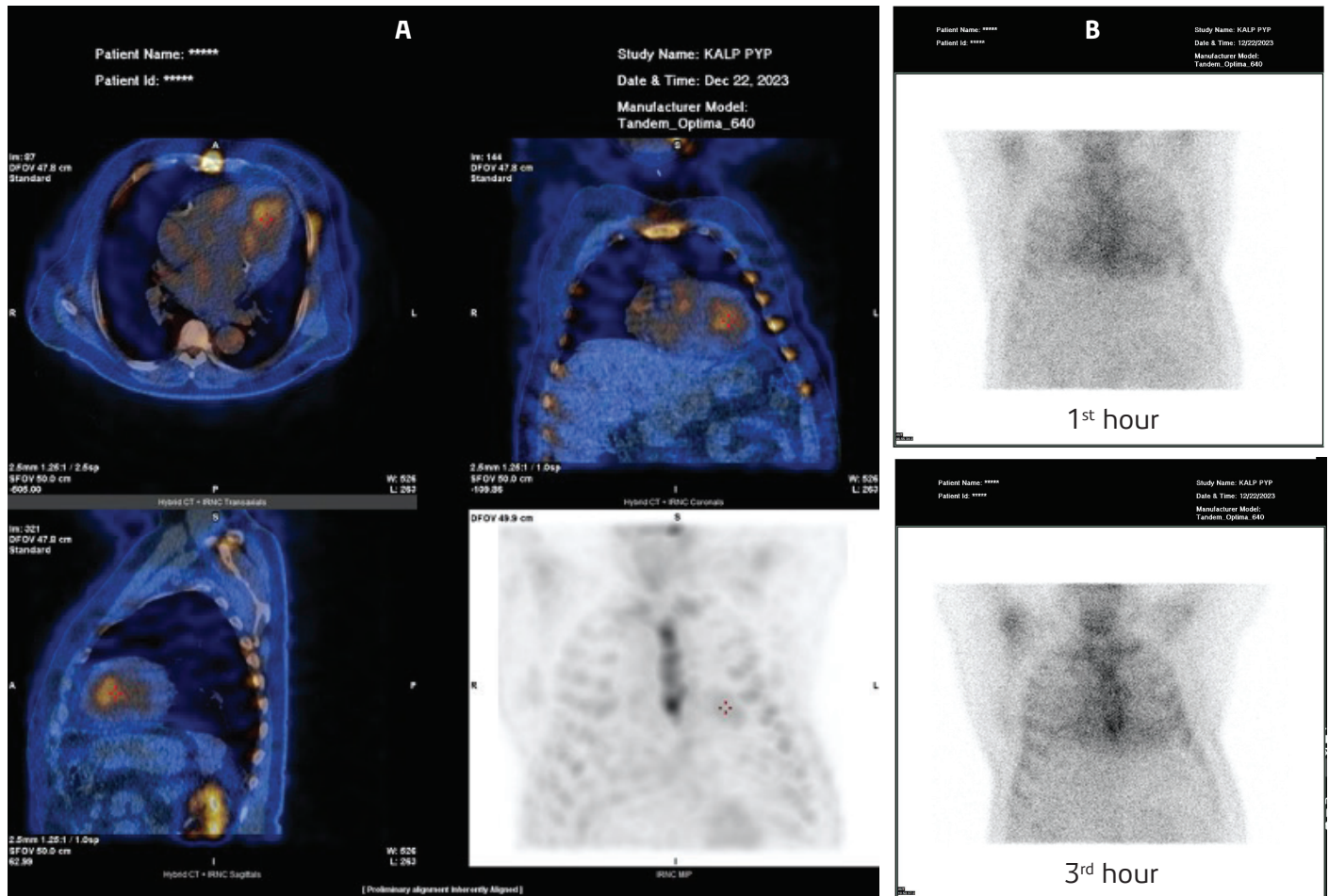


Figure 26. Planar and SPECT/CT sections. Blood pool activity. The accumulation of activity observed in the cardiac lobe was related to physiologic blood pool activity within the cardiac cavities and great vessels in SPECT/CT images.

all three laboratory parameters—serum protein immunofixation, urine protein immunofixation, and serum free kappa/lambda light chain ratios—should be evaluated simultaneously or before referral to nuclear medicine departments to ensure that AL amyloidosis is excluded.

If not ruled out, AL amyloidosis should be considered in all grades of uptake on bone scintigraphy, most commonly in Grades 0 and 1, and in nearly one in five cases in Grades 2–3.⁷⁵ The presence of AL amyloidosis is an oncologic emergency and requires prompt initiation of chemotherapy or, if feasible, stem cell transplantation or even heart transplantation.

Grade 1 and the Gray Zone

Grade 1 cases create a gray zone in diagnosis, posing challenges in patient management and often sparking the most debate. It has been reported that Grade 1 cases may indicate early disease, but the prognostic value of cardiac scintigraphy in these cases remains controversial. Another prognostic marker in cardiac scintigraphy is diffuse right ventricular (RV) involvement in ATTR amyloidosis, as identified in a recent publication. This so-called pattern is strongly associated with overall survival.⁷⁶

The diagnosis of ATTR amyloidosis should not be promptly ruled out in patients with a semiquantitative score of Grade 1 and

strong suspicion of amyloidosis, as referred by the cardiologist. Possible causes include AL amyloidosis or rare variants such as ApoA1 and ApoAIV amyloidosis, as well as mutations like Phe64Leu, Val30Met, or Ser77Tyr, which should be considered during the diagnostic process.^{77,78}

Role of Cardiac Scintigraphy in Treatment Response Assessment/Follow-Up

Studies exploring the role of cardiac amyloidosis scintigraphy in treatment response assessment are increasing; however, there is still insufficient evidence to support its routine use. Parameters obtained through SPECT/CT quantification, such as regional SUVmax and cardiac amyloid burden, show promise.^{73,74}

Microvascular Dysfunction and Coronary Flow Reserve

The presence of angina without epicardial CAD in individuals with amyloidosis is well established. Interstitial and perivascular amyloid deposits increase resistance by compressing coronary microvessels. Increased LV mass and elevated LV filling pressure can lead to coronary microvascular dysfunction, potentially explaining the susceptibility to ischemia and subclinical impairment of LV systolic function in patients with amyloidosis.

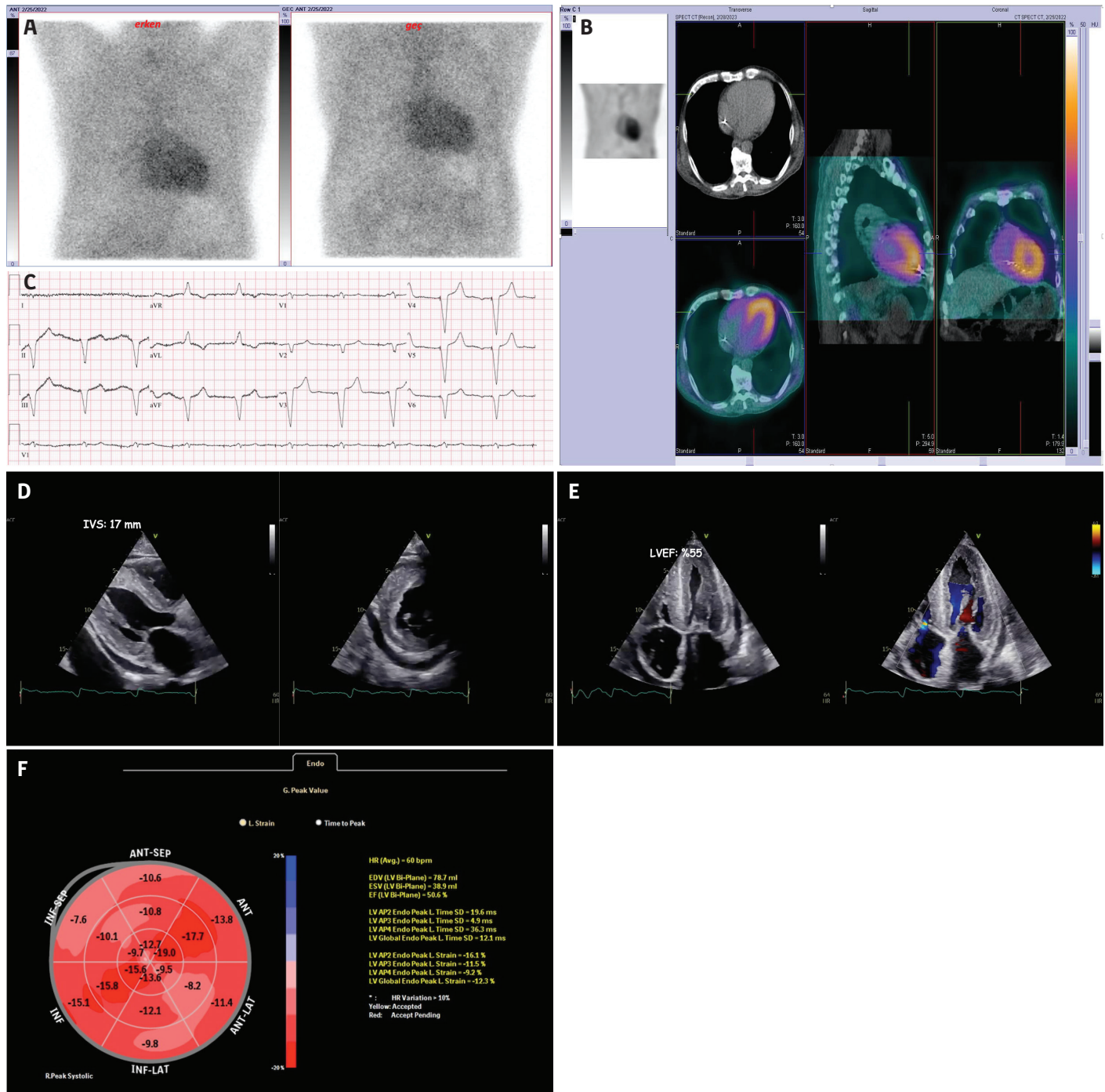


Figure 27. A 60 year- old -male on follow-up for polyneuropathy and dyspnea. A pacemaker is implanted due to AV block. (A) Early and late planar Tc-99m PYP cardiac scintigraphy images show intense uptake in the cardiac area compared to costal uptake. (B) Late SPECT/CT slices taken at 3 hours demonstrate that the uptake is localized apparently to the ventricular wall. Semiquantitative score: Grade 3, quantitative evaluation: H/CL ratio: 2.0. Cardiac SPECT/CT findings were compatible with ATTR amyloidosis in the patient in whom AL amyloidosis was excluded. Colon and salivary gland biopsies were resulted as amyloidosis and the final diagnosis was made as hereditary ATTR amyloidosis by genetic testing and Tafamidis was started. We cordially thank Professor Murat Sünbül from Marmara University (Department of Cardiology) for letting the permission of the ECHO images of the patient.

In a prospective study of 21 patients with amyloidosis (15 AL, 6 ATTR) without epicardial CAD, coronary microvascular dysfunction at rest and during vasodilatory stress was assessed using N-13 ammonia PET perfusion studies in combination with echocardiography to

verify ischemia.⁷⁹ Compared to a control group with hypertensive LV hypertrophy, patients with amyloidosis had significantly increased coronary vascular resistance and significantly reduced stress myocardial blood flow and coronary flow reserve.

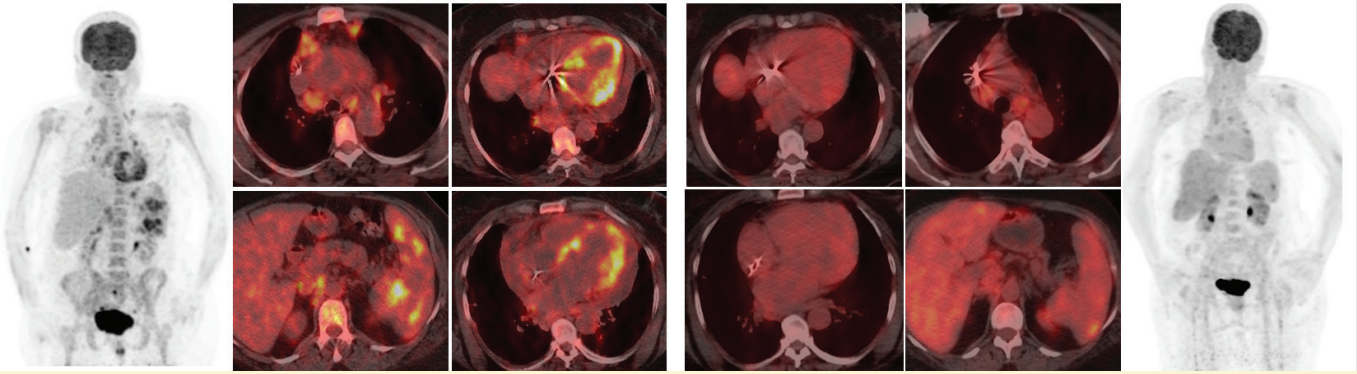


Figure 28. Aged 67, F. Cardiac Sarcoidosis, whole body and transaxial F-18 FDG PET/CT images before and after treatment. In addition to the typical patchy focal involvement in the heart, there are extracardiac involvement in the spleen and lymph nodes. In the post-treatment images, there is no involvement in the heart and most of the other lesions are inactive. FDG PET/CT images were used with the permission of Prof. Dr. Duygu Has Şimşek from Istanbul University Faculty of Medicine, Department of Nuclear Medicine and we cordially thank her for the permission.

Strategies aimed at improving coronary microvascular dysfunction are important for the therapeutic management of these patients.

Autonomic Dysfunction and Sympathetic Innervation Imaging

In cases of autonomic neuropathy, cardiac sympathetic innervation imaging can be valuable, particularly in hereditary amyloidosis.⁸⁰ Furthermore, I-123 MIBG cardiac innervation scintigraphy can reveal abnormalities in ATTRm cases earlier than any cardiac involvement observed with bone scintigraphy agents.

Interestingly, in a series involving 39 individuals with heart failure, including both ATTR mutation carriers and ATTRm patients (n=26), where both I-123 MIBG and Tc-99m HDP cardiac amyloidosis scintigraphy were evaluated together, it was demonstrated that I-123 MIBG scintigraphy reflects CMP rather than cardiac autonomic neuropathy in ATTRm patients and TTR mutation carriers.⁸¹

AL-Amyloid PET Imaging

Although amyloid-PET imaging agents specifically binding to amyloid fibrils for the diagnosis of light chain AL are not yet available in Türkiye, promising results from the literature suggest their potential. Certain radiopharmaceuticals developed for imaging beta-amyloid plaques in Alzheimer's disease, such as C-11 Pittsburgh compound B, F-18 florbetapir, and F-18 florbetaben, have been found to exhibit higher myocardial uptake in AL amyloidosis cases compared to ATTR amyloidosis. High spatial resolution and ease of quantification are also important advantages of PET.

In a meta-analysis comprising six studies and 98 patients, the sensitivity and specificity of amyloid-targeted PET agents in diagnosing cardiac amyloidosis were reported as 95% and 98%, respectively.⁸²

In a prospective three-arm, single-center, phase II FLORAMICAR2 study conducted by Genovesi et al.,⁸³ it was found that AL amyloidosis patients displayed notable, late, and persistent cardiac uptake on F-18 florbetaben PET/CT scans. Conversely, in ATTR and other amyloidosis subtypes, uptake decreased in early images. Therefore, it is suggested that F-18 florbetaben PET/CT could play a role in the differential diagnosis of ATTR and AL amyloidosis.

Sarcoidosis

Approximately 5% of patients with sarcoidosis have clinically evident cardiac involvement, often presenting with malignant arrhythmias. These arrhythmias are associated with the location and extent of granulomatous inflammation and scar tissue along the conduction pathway, leading to increased mortality rates. Additionally, asymptomatic cardiac involvement has been reported in 20-25% of patients.⁸⁴ Cardiac sarcoidosis (CS) most commonly involves the myocardium, and with decreasing frequency, affects the basal ventricular septum, LV free wall, papillary muscles, and RV. Rarely, the coronary arteries can also be affected. Noncaseous epithelioid granuloma formation is typical in cardiac or extracardiac tissue biopsies. However, due to the focal nature of lesions, the diagnostic sensitivity of endomyocardial biopsy is relatively low. Sampling guided by imaging techniques contributes significantly to diagnostic accuracy.

Recent advancements in PET imaging have significantly improved the diagnosis and monitoring of CS. F-18 FDG PET/CT serves as a valuable tool by reflecting the inflammatory activity inherent in the disease pathology, attributed to augmented macrophage-mediated glucose metabolism within areas of sarcoidosis-induced inflammation. According to a meta-analysis of seven studies, the diagnostic accuracy of F-18 FDG PET is high, with a sensitivity of 89% and specificity of 78%.⁸⁵ As non-invasive diagnostic approaches, both PET and MRI contribute to the diagnosis of CS by reflecting different aspects of the disease. While MRI directly delineates the presence and extent of scar tissue, FDG PET determines inflammatory activity and systemic involvement sites throughout the entire body.⁸⁶ Previous studies suggest that F-18 FDG PET/CT may offer earlier detection of CS compared to MRI.⁸⁷ However, recent evidence affirms MRI as the most sensitive imaging modality for early diagnosis.⁸⁸

In the 2023 ESC guidelines, FDG PET/CT is assigned a class IIa, level C recommendation for the diagnostic work-up of patients with suspected CS in the setting of CMP.¹ Although its utility in assessing response to immunosuppressive therapy during follow-up has been recognized,⁸⁹ monitoring CS with FDG PET currently is not among the indications in the latest ESC guidelines (Figure 28).

Under normal resting conditions, the heart utilizes both free fatty acids and glucose for energy production. Thus, assessing myocardial inflammation can be challenging due to physiological F-18 FDG uptake in the background. Adequate preparation, including adherence to a diet rich in fats and low in carbohydrates, prolonged fasting, and/or the administration of heparin, is necessary to suppress physiological F-18 FDG myocardial uptake.^{90,91} Not following these preparatory protocols may lead to inconclusive results in clinical practice.⁹² As a result, there is growing interest in new somatostatin receptor PET agents to enhance diagnostic specificity. In granulomatous conditions like sarcoidosis, somatostatin receptors are upregulated in macrophages and lymphocytes. Given that physiological somatostatin analog uptake is absent in the myocardium, any observed uptake in the heart indicates specific pathology. PET imaging with Ga-68 DOTA analogs presents promising results compared to FDG PET and MRI modalities.⁹³ Additionally, F-18 FLT PET has been investigated as an alternative agent, but its routine clinical implementation has yet to be realized.⁹⁴

For the diagnosis of CS, it is essential to exclude significant obstructive CAD or prior myocardial infarction. Therefore, before F-18 FDG PET/CT imaging, coronary angiography or rest/stress myocardial perfusion SPECT should be performed to rule out CAD.

In the context of sarcoidosis imaging, initial basal rest myocardial perfusion imaging should be conducted. This method helps detect inflammatory cells in regions with reduced blood flow on F-18 FDG PET images, aiding in identifying mismatch or match defects in perfusion/metabolism.

FDG uptake patterns in CS are defined as no uptake, focal uptake, diffuse uptake, or focal uptake on a diffuse background. In addition to the location, extent, and severity of decreased radiopharmaceutical uptake, perfusion/metabolism images may reveal accompanying features such as LV cavity dilatation, septal hypertrophy, pericardial photopenia, and RV hypertrophy, which

should all be noted. Any extracardiac areas of abnormal F-18 FDG uptake observed on whole-body images serve as biopsy guidance and should be included in the final report.⁹⁰

Abnormalities in both perfusion and F-18 FDG uptake, as well as the presence of focal F-18 FDG uptake in the RV, are the worst prognostic indicators. In a study conducted by Blankstein et al.⁹⁵ involving 118 patients with confirmed or suspected CS evaluated using Rb-82 perfusion and F-18 FDG PET imaging, individuals demonstrating abnormal perfusion and focal inflammation suggestive of CS had a fourfold higher annual rate of ventricular tachycardia and mortality during a 1.5-year follow-up period compared to those with normal PET imaging findings.

It's important to note that a positive FDG PET scan isn't specific for active sarcoidosis until other causes of inflammatory CMP are ruled out. Similarly, a negative FDG PET scan doesn't rule out the presence of inactive/chronic sarcoidosis. Combining PET findings with cardiac MRI findings is anticipated to yield a synergistic effect on diagnostic accuracy, highlighting the potential significant role of hybrid PET/MRI in the future diagnosis and management of CS.

Conclusion

In summary, the underlying causes of CMPs often remain uncertain. Nuclear cardiology techniques guide clinical decision-making by ruling out or indicating ischemia, determining myocardial viability, detecting global flow reserve, demonstrating global and regional sympathetic denervation, and identifying molecular cardiac involvement in systemic diseases. Beyond contributing to prognosis, these techniques provide guidance for interventional, medical, and cardiac device therapy.

As emphasized in the 2023 ESC guidelines, with the growing spectrum of molecular-targeted tracers, nuclear imaging is poised to guide therapy through non-invasive biopsy and highly specific tissue analysis in CMPs of various origins. It will likely become the key to personalized treatment in the future.

Differentiation of Constrictive Pericarditis and Restrictive Cardiomyopathy Using Multi-Modality Imaging Methods

Constrictive pericarditis (CP) and restrictive cardiomyopathy (RCM) are two diseases that are generally difficult to distinguish clinically due to their similar symptoms and findings and are diagnosed with various imaging tests. These imaging methods include transthoracic echocardiography (TTE), computed tomography (CT), cardiac magnetic resonance (CMR), nuclear imaging methods and cardiac catheterization. Clinical manifestations in both diseases are mainly dominated by the symptoms and findings of heart failure with preserved ejection fraction (HFpEF), although the underlying mechanisms differ.

Etiology

CP may result from various pericardial diseases, with the most common cause being primary CP. Primary CP may be idiopathic, viral, tuberculosis-related, neoplastic, or bacterial in origin. In developed countries, after idiopathic and viral causes, CP most commonly occurs following radiotherapy, cardiac surgery, or interventions. Pericarditis that develops during the course of connective tissue diseases is considered to be of secondary origin.⁹⁶⁻⁹⁸

RCMP, like CP, may develop due to primary and secondary causes. Primary RCMP, which is mostly idiopathic, may also have a genetic origin. Autosomal dominant inheritance, less frequently autosomal recessive inheritance, or sporadic inheritance is also known. All sarcomeric gene mutations can lead to RCMP. The most commonly involved gene is a mutation in the TNNI3 gene, which encodes the thin filament of troponin I.⁹⁹ Secondary causes of RCMP include amyloidosis, sarcoidosis, primary and secondary hemochromatosis, mucopolysaccharidoses, systemic sclerosis, inflammatory and granulomatous diseases, diabetic heart disease, Danon's disease, glycogenoses, storage diseases such as Anderson-Fabry disease, and myocardial fibrosis due to radiation and chemotherapy.¹⁰⁰ Other causes of RCMP may be endomyocardial diseases with fibrosis, fibroelastosis, and thrombosis. These can be classified into those with and without hypereosinophilia. Those without hypereosinophilia are endemic in tropical and subtropical Africa, India, South and Central America and are very rare outside these regions. Sporadic cases without hypereosinophilia include carcinoid syndrome, endocardial fibroelastosis, and endocardial neoplasms.¹⁰¹ Valvular and ischemic diseases, as well as advanced stages of hypertrophic and dilated cardiomyopathy, may present with increased left ventricular filling pressures similar to RCMP. However, it should be kept in mind that not all restrictive-type hemodynamic changes indicate RCMP.

Clinical Features

Patients with CP and RCMP, who usually present with symptoms of HFpEF, experience impaired diastolic filling of the ventricles in CP as a direct result of reduced pericardial compliance. These patients typically exhibit signs of right heart failure, which occurs despite preserved left ventricular function and in the absence of preexisting or concomitant myocardial disease. The main complaints include fatigue, peripheral edema, dyspnea, and abdominal distension. Venous congestion, hepatomegaly, pleural effusion, and ascites may develop. If myocardial fibrosis is present or if the disease progresses, systolic dysfunction can develop to the point of hemodynamic impairment.¹⁰²

Table 5. General Features of Restrictive Cardiomyopathy and Constrictive Pericarditis	
Restrictive Cardiomyopathy	Constrictive Pericarditis
· Kussmaul's Sign +/- · Apical knock · S3, S4+ and regurgitation murmurs · Low voltage, pseudo-infarction patterns, AF, conduction disorders on ECG · No pericardial calcification · CT/CMR pericardium is normal	· Kussmaul sign +/- · Apical beat - · Pericardial beat + · There is no regurgitation murmur · Low voltage on ECG < 50% · Pericardial calcification may occur · CT/CMR pericardial thickening and calcification
ECG, Electrocardiogram; AF, Atrial fibrillation; CT, Computed tomography; CMR, Cardiac magnetic resonance.	

Table 6. Recommendations for the Use of Imaging Methods Used in Constrictive Pericarditis ¹⁰²		
Recommendations	Class	Level of evidence
Echocardiography should be performed in all patients with suspected CP.	1	C
All patients with suspected CP should have a chest x-ray from anteroposterior and lateral aspects using appropriate technical features	1	C
CT and/CMR are secondary imaging methods to evaluate calcification, pericardial thickness, degree, and extent of involvement.	1	C
Cardiac catheterization is indicated if the diagnosis of constriction cannot be definitively established with non-invasive imaging methods.	1	C
CP, Constrictive pericarditis; CT, Computed tomography; CMR, Cardiac magnetic resonance.		

In restrictive cardiomyopathy, symptoms of right heart failure develop in a similar manner. However, they can sometimes appear years after the initial symptoms and signs are detected. Additionally, underlying disease findings can also be observed in RCMPs that develop due to secondary causes.¹⁰³ Table 5 summarizes the comparison of clinical findings in RCMP and CP.

Hemodynamic Characteristics

To differentiate between these two disease groups, their hemodynamic characteristics must be well understood. In both groups of patients presenting with HFpEF, the pericardium's impaired compliance in CP decreases total cardiac volumes by impairing diastolic function and prevents the reflection of intrathoracic pressures to the cardiac chambers.¹⁰⁴ In a person with normal diastolic function, the amount of blood returning to the right heart chambers via the inferior vena cava (IVC) and superior vena cava (SVC) increases as intrathoracic pressure decreases during inspiration. Since pulmonary venous return also increases, the amount of blood returning to the left heart chambers also increases. In expiration, the opposite of these mechanisms occurs. As a result, there is an increase in mitral flow.

In CP, as intrathoracic pressure decreases during inspiration, venous return and thus the amount of blood returning to the right heart chambers increases, resulting in increased tricuspid flows. Simultaneously, the amount of blood coming from the extra-pericardial pulmonary veins to the left heart chambers decreases. Because the amount of blood returning to the left heart is less than that returning to the right heart, a right-to-left shift in the interventricular septum is observed. During expiration, the opposite mechanisms occur, leading to an increase in mitral flows.¹⁰⁵ Another important hemodynamic change in CP is the marked increase in early diastolic pressures of the ventricles due to increased mean atrial pressures and

the early reaching of the reserve volume allowed by the pericardium. This change leads to the cessation of ventricular filling in early mid-diastole.¹⁰⁶

In RCMP, diastolic dysfunction and increased intracardiac pressures occur due to impaired relaxation and compliance in the ventricular myocardium. As in CP, increased filling pressures and rapid filling waves are observed, but unlike in CP, there is ventricular concordance. Consequently, changes in systolic pressure and stroke volume with respiration are similar to those in patients with normal myocardium.¹⁰⁶

Imaging Methods

TTE is known to be diagnostic in 70% of surgically proven cases of CP without the need for invasive hemodynamic evaluation.¹⁰⁷ However, the use of various imaging modalities is particularly recommended in patients with suspected CP, both to confirm the diagnosis and to evaluate involvement outside the pericardium. Table 6 summarizes the main diagnostic modalities, their areas of use, and their level of evidence.¹⁰²

Transthoracic Echocardiography

Transthoracic echocardiography is the most commonly used diagnostic method for differentiating CP and RCMP. It is useful for examining the pericardial structure and identifying concomitant myocardial diseases.^{108,109}

Echocardiographic Findings of Constrictive Pericarditis

In TTE, parasternal windows are optimal for evaluating septal motion, while M-mode echocardiography provides the best temporal resolution. Findings supporting the diagnosis of CP include pericardial thickening, septal bounce, and diastolic flattening of the LV posterior wall seen with M-mode echocardiography. Evaluation of propagation velocity (Vp) with

color flow on color M-Mode echocardiography may also aid in diagnosis. A Vp greater than 45 cm/s supports a diagnosis of CP, while a Vp less than 45 cm/s indicates RCMP.¹¹⁰

The actual diagnostic algorithm begins with 2D echocardiography. Generally, 2D echocardiography reveals a thickened pericardium (>3 mm) with increased echogenicity. However, in cases of obesity, cachexia, or anatomically distorted chest structures, the pericardium may not be clearly evaluated. It is important to note that even in patients with hemodynamically and surgically proven CP, a pericardium with normal thickness may be present. In such cases, other accompanying findings and hemodynamic evaluations should be included in the diagnostic algorithm. On 2D echocardiography, additional findings supporting CP include pericardial thickening, deformation of the cardiac chambers, retraction of the hepatic margin with right ventricular (RV) contraction, and the presence of pericardial bounce and acoustic shadowing. These features are observed when the left ventricle (LV) cannot slide off the pericardial surface due to adhesions in the pericardium and are more common in CP than in RCMP.¹¹⁰

Respiratory septal shift, one of the two CP-specific septal motion defects seen in 2D real-time images, is caused by interventricular interaction, whereas septal bounce reflects the difference in early diastolic filling of the LV and RV. Although septal bounce is a sensitive finding, it is not specific to CP and can also be observed in patients with bundle branch block or during the postoperative period. Therefore, it should not be solely relied upon for diagnosis.

Additionally, respiratory septal shift may occur in conditions such as severe tricuspid regurgitation, obesity, and obstructive pulmonary disease, which can lead to enlargement and increased pressure in the right heart chambers. Thus, the clinical context and other findings should be considered when diagnosing CP.

In diseases included in the differential diagnosis of CP, the mechanism causing septal bounce is decreased pulmonary venous return on inspiration and increased systemic venous return due to an excessive increase in intrathoracic pressure. These findings can mimic those of CP and are referred to as pseudo-constriction. Differentiating septal shift due to true constriction from pseudo-constriction is crucial because accurate assessment of septal shift according to respiratory phases is an important indicator of interventricular involvement. To ensure accurate assessment, long (10-beat) recordings should be taken and evaluated to include all respiratory phases. Spirometry should be used to determine the correct phases of respiration. In the absence of spirometry, the lowest rate of mitral E wave velocity can be considered inspiratory, and the highest rate expiratory. The opposite is true when evaluated based on hepatic vein or tricuspid flows, with the highest flow velocities being obtained during inspiration.¹¹¹

Hemodynamic changes due to respiratory variations are evaluated using continuous wave (CW) and pulse wave (PW) Doppler techniques in TTE. During inspiration, the increase in blood returning to the right heart chambers results in a $\geq 25\%$ increase in tricuspid inflow. The restriction of cardiac volume, secondary to decreased pericardial compliance, causes the septum to shift to the left, which is seen as a septal jump on echocardiography. Additionally, during inspiration, the left ventricle shows a

$\geq 25\%$ decrease in filling gradients due to decreased return flow from the pulmonary veins and increased left ventricular diastolic pressure.^{15,112,113} This septal jump significantly restricts left ventricular filling. Conversely, during expiration, there is an expected increase of at least 25% in the transmitral E wave and a decrease of at least 25% in the transtricuspid E wave ratio. Rare cases of altered Doppler findings occur in patients with markedly elevated left atrial (LA) pressure. In such patients, the expected 25% changes in transmitral and transtricuspid flows may not be observed due to increased LA pressure. Therefore, measurements should be performed in the tilt position or while sitting, and repeated after intensive diuretic administration. It is also important to remember that restrictive physiology can be demonstrated by maneuvers that reduce blood flow to the heart, such as nitrate administration.¹¹⁰

In patients presenting with heart failure with preserved ejection fraction (EF), evaluating diastolic dysfunction due to pericardial tension in CP is very important but can also be complex. The simplest and most practical echocardiographic approach using Doppler techniques is the measurement of E/e'. It is recommended that this value be evaluated in conjunction with the peak velocity of tricuspid regurgitation used for measuring systolic pulmonary artery pressure (PAP), the peak E velocity of the transmitral pressure gradient indicating increased LA pressures, and increased LA volumes.^{15,12,113}

In PW measurements taken in diastole through the mitral valve cusps, the isovolumetric relaxation time (IVRT) is prolonged as myocardial relaxation decreases. The early transmitral gradient decreases, leading to a decrease in the amplitude of the E wave, while the amplitude of the A wave increases as the majority of diastolic filling is provided by atrial contraction.¹¹⁴ In grade 1 diastolic dysfunction, the E/A ratio decreases below 1, and both the deceleration time (DT) and IVRT are prolonged. As diastolic dysfunction worsens, left ventricular (LV) filling becomes incomplete, and the LV cannot accommodate all the blood pumped by the right ventricle (RV). This results in further increases in LA and LV pressures, causing the LA to dilate. With the increase in LA pressure, the pressure transition between the LA and LV becomes higher. Decreased myocardial relaxation, an increase in the early transmitral gradient, and increased early LV diastolic pressures steepen and cause an increase in end-diastolic pressures. This results in an E>A wave, but DT and IVRT are shortened. In this phase, called the pseudo-normal pattern, second-order diastolic dysfunction is present.

In patients with advanced diastolic dysfunction and the onset of heart failure symptoms, early diastolic filling pressures increase very rapidly and become prominent, leading to stage three diastolic dysfunction. This stage is characterized by a DT of less than 160 ms and an E/A ratio greater than 1.5.¹¹⁴ Figure 29 illustrates the mitral Doppler flow patterns according to the stages of diastolic dysfunction.¹¹⁵

Tissue Doppler Findings

Due to pseudo-normalization, assessing LV myocardial relaxation is highly sensitive to filling pressures, but its use alone in the assessment of diastolic function is limited. Therefore, the

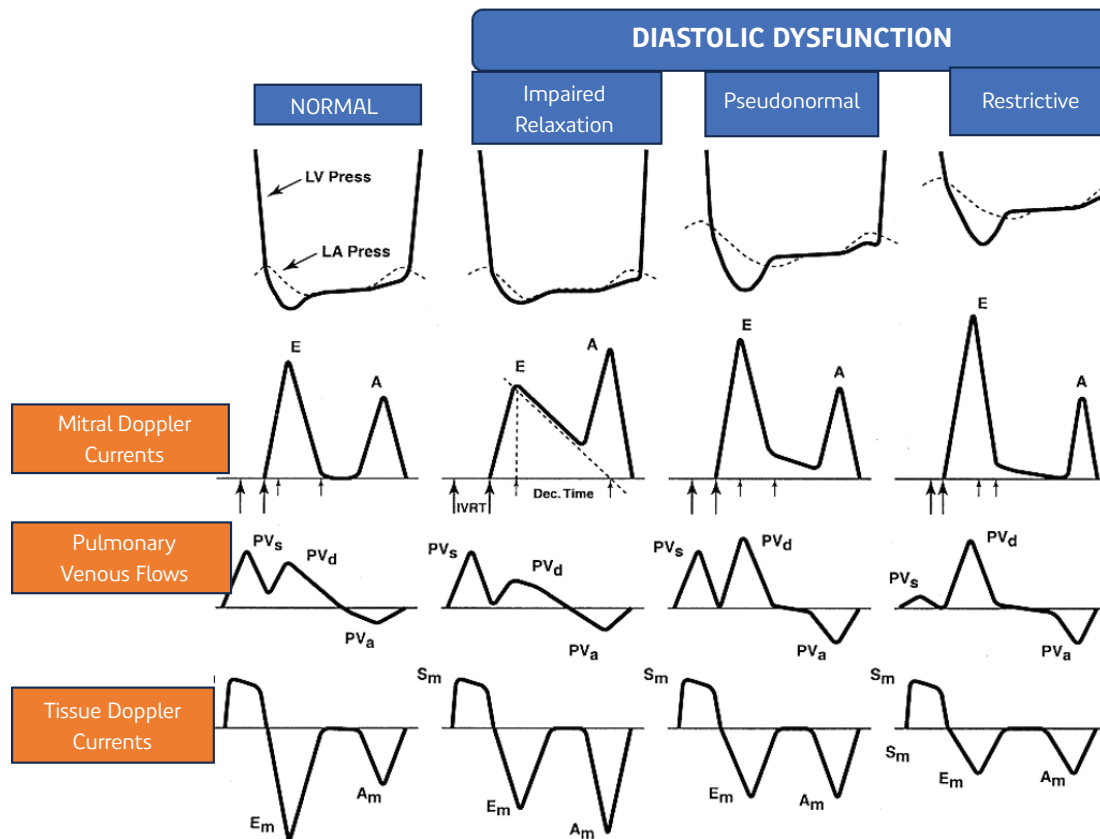


Figure 29. Changes in mitral Doppler flows, pulmonary venous flows and tissue Doppler flows in normal and impaired diastolic function phases.¹¹⁵

assessment of mitral annular velocities is used. Early diastolic mitral annular motion, a marker of myocardial relaxation, is independent of preload and decreases in all stages of diastolic dysfunction. Its use in combination with mitral inflow velocities provides a simple interpretation of diastolic function. In the presence of normal left ventricular diastolic function, the septal e' wave is lower than the lateral e' wave. When the lateral e' wave is ≥ 10 cm/s and the septal e' wave is ≥ 8 cm/s, diastolic function can be considered normal. However, if these high levels are measured in a patient with symptoms of heart failure (such as increased jugular venous pressure, edema, or pleural effusion) and EF is normal, the diagnosis of CP should be considered.¹¹⁶ In the presence of CP, although myocardial involvement is not expected, there is a decrease in the lateral e' wave due to possible pericardial adhesions in the lateral wall and an increase in the septal e' wave due to increased longitudinal septal motion to compensate for this situation. This condition, defined as 'annulus reversus,' can also be seen in atrial fibrillation and high-output heart failure. Welch et al.¹⁰⁵ concluded that a septal e' value of ≥ 9 cm/s has a positive predictive value of 94% for CP and a septal/lateral e' ratio of ≥ 0.91 has a positive predictive value of 95%. If the septal e' wave is observed to be decreased in CP patients (< 9 cm/s), mixed-type involvement with concomitant cardiomyopathy should be considered. In these patients, 5-year survival after pericardiectomy is predicted to be worse.¹¹⁷ In radiation-induced CP, an example of mixed-type involvement, the septal e' wave is observed to be lower than in primary CP, but

the septal e' value is moderately decreased in cases that develop after cardiac surgery.¹⁰⁵

Evaluation of Vein Flow

In addition to intracardiac measurements, Doppler evaluations of pulmonary and hepatic vein (HV) flows, which change during respiration, are also important. In CP, HV forward flow is markedly increased on inspiration and decreased on expiration, which is associated with significant holosystolic flow reversal. Depending on the etiology, rhythm status, and signal quality, the expiratory diastolic flow pattern is increased. Reversal of this ratio is the most specific Doppler finding in CP, including mixed-type disease.^{15,105-118} Figure 30 shows hepatic vein flow patterns due to changes in diastolic function.

Non-invasive examination is particularly challenging in the presence of atrial fibrillation (AF), which occurs in approximately 15% of patients with CP. In patients with AF, parameters such as ventricular septal shift, increased e' velocity (using a limit of 11 cm/s instead of 9 cm/s), "annulus reversus," and increased expiratory HV-diastolic reversal flow velocity ratio have proven to be reliable in studies.¹⁰⁵ However, interpreting measurements can be difficult due to the variability in R-R intervals. In selected cases, pharmacologic or electrical suppression of arrhythmia and repeat measurements may be considered. For patients in whom sinus rhythm cannot be achieved, it is recommended to perform temporary ventricular pacing and repeat measurements after stabilization of R-R intervals.¹⁰⁵

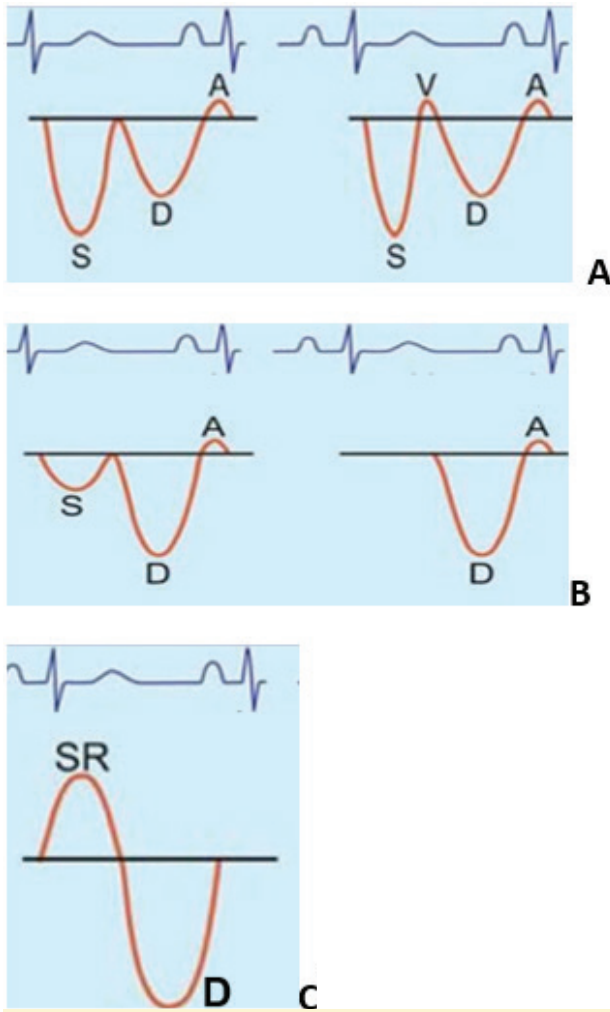


Figure 30. Hepatic vein flow patterns due to changes in diastolic function A) In the normal hepatic vein tracing, the S wave is >D wave and is observed in negative deflection, while the A wave is observed as a small wave in positive deflection. B) The figure showing the flow pattern with $S < D$ and disappearance of the S wave shows the pressure change curves that develop during diastolic dysfunction C) The flow pattern curve with systolic flow return is seen in advanced stages of diastolic dysfunction

Echocardiographic Findings in Restrictive Cardiomyopathy

Morphologic findings of restrictive cardiomyopathy on 2D TTE typically show normal-sized ventricles and enlarged atria with preserved or slightly reduced EF. The ventricle is usually not hypertrophied or dilated. These findings are non-specific and can also be observed in chronic CP.¹⁰¹

In amyloidosis, which is among the secondary causes of RCMP, specific findings such as increased thickness of the right atrial free wall, interatrial septum, and atrioventricular valve, as well as pericardial effusion, can be observed. In another cause, hypereosinophilic disease (Loeffler endocarditis), endocardial thickening is observed in the inflow and apical parts of the ventricles.

In the evaluation of diastolic dysfunction, RCMP exhibits increased diastolic filling pressure velocities and decreased atrial filling

velocities in a restrictive pattern similar to CP in hemodynamic terms. Consequently, there is an increased early diastolic filling/atrial filling ratio (>2), decreased E-wave DT (<150 ms), and shortened IVRT (<70 ms).¹⁰¹

Tissue Doppler Findings

Tissue Doppler examination is critical in evaluating diastolic function and differentiating between CP and RCMP. Early mitral annular velocity (e') is the parameter used to assess myocardial relaxation. Under normal conditions, the amplitude of the lateral e' wave is higher than the septal e' wave because the lateral wall is free. In myocardial diseases, including RCMP, annular velocities are generally reduced, preserving this difference. Exceptionally, in young patients and in the early stage of the disease, there may be a slight decrease (7–8 cm/s), but the septal e' wave can be as low as 2–3 cm/s. If measurements appear too normal for RCMP, a combination of CP and RCMP should be suspected.¹¹¹

Evaluation of Vein Flow

Increased reverse flows to the pulmonary veins are associated with early cessation of mitral inflow due to increased LV end-diastolic pressures in a restrictive pattern. The presence of increased and prolonged reverse pulmonary venous flows, along with a low amplitude and short duration transmitral A wave, typically indicates increased ventricular end-diastolic pressure. Diastolic pulmonary venous flow (D) begins with transmitral filling, and the peak of the D wave correlates with the transmitral E wave. The early systolic pulmonary venous wave (S1) is generated by atrial relaxation and the systolic movement of the atrioventricular annulus, which draws blood from the pulmonary bed into the atria. The second systolic pulmonary venous wave, termed S2, is initiated by a similar mechanism but is primarily associated with the driving force of right ventricular systole on the pulmonary bed.^{119,120} Normally, the pulmonary venous systolic velocity (S) is expected to be greater than the D wave and to increase even more in stage 1 diastolic dysfunction. As LA pressure increases (in stage 2 and 3 diastolic dysfunction), the majority of LV filling occurs in early diastole, causing the D wave to increase while the S wave becomes smaller. As LV diastolic pressures rise, atrial contractions with decreased LV compliance send more blood volume into the pulmonary veins, prolonging the duration of reversed pulmonary venous flow (Ar) and increasing the peak flow velocity to over 40 cm/s. The S1 wave in pulmonary flows is associated with atrial relaxation, allowing pulmonary venous flows to return to the LA and decrease LA pressure. This wave immediately precedes the S2 wave and is usually hidden within S2, becoming visible only in cases of prolonged atrioventricular conduction or prolonged PR interval.^{119,121} Pulmonary venous Doppler flow patterns according to the stages of diastolic dysfunction are shown in Figure 29.¹¹⁶

Similar to CP, PW Doppler velocities of the pulmonary and hepatic veins in RCMP are higher in diastole than in systole. Additionally, atrial reversal velocities are increased, and their duration exceeds the duration of mitral filling.¹⁰¹ In cases of RCMP, HV flows show an increase in inspiratory flow due to the inability of the RV to adapt to inspiratory changes.¹²² Table 7 summarizes the main echocardiographic measurements and threshold values used to differentiate CP and RCMP.¹⁰²

Table 7. Main echocardiographic measurements and threshold values used to differentiate constrictive pericarditis and restrictive cardiomyopathy.¹⁰²

	Constrictive Pericarditis	Restrictive Cardiomyopathy
Transmitral Flow	Respiratory ΔE ≥ 25%	ΔE does not change with respiration
Transtricuspid Flow	Respiratory ΔE ≥ 35%	ΔE changes ≤ 15% with respiration
Mitral annular motion (septal)	E' ≥ 8 cm/s	E' < 8 cm/s
Flow propagation Velocity	>55cm/s	Decreased
Hepatic vein flow	Increased expiratory diastolic return wave	Increased inspiratory return wave

Advanced Echocardiographic Methods for Differentiation of Constrictive Pericarditis and Restrictive Cardiomyopathy

In addition to the methods described so far in this chapter, two-dimensional speckle tracking echocardiography (2D-STE) is an advanced echocardiographic evaluation method used in the differential diagnosis of CP and RCMP. It is particularly useful in recognizing mixed-type disease. Since torsion and circumferential strain analysis mainly evaluate the epicardial myocardium, low values indicate CP and suggest the presence of asymmetric adhesions in the pericardium or involvement of the epicardial region.¹²³ In contrast, the measurement mainly affected in RCMP is global longitudinal strain (GLS) due to involvement of the subendocardial area. Although all deformation measurements provide valuable information in the differential diagnosis, their use in combination with the classical measurements mentioned previously is recommended. In strain measurements, which may vary in both conditions, pericardial adhesions in CP are more likely to be in the free walls of the LV and RV. Consequently, strain measurements are observed to decrease more in the lateral and inferior walls than in the septum, a condition termed "strain reversus." These impaired measurements are expected to recover after pericardiectomy. Decreased strain measurements in RCMP may be localized, but specific patterns, such as apical sparing in amyloidosis, are considered directly diagnostic.¹²³

Imaging Methods Other Than Echocardiography

Chest X-ray

Pericardial calcification, seen in approximately 25% of patients, is valuable if visible on a chest x-ray. However, its absence does not exclude the diagnosis, especially in CP with acute and subacute adhesions. Enlargement of the cardiac chambers and pulmonary venous congestion may support a diagnosis of RCMP. It is important to note that these findings are non-specific as they may accompany various conditions. With the advent of more advanced imaging techniques, the significance of these findings has diminished.¹¹¹

Computed Tomography

Due to its superior spatial resolution and three-dimensional evaluation capabilities, CT surpasses X-ray among imaging modalities involving ionizing radiation.¹²⁴ Non-contrasted images allow for the evaluation of pericardial thickness and content, while contrast-enhanced images can assess pericardial involvement and peri-pericardial adipose tissue findings that may indicate pericardial inflammation. Secondary findings such

as increased pericardial thickness, calcification, deformations of the cardiac chambers due to adjacent pericardial recesses, and IVC enlargement are typical findings observed on tomography.¹²⁵ When evaluating pericardial thickening, it is important to note that while a thickness over 4 mm is more likely to indicate CP, CP may still be present in cases where pericardial thickness is measured at normal levels (<2 mm).¹²⁶ Additionally, a thickened pericardium may not always indicate CP and could be due to acute pericarditis without constriction, radiotherapy, or some infiltrative diseases.¹²⁵

The advantages of contrast-enhanced images include providing information about coronary anatomy, evaluating extracardiac tissues, and assessing residual pericardium in the post-pericardiectomy process.

Cardiac Magnetic Resonance

Due to its high temporal and spatial resolution, cardiac magnetic resonance (CMR) is at the forefront of evaluating cardiac anatomy and function and characterizing cardiac tissues. It is extremely useful in identifying acute and active inflammation, diagnosing chronic processes such as fibrosis, and differentiating infiltrative cardiomyopathies such as amyloidosis.^{127,128}

On CMR, several findings can indicate CP. These include increased pericardial thickness (>4 mm), visualization of deformations of elongated ventricles caused by shrinkage due to a rigid pericardium, presence of pericardial effusion, and presence of edema or fibrosis indicated by contrast uptake.^{129,130} In cases indicating fibrosis where the pericardium shows abnormal late gadolinium enhancement (LGE) uptake, acute inflammation is considered, and differential diagnosis can be made by evaluation in other sequences. For example, increased T2 signals in pericardial tissue with early and late contrast uptake are diagnostic for acute pericarditis.^{131,132} Another important finding is pericardial tethering, which is observed on 'cine' imaging. This is defined as the inability to show the sliding motion of the marked myocardial segments independent of the pericardial tissue and is also indicative of CP.^{133,134} Measurements made with this technique have been shown to be highly compatible with "speckle-tracking" analyses obtained by echocardiography.¹³⁵ Additionally, a parameter that can be used in the differential diagnosis of CP and RCMP in "cine" imaging is the evaluation of the relative atrial ratio in cases of biatrial enlargement with preserved ventricular diameters, which can be observed in both conditions. A ratio of 1.32% is considered the highest specificity (86.4%) and sensitivity (82.6%) threshold.^{129,130}

In RCMP, T1 and T2 imaging based on the spin properties of myocardial protons and contrast uptake are used to evaluate the myocardial structure.

In pure CP, myocardial uptake is not expected, whereas the presence of uptake indicates myopericarditis, which is associated with a poor clinical prognosis. In contrast studies, interstitial fibrosis can be demonstrated by late gadolinium enhancement (LGE), and abnormal LGE is observed in one-third of patients with RCMP. Specific uptake, such as subendocardial LGE indicating amyloidosis, is considered diagnostic.^{136,137}

CMR allows hemodynamic evaluations similar to those performed with echocardiography. With four-dimensional flow imaging techniques, flows can be assessed in 3D throughout the entire cardiac cycle with less operator dependency. This enables the demonstration of specific hemodynamic features, including interventricular interactions, particularly in CP.¹¹¹ For this purpose, respiratory ventricular septal abnormal movement can be demonstrated with real-time free-breathing cine CMR imaging. Although qualitative measurements are usually sufficient for evaluation, quantitative measurements can also be performed if desired. A threshold value of 11.8% has been shown to clearly differentiate CP from RCMP.¹³⁸ In another study, the ratio of the biventricular end-diastolic area to whole heart volume and its respiratory variation were used to differentiate CP from control patients (1.03 ± 0.03 in CP vs. 1.28 ± 0.10 in control groups).¹³⁹

Another benefit of CMR is that it provides information about extracardiac tissues. It is especially useful in evaluating increased central venous pressures in CP, as well as congestive hepatopathies and subsequent cirrhosis that may develop. The presence of this condition is associated with a poor prognosis.^{140,141} Table 7 summarizes the criteria of TTE, CT, and CXR used in the diagnosis of CP.¹⁰²

Because of all these features, the use of CMR is extremely important not only for diagnosis but also for individualized guidance of treatment. It is particularly useful in guiding the use of anti-inflammatory therapies in patients with active inflammatory processes and in evaluating the response to treatment. In cases where inflammation is not demonstrated, it helps decide on the timing of pericardiectomy when the diagnosis of CP is certain.^{131,142,143}

Nuclear Imaging

Technetium-99m-pyrophosphate scintigraphy is increasingly used in diagnosing transthyretin-type amyloidosis in patients with restrictive cardiomyopathy due to its 100% specificity and 100% sensitivity. This technique can differentiate transthyretin from light chain amyloidosis with high accuracy, especially after excluding systemic light chain amyloidosis, as demonstrated in a study by Perugini et al.⁷⁰ in 2005.¹¹¹

Fluorodeoxyglucose positron emission tomography (FDG- PET), on the other hand, is uniquely useful for demonstrating tissue metabolism and pathology, detecting increased cellular activity and inflammation, and guiding treatment strategy. It has a specificity of up to 90% for diagnosing sarcoidosis. FDG-PET is useful in the differential diagnosis of tuberculous pericarditis, idiopathic pericarditis, and pericarditis due to malignancies.

Additionally, it can be used in follow-up to assess the response to anti-inflammatory therapy.¹¹¹

Cardiac Catheterization

Cardiac catheterization is valuable in diagnosing CP and RCMP. It allows for patient evaluation both in the basal state and after controlled fluid support, with rhythm control (using pacemaker support) if necessary. This method is particularly useful for patients with exercise symptoms, uncontrolled arrhythmia, and hypovolemia, for whom non-invasive diagnostic methods are inconclusive.¹¹¹

Invasive measurement of atrial pressure waves can show 'square root' or 'dip-plateau' waveforms, indicating impaired ventricular filling. Pressure equalization in the cardiac chambers at the end of diastole (typically within 5 mmHg) is a typical sign of CP. Increased systolic pressure of the pulmonary artery indicates RCMP, whereas it is usually normal in CP.¹¹⁰ The 'systolic area index,' which is the ratio of the areas of the RV and LV systolic pressure-time curves obtained during inspiration and expiration, is a reliable measure used to assess ventricular interaction. In patients with CP, there is an increase in the RV pressure area curve on inspiration compared to expiration, while the area of the LV pressure curve decreases. In contrast, RCMP patients show a decreasing RV pressure curve area on inspiration, with no change in the LV pressure curve on inspiration compared to expiration. This method diagnoses CP with 97% specificity and 100% predictive accuracy.¹¹⁰

In invasive evaluations, respiratory septal shift and abnormal ventricular septal motion, which are indirect signs of CP, can be demonstrated, and pericardial calcifications can also be visualized during fluoroscopy. During coronary angiography, coronary arterial fixation may be demonstrated, and immobility, especially involving the distal segments of the coronary arteries, may be encountered due to CP. Finally, endomyocardial biopsy is the only method available for the histopathologic evaluation of myocardial diseases.

In conclusion, Echocardiography is the primary diagnostic modality for patients with primary CP. If the results are consistent with the patient's clinical findings and physical examination, further investigations may not be necessary. When CP is confirmed and suspected to be part of an inflammatory process, chest X-ray (CXR) should be included in the treatment algorithm to confirm inflammation and evaluate the response to treatment. If the diagnosis cannot be differentiated by echocardiography, CXR, or tomographic examination may be considered based on the experience of the center and potential interventions.

While echocardiography provides superior anatomical, functional, and structural evaluation, tomography offers features such as evaluation of calcifications, visualization of coronary arteries, and assessment of surrounding tissue for surgical intervention. In inconclusive cases, nuclear imaging may be considered as a final step. It is important to keep in mind that CP and RCMP may coexist, and in some cases, treatment should address both diseases.

In cases where non-invasive evaluation is inadequate, catheterization may be performed for invasive evaluation, and

Table 8. Distinctive findings of the clinical and main imaging methods used to differentiate Constrictive Pericarditis and Restrictive Cardiomyopathy ¹¹⁰		
Diagnostic Method	Constrictive Pericarditis	Restrictive Cardiomyopathy
Physical examination	Kussmaul's sign, pericardial knock	Regurgitation murmurs, rarely Kussmaul's sign, S3 in advanced cases
ECG	Low voltages, Non-specific ST/T changes, AF	Low voltages, pseudo-infarction, QRS widening, Left axis, AF
Chest X-Ray	Pericardial calcifications (in 1/3 of patients)	No pericardial calcification
Echocardiography	-Abnormal septal motion -Pericardial thickening and calcifications - >25% change in mitral peak E velocity and >20% change in pulmonary venous flow peak D flow velocity with respiration -Color M- Mode propagation velocity (Vp) >45 cm/s -Medial e' peak value in > 8.0 cm/s on tissue Doppler	-Normal sized left ventricle with enlarged atria -E/A ratio >2 and decreased deceleration time -No respiratory change on mitral flows - Color M- Mode propagation velocity (Vp) <45 cm/s - Medial e' peak value in tissue Doppler is < 8.0 cm/s
CT/CMR	Pericardial thickness >3-4mm, pericardial calcifications (CT), ventricular interaction (cine MR)	Normal pericardial thickness (<3 mm), presence of myocardial involvement in morphological or functional studies (CMR)
Cardiac Catheterization	Bottom plateau or square root sign, equal right and left ventricular diastolic pressures, ventricular interaction (systolic area index being >1.1)	Significant right ventricular systolic pressure increase (>50 mmHg), lowering of LVEDP at rest or during exercise 5 mmHg or more than RVEDP (RVEDP<1/3 RVSP)

ECG, Electrocardiography; AF, Atrial Fibrillation; CT, Computerized Tomography; CMR, Cardiac magnetic resonance; LVEDP, Left ventricular end-diastolic pressure; RVEDP, Right ventricular end-diastolic pressure.

endomyocardial biopsy may be conducted for pathological diagnosis if necessary. A summary of the diagnostic algorithm described in detail in this article is presented in Table 8.¹¹⁰ In very rare cases where the diagnosis remains elusive,

diagnostic surgical interventions may need to be performed in selected patients. Such patients should be referred to multidisciplinary centers experienced in managing pericardial diseases.

Multimodality Imaging in Dilated Cardiomyopathy

Dilated cardiomyopathy (DCM) is one of the most common causes of heart failure and a leading cause of heart transplantation worldwide.¹⁴⁴ The 2023 Cardiomyopathy Guidelines updated the clinical classification of cardiomyopathies and introduced a new phenotypic description to simplify terminology. According to the guidelines, DCM is characterized by global or regional left ventricular (LV) systolic dysfunction accompanied by LV dilatation that is not explained by abnormal loading conditions or coronary artery disease (CAD). Right ventricular (RV) dysfunction is not required for diagnosis.¹ The definition also introduces a new category characterized by LV systolic dysfunction without LV dilation, known as hypokinetic non-dilated cardiomyopathy.¹

DCM encompasses a diverse group of patients with varying underlying pathologies, disease courses, and outcomes. The estimated prevalence of DCM ranges from 3.6 to 4 per 100,000 individuals, with familial cases accounting for 30–50% of occurrences.¹⁴⁵ An identifiable genetic cause has been found in 40% of familial DCM patients.¹⁴⁵ It is important to obtain a family history that includes at least three generations. Since different types of cardiomyopathies share a common genetic substrate, significant overlap between DCM and other types of cardiomyopathies is not uncommon.¹⁴⁶

During the diagnostic work-up, it is crucial to consider the interaction between genetic and acquired causes. Non-genetic causes of DCM include infections (postmyocarditis), toxicity and drug overload, hormonal-nutritional causes, electrolyte disturbances, peripartum cardiomyopathy, and autoimmune diseases.¹ Table 9 shows the main causes of DCM. Clarifying the diagnosis is of paramount importance to guide management and prognosis. Identifying a specific cause may be vital for guiding treatment; for example, the presence of Lamin A/C mutations is associated with ventricular arrhythmias and may lower the threshold for implantable defibrillator therapy.¹

Table 9. Main causes of dilated cardiomyopathy

Causes	Examples
Genetic	Cardiac genetic diseases Neuromuscular genetic diseases Syndromes
Infectious	Viral, fungal parasitic, protozoal diseases
Systemic immune-mediated	Autoimmune, autoinflammatory diseases
Nutritional deficiency	Selenium, thiamine, zinc, copper
Electrolyte disturbance	Hypocalcemia, hypophosphatemia
Toxic	Alcohol, cocaine, amphetamines, iron overload
Drugs	Antineoplastic, psychiatric drugs
Endocrine metabolic	Hypo-hyperthyroidism, Cushing's disease, Addison's disease, pheochromocytoma, acromegaly, diabetes
Tachycardia-arrhythmia induced	
Peripartum	

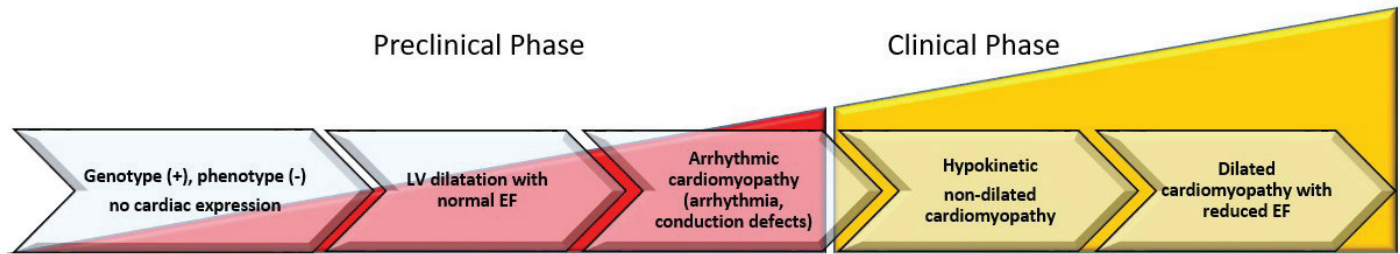


Figure 31. Phenotypal spectrum of dilated cardiomyopathy.

The clinical course of DCM patients is highly variable, ranging from rapidly progressive heart failure (HF) or sudden cardiac death (SCD) to LV reverse remodeling (substantial LV volume reduction with sustained left ventricular ejection fraction (LVEF) recovery).¹⁴⁶ Generally, the disease has a long preclinical phase with no or few symptoms. Figure 31 illustrates the phenotypal spectrum of DCM. Nearly 40% of patients with newly diagnosed DCM experience a reduction in LV size with optimal medical therapy at a median follow-up of 2 years, indicating a favorable prognosis.¹

LV dilatation and systolic dysfunction are important prognostic factors for DCM. While dilatation is associated with adverse outcomes, LV reverse remodeling and normalization of LV dimensions are linked to improved survival. Other imaging parameters associated with the risk of death or HF hospitalization include left atrial (LA) dilatation, RV dilatation, and RV systolic dysfunction.¹

Imaging modalities are the cornerstone for diagnosing, following up, and excluding alternative causes of cardiomyopathy. In addition to identifying the phenotype, ventricular morphology, and function, multimodality imaging is recommended for detecting abnormalities through tissue characterization. DCM has a long asymptomatic period with subclinical myocardial dysfunction that can be detected using advanced imaging techniques.

It is important to proceed hierarchically, starting with simpler, less expensive tests before moving to more complex, costly ones. Data from imaging studies should not be used in isolation but should be evaluated in the context of the patient's clinical presentation, medical and family history, and exposure to potential triggers. Excluding CAD and prior myocardial infarction are crucial steps in evaluating a patient with suspected DCM.

Echocardiography

Echocardiography, which is widely available and easy to perform, is one of the main imaging modalities for diagnosing and following up on dilated cardiomyopathy. Transthoracic echocardiography (TTE) with Doppler imaging provides information about anatomical and functional abnormalities of the LV and RV, enabling the assessment of valve function, pulmonary arterial pressure, and the presence of pericardial effusion.² Tissue Doppler or speckle tracking myocardial deformation techniques with strain imaging provide a more sensitive evaluation of regional and global ventricular functions.

A comprehensive echocardiographic examination, including strain analysis and 3D imaging, should be performed for each patient

with DCM. 3D echocardiography is increasingly used due to technological advances and shows better agreement with cardiac magnetic resonance imaging (CMR) results. If a thrombus is suspected, a contrast agent may be used to improve imaging.

Echocardiographically, an LV end-diastolic diameter equal to or greater than 58 mm in men and 52 mm in women, and an LV end-diastolic volume index equal to or greater than 75 mL/m² in men and 62 mL/m² in women indicate LV dilatation.¹⁴⁷ Figure 32 shows the parasternal long-axis and apical 4-chamber views. There is a moderate jet of functional mitral regurgitation (MR). LV systolic dysfunction is defined as a LVEF of less than 50%. During LVEF measurement, care should be taken to avoid apical foreshortening.

Early in the course of the disease, LV dilatation without systolic dysfunction or systolic dysfunction without LV dilatation (hypokinetic non-dilated cardiomyopathy) may be observed. Figure 33 illustrates LVEF measurement by using M-mode (Figure 33A), the biplane Simpson method (Figure 33B, 33C) and 3D echocardiography (Figure 33D). The strain map shows severely impaired global longitudinal strain (GLS)(Figure 33E, 33F).

Isolated LV dilatation should be distinguished from pathological forms, with physiological adaptation in the latter associated with normal GLS.¹⁴⁸ During echocardiographic examination, LV filling pressure and diastolic dysfunction should be assessed by measuring the early to late diastolic transmitral flow velocity (E/A), early diastolic mitral annular tissue velocity (e'), E velocity deceleration time, and the maximum velocity of the tricuspid regurgitant jet. Figure 34 shows grade III-IV diastolic dysfunction in a patient with DCM.

An increase in the relative wall thickness of the LV should suggest a diagnosis of hypertension, a burn-out phase of hypertrophic cardiomyopathy, or infiltrative cardiomyopathy.¹⁴⁹ Reduced lateral mitral annular tissue Doppler velocity is accepted as an indicator of LV longitudinal dysfunction.¹⁵⁰ Studies have shown that a decrease in GLS precedes LVEF deterioration and may have additional value in cardiac screening of individuals with a family history of DCM.¹⁵¹ Similarly, abnormal radial and circumferential strain values have been reported in preclinical DCM patients.¹⁵² GLS and mechanical dispersion, calculated as the standard deviation of time to peak strain values in a 16-segment model, have been found to be predictive of adverse arrhythmic outcomes.¹⁵²

During echocardiography, it is important to measure RV anatomy and function because RV functional abnormalities provide prognostic information, including transplant-free survival.¹⁵³ RV systolic dysfunction is defined as an RV fractional area change

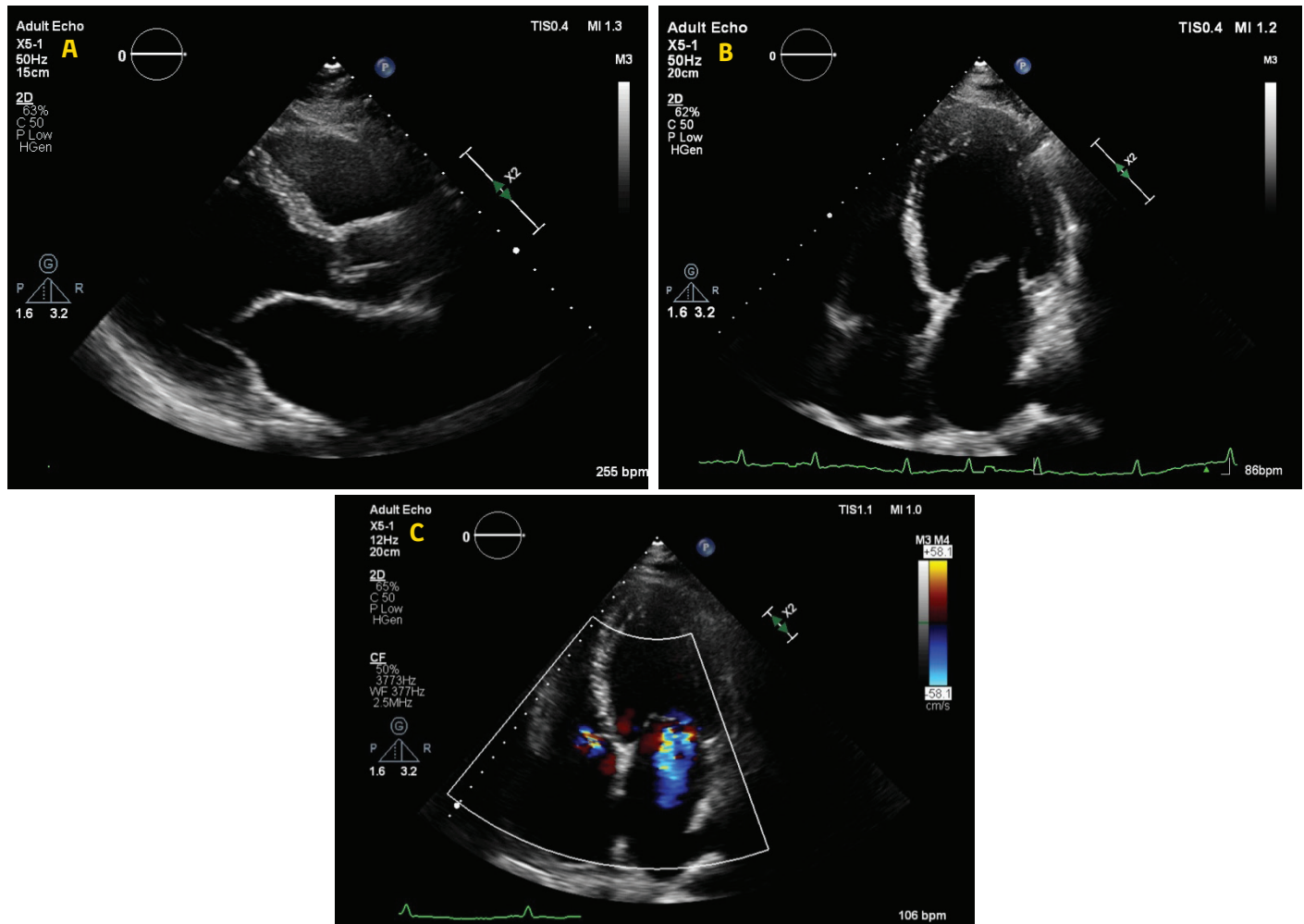


Figure 32. Transthoracic echocardiography of a patient with dilated cardiomyopathy showing a parasternal long-axis view (A) and an apical 4-chamber view (B). Note the marked dilatation of the left ventricle and the spherical pattern. There is also dilatation of the mitral annulus with leaflet tethering. Moderate jet of functional mitral regurgitation (C).

of less than 35%, a tricuspid annular plane systolic excursion (TAPSE) of less than 17 mm, and a tricuspid annulus S velocity of < 9.5 cm/s.¹⁵⁴

Currently, an LVEF of less than 35% is required to qualify for cardiac resynchronization therapy (CRT) and implantable cardioverter-defibrillators (ICDs).¹⁵⁵ However, LVEF has poor specificity and sensitivity in predicting sudden cardiac death. Although GLS imaging is a sensitive measure of LV function, there is no cutoff value that serves as an indication for CRT and ICD therapy.

Echocardiographic findings such as septal bounce, septal flash, and apical rocking motion of the apex toward the late-contracting lateral wall predict the response to CRT.¹⁵⁶ In patients where mechanical desynchrony is difficult to assess, low-dose dobutamine testing may aid in the diagnosis.¹⁵⁷ Following CRT implantation, an increase in LVEF and a decrease in LV volume are indicative of a favorable response. Strain curves calculated from intra-LV pressures (pressure-strain loops) have predictive value for reverse remodeling after CRT.¹⁵⁸

Stress echocardiography can provide information on systolic and diastolic reserve, myocardial ischemia, viability, and dynamic MR.

The presence of a contractile reserve is associated with better outcomes and may help identify patients with preclinical DCM.¹⁵⁹

Secondary MR in patients with DCM is associated with adverse outcomes.¹⁶⁰ MR is caused by symmetric or asymmetric dilatation of the LV rather than by leaflet pathology. MR should be detected in the presence of severe LV dysfunction. The prognostic value of MR is lost when LV dilatation becomes severe.¹ Patients with severe MR benefit from transcatheter edge-to-edge mitral valve repair.

Transesophageal echocardiography plays a key role in assessing mitral valve anatomy and the mechanism of MR. Patients who remain symptomatic despite optimal medical therapy and have an effective orifice area ≥ 30 mm², an LVEF of 20–50%, an LV end-systolic diameter of < 70 mm, systolic pulmonary artery pressure < 70 mmHg, no RV dysfunction, or severe tricuspid regurgitation are candidates for transcatheter edge-to-edge repair.¹⁶¹

All patients who are candidates for a left ventricular assist device (LVAD) should undergo echocardiography to assess RV function, detect thrombi, and identify coexisting valvulopathies. Severe RV failure is a major cause of mortality after LVAD implantation, with an incidence of 10–30%. The echocardiographic parameters that

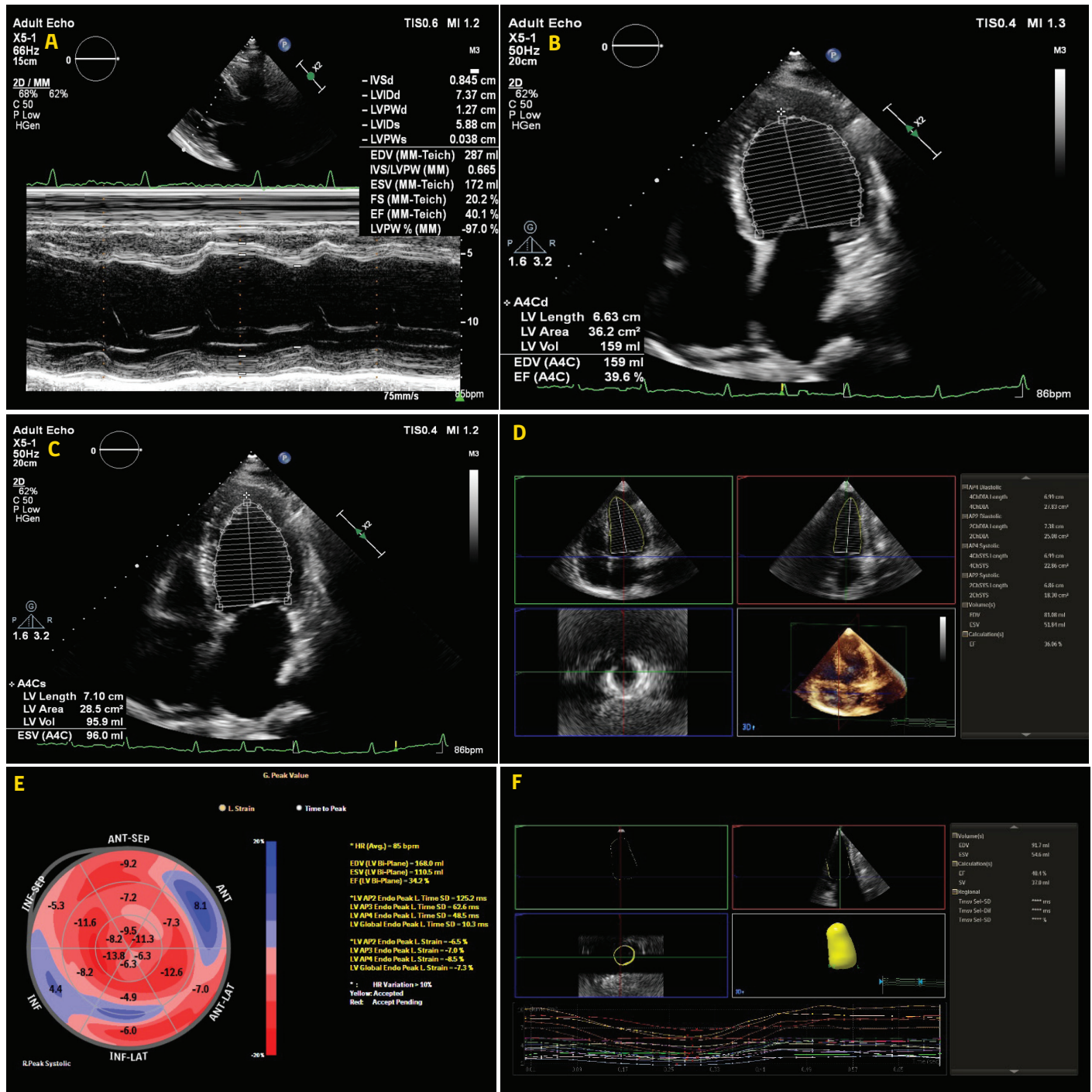


Figure 33. Measurement of ejection fraction in a patient with dilated cardiomyopathy using M-mode (A), biplane Simpson (B,C), and 3D echocardiography (D). Strain map showing peak longitudinal strain; global longitudinal strain severely impaired at -7,3% (E,F).

predict RV failure after LVAD surgery include increased tricuspid annular dilatation (>43 mm), reduced TAPSE (<8 mm), and an RV-LV end-diastolic diameter ratio >0.72.¹⁶²

Echocardiography is also an ideal modality for monitoring LVAD dysfunction, adjusting settings/speed, and assessing myocardial recovery. It also helps determine the optimal timing for weaning.¹⁶²

Cardiac Computed Tomography and Coronary Angiography

Cardiac computed tomography (CT) and coronary angiography are highly valuable for ruling out CAD, especially in patients with risk factors.¹ Diagnosing epicardial CAD allows for the identification of a small group of patients who may benefit from coronary revascularization. As the elderly population increases, the coexistence of primary myocardial disease and CAD is also

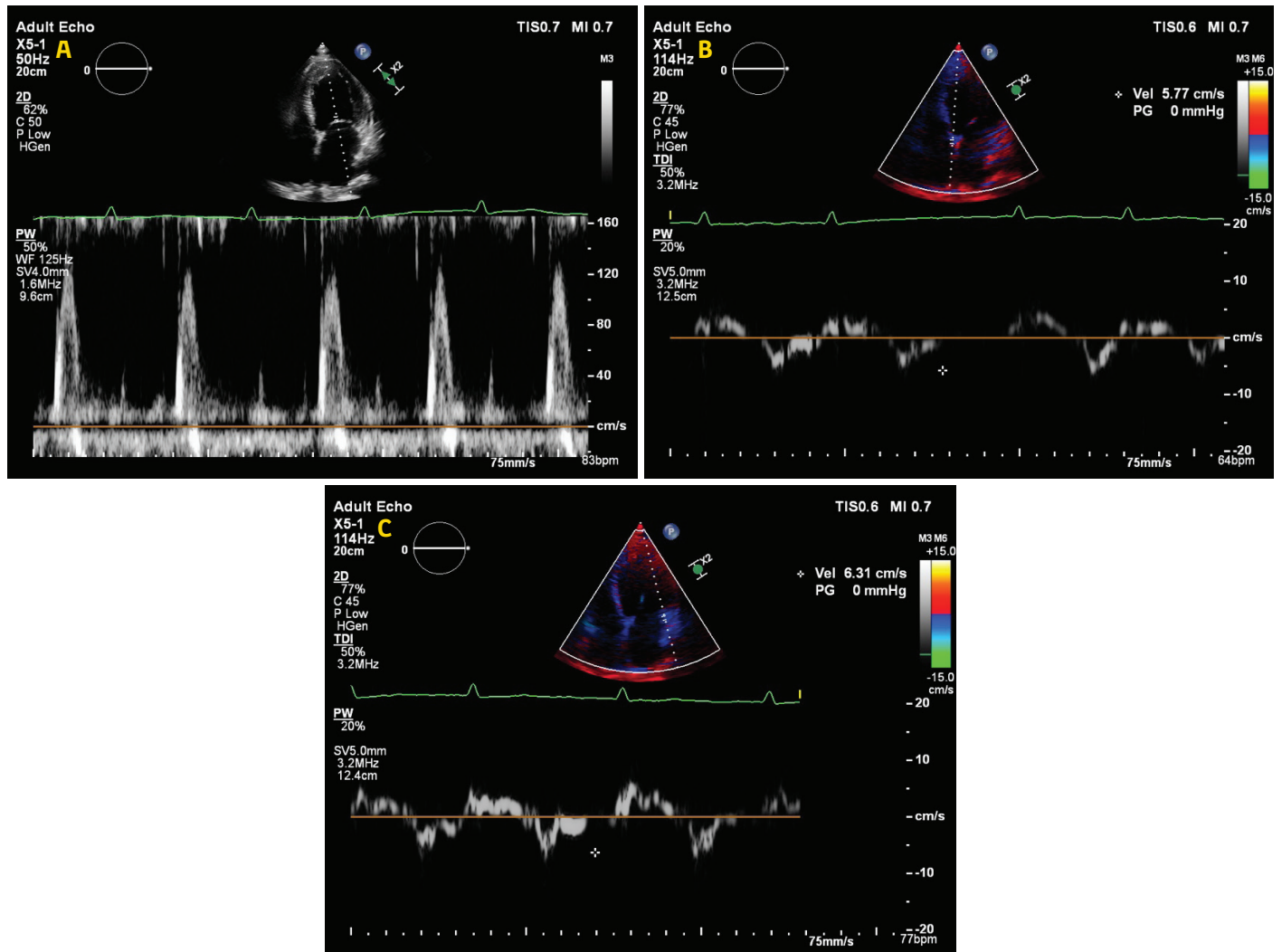


Figure 34. Grade 3–4 diastolic dysfunction in dilated cardiomyopathy; E/A>2 (A), septal e'<7 cm/sn (B), lateral e'<10 cm/sn (C).

becoming more common. Therefore, patients with bystander CAD should receive primary prevention treatment strategies. CT is also useful for evaluating coronary vein anatomy prior to CRT implantation.

Cardiac Magnetic Resonance Imaging

CMR is the gold standard for assessing LV and RV function. CMR, with tissue characterization, provides insight into the etiology of DCM. It can complement coronary angiography in evaluating the cause of systolic dysfunction. It has been reported that nearly 10% of patients with new-onset heart failure without obstructive CAD show evidence of prior infarction on CMR.¹⁶³

CMR may also help identify alternative causes of DCM. Acute myocarditis is characterized by increased T2 signals indicative of myocardial edema and subepicardial/midwall late gadolinium enhancement (LGE), whereas Takotsubo cardiomyopathy is characterized by an isolated increase in T2 signals.^{164,165} The presence of midwall or epicardial LGE in the basal septal and lateral walls increases the likelihood of cardiac sarcoidosis.¹⁶⁶

CMR is the only noninvasive technique for quantifying myocardial iron overload. Myocardial iron causes a reduction in T1, T2, and T2* relaxation times.¹⁶⁷ Among these, the T2* technique is the preferred method for cardiac iron evaluation and is considered a reference method according to the guidelines. Early identification of patients at risk for heart failure enables the intensification of chelation therapy, providing prognostic value in this population.¹⁶⁸

CMR may help physicians diagnose the genetic causes of DCM. Nearly one-fifth of patients with DCM have a rare genetic variant underlying the disease.¹⁶⁹ Disease-causing mutations in desmoplakin and filamin C present as subepicardial ring-like LGE patterns.¹⁷⁰ Arrhythmogenic right ventricular cardiomyopathy (ARVC) typically affects the RV; however, 76–84% of ARVC patients also show histopathologic and functional evidence of LV involvement.¹⁷¹ Left-dominant forms of the disease have also been reported.¹⁷¹ Nearly 4% of patients diagnosed with DCM have causative desmosomal gene variants, suggesting a left-dominant form of ARVC.

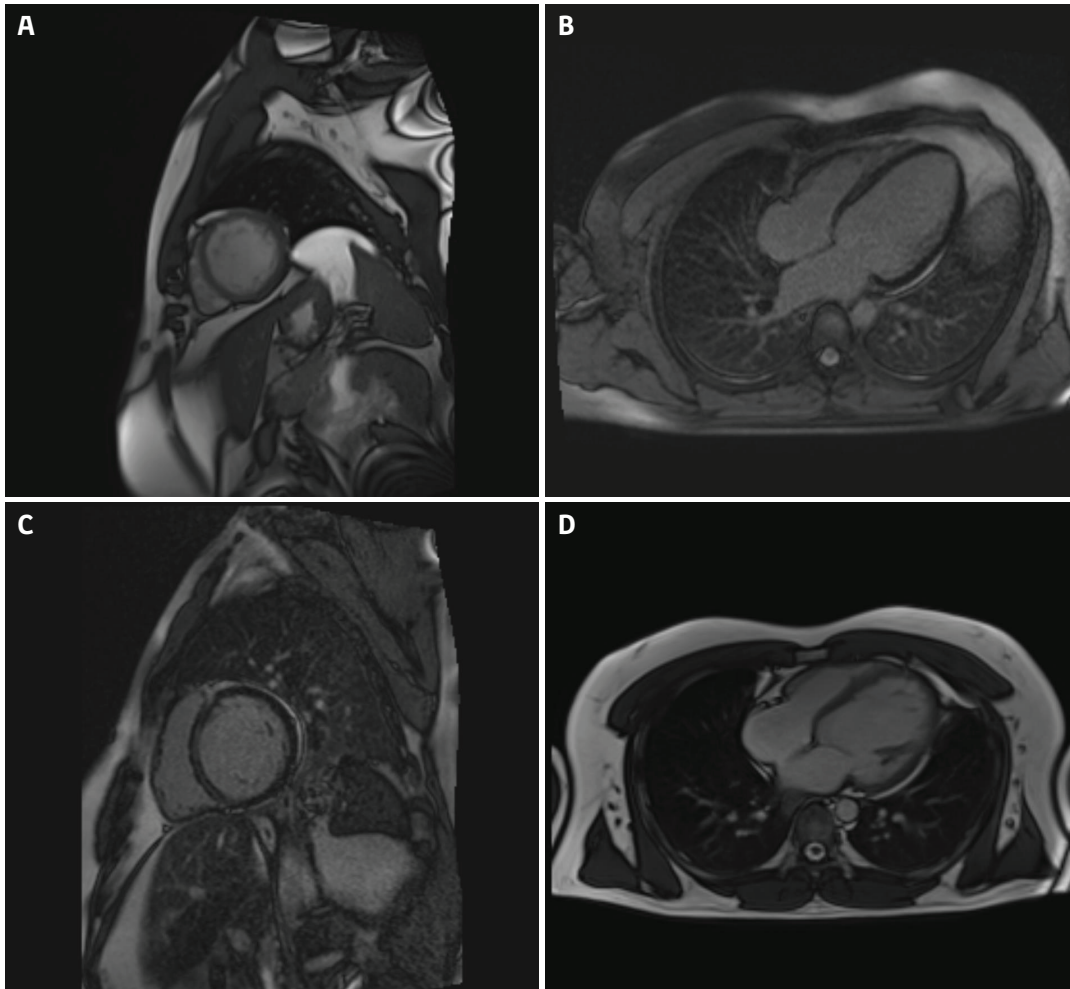


Figure 35. CMR study in a patient with dilated cardiomyopathy. Short axis cine stack and four chamber view (A,B). Post-contrast T1 sequences show a typical LGE pattern with linear midwall uptake (C,D).

CMR is recommended as a first-line imaging modality for assessing RV structure and function.¹ Contrast-enhanced CMR can detect LV involvement, while electroanatomic voltage mapping can reveal fibrofatty replacement of myocardial tissue.¹⁷¹ Although most cardiomyopathy patients with lamin A/C gene variants exhibit midwall fibrosis, this finding lacks specificity. X-linked muscular dystrophies, including Duchenne muscular dystrophy and Becker muscular dystrophy, are characterized by subepicardial and midwall myocardial fibrosis of the LV. Skeletal muscle degeneration usually precedes cardiac involvement in patients with Duchenne muscular dystrophy, whereas heart failure may be the first clinical presentation in patients with Becker muscular dystrophy.¹⁷²

Myocardial fibrosis is prognostic because its presence is associated with sudden cardiac death, all-cause mortality, adverse ventricular remodeling, and arrhythmias. Different patterns of fibrosis may have varying prognostic significance; fibrosis occurring in multiple locations is reported to have the worst outcomes.¹⁷³ Figure 35 shows a CMR scan of a patient with DCM, demonstrating a typical LGE pattern with linear midwall uptake.

Observational studies suggest that LGE with the assessment of replacement fibrosis can identify patients at high risk for sudden cardiac death. Masci et al.¹⁷⁴ demonstrated that the absence of LGE at baseline on CMR is an independent predictor of LV reverse remodeling. CMR assessment of RV function provides crucial information regarding patient survival, with lower right ventricular ejection fraction values indicating adverse heart failure outcomes.¹⁵³ Patients receiving CRT who have midwall fibrosis on CMR are less likely to experience reverse LV remodeling at follow-up.¹⁷⁵ However, the cutoff value for fibrosis to identify patients who may benefit from ICD implantation or CRT is currently unknown.

Nuclear Imaging

The diagnostic value of nuclear imaging in DCM is limited. Single-photon emission computed tomography (SPECT) is particularly useful for ruling out myocardial ischemia and, when used to quantify LVEF, provides prognostic information.¹⁷⁶ Myocardial perfusion reserve can be assessed by positron emission tomography (PET) in patients with both ischemic and non-ischemic cardiomyopathy.⁵⁴ PET with 18F-fluorodeoxyglucose

(¹⁸F-FDG) has become a diagnostic tool for sarcoidosis and helps physicians determine treatment response.⁸⁸

Cardiac amyloidosis usually presents with restrictive cardiomyopathy and mildly reduced LVEF, but in advanced stages, it can progress to severe systolic dysfunction. ⁹⁹mTc-pyrophosphate, ⁹⁹mTc-methylene diphosphonate, and ⁹⁹mTc Tc-3,3-diphosphono-1,2-propanodicarboxylic acid SPECT are used to diagnose transthyretin amyloidosis.

123I-Metaiodobenzylguanidine (123I-MIBG) SPECT is used for risk stratification of patients with DCM by assessing sympathetic innervation. This imaging modality evaluates regional denervation, and the extent of 123I-MIBG SPECT has been found to correlate with the risk of ventricular arrhythmias.¹⁷⁷ PET, which allows for the quantification of both presynaptic and postsynaptic sympathetic receptor density, has prognostic value in predicting symptomatic heart failure.¹⁷⁸

Future Perspectives

Advanced imaging techniques enable clinicians to better understand the intracellular dysregulation processes underlying the pathogenesis of cardiomyopathies. Consequently, therapeutic modalities targeting the underlying pathophysiological pathways may prove effective. Hybrid PET-CMR scanners can provide morphological and functional cardiac data, tissue characterization, and metabolic information. Areas of active inflammation appear as increased ¹⁸F-FDG uptake on PET. Adding PET imaging to CMR may help distinguish acute inflammation from chronic inflammatory cardiomyopathies and could represent an effective therapeutic approach.¹⁷⁹

³¹P phosphorus magnetic resonance spectroscopy, which provides information about the myocardial energetic profile, has proven useful in the risk stratification and prognosis of patients

with DCM.¹⁸⁰ CMR with manganese-based contrast media offers insights into myocardial calcium handling and identifies dysfunctional myocardium in patients with cardiomyopathies, presenting potential for early intervention and prognostication.¹⁸¹

A significant proportion of patients with DCM have an identifiable genetic cause of the disease. Targeted gene therapy is emerging as a promising approach for treating these patients. Imaging techniques like diffusion tensor CMR, which can visualize cardiac microstructures and assess the response to sarcomeric therapies, could aid physicians in evaluating the effectiveness of these treatments. In DCM, cardiac microstructures are oriented in the diastolic conformation, while in hypertrophic cardiomyopathy, they are predominantly positioned in the systolic conformation.¹⁸²

Conclusion

In conclusion, multimodal cardiac imaging plays an essential role in patients with DCM. Because it is readily available, initial evaluation usually begins with echocardiography, with additional imaging techniques refining the diagnosis. CMR provides critical information about the disease's etiology, while PET imaging is increasingly important for identifying inflammatory pathologies.

Hybrid PET-CMR imaging allows for a more comprehensive examination and provides insight into the inflammatory, fibrotic, and metabolic components of the disease. Multimodal cardiac imaging techniques are also crucial for assessing the prognosis of patients with cardiomyopathies, with LVEF and LGE being two of the primary risk stratification variables used in clinical practice guidelines.

Finally, due to the changing and progressive natural history of most cardiomyopathies, regular cardiac imaging surveillance should be performed.

Basic Echocardiographic Evaluation in Patients with Hypertrophic Cardiomyopathy

Hypertrophic cardiomyopathy (HCM) is the most prevalent inherited cardiomyopathy, marked by left ventricular hypertrophy (LVH) and preserved ejection fraction (EF) in the absence of abnormal loading conditions or systemic, syndromic, or metabolic diseases.^{1,183} It affects 0.2% to 0.5% of the population.^{183,184} Based on genetic evaluation, HCM patients are divided into two categories: sarcomeric HCM (s-HCM), where a specific sarcomeric gene mutation is identified, and non-sarcomeric HCM (nons-HCM), where no mutation is identified.^{1,183–185} While sarcomeric gene mutations are found in about 40% of patients, no typical mutation can be identified in the remaining 55%.^{186–188} Certain conditions that mimic the HCM phenotype, such as Fabry disease, amyloidosis, and Danon disease, constitute approximately 3–5% of this group. Around 50% of familial HCM cases carry an underlying pathogenic mutation.^{186,187} The genes linked to HCM and its phenotypes are summarized in Table 10.

Table 10. The genes associated with cardiac hypertrophy

Sarcomeric genes associated with HCMP	Non-sarcomeric genes associated with HCMP	Genes associated with diseases expressing HCMP phenotype
MHY-7 (β-Myosin heavy chain 7)	CSRP3 (Cysteine and glycine rich protein 3)	PRKAG2 (Protein kinase AMP-activated non- catalytic subunit γ 2)
MYBPC-3 (Myosin-binding protein C3)	FHL1 (Four and half LIM domains protein 1)	GAA (α- glucosidase)
TPM1 (α-Tropomyosin 1)	FLNC (Flamin C)	GLA (Galactosidase α)
TNNI3 (Cardiac troponin I3)	FHOD3 (Formin Homology 2 domain containing 3)	LAMP2 (Lysosomal associated membrane protein 2)
TNNT2 (Cardiac troponin T2)	JPH2 (Junctophilin 2)	TTR (Transthyretin)
ACTC1 (Cardiac α-actin 1)	PLN (Phospholamban)	mtDNA (Mitochondrial DNA)
MYL2 (Myosin light chain 2)	TRIM63 (Tripartite motif containin 63)	FRDA (Fragile X)
MYL3 (Myosin light chain 3)	KLHL24 (Kelch like family member 24)	DMPK (Myotonic dystrophy protein kinase 1)
MYOZ2 (Myozenin 2/Calcium 1)		ZNF9 (Zinc finger factor 9)
TCAP (Tcap/Telethonin)		PTPN11 (Protein tyrosine phosphatase non-receptor type 11)
TNN (Titin)		SOS1 and SOS2 (SOS Ras/Rac guanine nucleotide exchange factor 1 ve 2)
ACTN2 (Actinin α2)		RAF1 (RAF proto-oncogene, serine/threonine kinase)
ANKRD1 (Ankyrin repeat domain 1)		KRAS (Ki-ras2 Kirsten mouse sarcoma viral oncogene homologue)
CASQ2 (Calsequestrin 2)		NPC1 (Niemann-Pick disease C1)
CAV3 (Caveolin 3)		PAHX (PHYH) (Phytanoyl-CoA α-hydroxylase)
LDB3 (LIM domain-binding protein)		MYO6 (Myosine VI)
MYH6 (Myosin heavy chain α)		
MYLK2 (Myosin light chain kinase 2)		
NEXN (Nexilin)		
TNNC1 (Cardiac troponin C)		
VCL (Vinculin)		

Table 11. Different imaging modalities utilized to assess HCMP

	TTE	Contrast Echo	TEE	CMR
LV Wall thickness	++	+++	+	++++
LV systolic function	+++			++++
LV diastolic function	++++			
LVOTO	++++		+++	+++
Mitral valve structure and function	+++		++++	++
Apical aneurysm	++	+++		++++
LA dimensions	++++			++++
Papillary muscle anomalies	++	+++	++	++++
Myocardial fibrosis	GLS			++++

(+) indicates the applicability and benefit rate of the technique in the detection of existing pathology. CMR, cardiac magnetic resonance imaging; GLS, global longitudinal strain; LA, left atrium; LV, left ventricle; LVOTO, left ventricular outflow tract obstruction; TEE, transesophageal echocardiography, TTE, transthoracic echocardiography.

Along with genetic differences, HCM presents with varying clinical and morphological profiles.^{13,183,189} Patients can be asymptomatic or may have advanced heart failure requiring heart transplantation. Picture 1 summarizes the different clinical morphologies of HCM and their characteristics. Although patients can present in any of these clinical scenarios, some may have overlapping features, and their presentation may change over time.^{13,189} While data on the relationship between genetic differences and clinical or morphological presentations remain inconclusive, some studies have identified specific characteristics in certain patient groups.^{1,183,186–188} s-HCM patients tend to be diagnosed at a younger age than nons-HCM patients, and nearly all have a family history suggestive of clinical clues.^{186,187} In s-HCM patients, wall thickness generally exceeds 20 mm, showing a reverse curvature morphology in the septum, and left ventricular outflow tract obstruction (LVOTO) is less common.^{186–188} In contrast, nons-HCM patients are generally older, with a rare family history, and systemic diseases like obesity or hypertension are more prevalent.^{186,188} These patients often exhibit apical or basal septal hypertrophy, and a significant proportion have severe LVOTO.^{183,186} Cardiac fibrosis is more prominent in s-HCM (often evident on cardiac magnetic resonance imaging [CMR]), and the prognosis for these patients is worse than for nons-HCM patients.^{1,183,186,187} Cardiac imaging is crucial for diagnosing HCM patients, and various imaging techniques are employed for both diagnosis and follow-up (Table 11). Echocardiography is a commonly used, non-invasive, cost-effective, radiation-free, and easily accessible imaging method for evaluating HCM patients. It helps determine diagnostic features such as wall thickness, LV function, and left atrium (LA) size, and also aids in identifying the location and mechanisms of LV obstruction. Additionally, it guides treatment and reveals prognostic features such as the presence of an apical aneurysm. Current guidelines recommend that patients with suspected HCM be evaluated using transthoracic echocardiography (TTE) (Table 12).^{1,183} Baseline CMR is advised during the initial examination of patients where TTE indicates HCM.¹ Additionally, provocation tests are recommended for patients with a resting LVOT gradient of less than 50 mm Hg. Exercise echocardiography is also indicated for symptomatic patients who do not show a gradient increase with provocation.^{1,183,190} Transesophageal

echocardiography (TEE) is recommended for some patients with HCM in whom the mechanism of LVOTO is uncertain, where severe mitral regurgitation (MR) due to intrinsic valve abnormalities is suspected, or where evaluation of the mitral valve (MV) apparatus is necessary before septal reduction procedures.¹ In clinically stable HCM patients, echocardiography should be re-examined every 1–2 years to assess hypertrophy, obstruction, and changes in cardiac function, or whenever new clinically significant symptoms develop.^{1,183} This review summarizes key clues and practical points in echocardiographic imaging of s-HCM patients.

Ventricular Wall Thickness Measurement in Patients with HCM

The diagnostic criteria for HCM include the presence of a wall thickness ≥ 15 mm in any left ventricular (LV) segment.^{1,183,190} For individuals with a family history of HCM or known disease-causing gene mutations, and in those with electrocardiographic abnormalities along with dynamic LVOT obstruction, a wall thickness ≥ 13 mm is also considered diagnostic.^{1,183,184} Thus, measuring wall thickness is crucial for HCM patients. Wall thickness measurement is typically performed using two-dimensional (2D) imaging in the parasternal long axis (PLAX) at the end of diastole.^{3,190,191} It's important to ensure that papillary muscles and right ventricular (RV) structures are excluded from the measurement.^{3,190} Parasternal short axis (PSAX), bi-plane/x-plane measurements, or contrast echocardiography can be used to verify measurement accuracy.^{190,191} (Figure 36A). Using PSAX imaging, basal, mid, and apical measurements are crucial for determining actual wall thickness and localized hypertrophy. The most typical pattern of hypertrophy in s-HCM is pronounced septal hypertrophy with a reverse septal curvature.^{1,186,13} Other morphologies include focal asymmetric hypertrophy of the basal anterior septum, a sigmoid septum, and concentric or focal mid-wall LV hypertrophy (Figure 37).^{183,13} The location, morphology, and size of the hypertrophy should be described in detail.^{13,190,191} Enhanced RV thickness is rarely observed in HCM patients.^{1,13,183,190} The thickness of the RV free wall is measured at the level where the tricuspid leaflet contacts the RV wall at the end of diastole on subcostal zoomed images (Figure 36B).^{3,190,191} It's known that TTE tends to overestimate wall thickness, even when following the guidelines for measuring wall thickness in HCM patients.^{1,183} Therefore, in HCM patients, it's essential to measure wall thickness

Table 12. Current recommendations for transthoracic echocardiographic evaluation in hypertrophic cardiomyopathy	
2014– 2023 ESC	2020 AHA
In every HCM patient transthoracic 2D and Doppler echocardiography are advised at the first assessment, both at rest and during the Valsalva maneuver in the sitting and semi-supine positions–and on standing if no gradient is elicited. (LEVEL OF EVIDENCE B)	In patients with suspected HCM, a TTE is recommended in the initial evaluation. (LEVEL OF EVIDENCE B–NR)
It is recommended to measure the maximal diastolic wall thickness in each LV segment, from base to apex, using 2D short-axis images. (LEVEL OF EVIDENCE C)	In patients with HCM with no change in clinical status or events, repeat TTE is recommended every 1 to 2 years to assess the degree of myocardial hypertrophy, dynamic LVOTO, MR, and myocardial function. (LEVEL OF EVIDENCE B–LD)
It is recommended to do a comprehensive evaluation of the diastolic function of the left ventricle (LV), which should include measurements of the size and volume of the left atrium, pulsed Doppler of mitral valve inflow, tissue Doppler velocities at the mitral annulus, pulmonary vein flow velocities, and pulmonary artery systolic pressure. (LEVEL OF EVIDENCE C)	For patients with HCM who experience a change in clinical status or a new clinical event, repeat TTE is recommended. (LEVEL OF EVIDENCE B–NR)
To identify provokable LVOTO and exercise-induced mitral regurgitation in symptomatic patients with a resting or provoked peak instantaneous LV outflow tract gradient <50 mm Hg, 2D and Doppler echocardiography in the standing, sitting, or semi-supine position is recommended during exercise. (LEVEL OF EVIDENCE B)	For patients with HCM and resting LVOT gradient <50 mm Hg, a TTE with provocative maneuvers is recommended. (LEVEL OF EVIDENCE B–NR)
In patients with sub-optimal images or with suspected LV apical hypertrophy or aneurysm, TTE with LV cavity opacification–using intravenous echocardiographic contrast agents–should be considered as an alternative to CMR imaging. (LEVEL OF EVIDENCE C)	For symptomatic patients with HCM who do not have a resting or provokable outflow tract gradient ≥50 mm Hg on TTE, exercise TTE is recommended for the detection and quantification of dynamic LVOTO. (LEVEL OF EVIDENCE B–NR)
	For asymptomatic patients with HCM who do not have a resting or provokable outflow tract gradient ≥50 mm Hg on standard TTE, exercise TTE is reasonable for the detection and quantification of dynamic LVOTO. (LEVEL OF EVIDENCE C–LD)
Perioperative TEE is recommended in patients undergoing septal myectomy, to confirm the mechanism of LVOTO, to guide the surgical strategy, to assess post-surgical complications and to detect residual LV outflow tract obstruction. (LEVEL OF EVIDENCE C)	For patients with HCM undergoing surgical septal myectomy, intraoperative TEE is recommended to assess mitral valve anatomy and function and adequacy of septal myectomy. (LEVEL OF EVIDENCE B–NR)
	For patients with HCM, TEE can be useful if TTE is inconclusive in clinical decision-making regarding medical therapy, and in situations such as planning for myectomy, exclusion of subaortic membrane or MR secondary to structural abnormalities of the mitral valve apparatus, or in the assessment of the feasibility of alcohol septal ablation. (LEVEL OF EVIDENCE C–LD)
Transoesophageal echocardiography should be considered in patients with HCM and LVOTO if the mechanism of obstruction is unclear or when assessing the mitral valve apparatus before a septal reduction procedure, or when severe mitral regurgitation caused by intrinsic valve abnormalities is suspected. (LEVEL OF EVIDENCE C)	For patients with HCM in whom the diagnoses of apical HCM, apical aneurysm, or atypical patterns of hypertrophy is inconclusive on TTE, the use of an intravenous ultrasound enhancing agent is reasonable, particularly if other imaging modalities such as CMR are not readily available or contraindicated. (LEVEL OF EVIDENCE B–NR)
CMR, cardiac magnetic resonance imaging; HCM, hypertrophic cardiomyopathy; LA, left atrium; LVOTO, left ventricular outflow tract obstruction; LV, left ventricle; MR, mitral regurgitation; TEE, transoesophageal echocardiography TTE, transthoracic echocardiography. Green lines class I recommendation, Yellow lines class IIa recommendation.	

using baseline CMR and to follow up with TTE over the same regions identified on CMR.

Evaluation of Left Ventricular Outflow Tract Gradient

Left ventricular outflow tract (LVOT) obstruction occurs at rest in approximately one-third of HCM patients and with provocation in another third.^{1,183,190,192} An LVOT gradient ≥30 mm Hg at rest is

considered significant for obstruction. These patients are usually symptomatic and have an increased risk of sudden death (SD).^{1,183} Moreover, symptomatic patients with an LVOT gradient ≥50 mm Hg at rest or with provocation, despite maximal tolerable medication, are candidates for septal reduction therapy.^{1,183} The location and mechanism of obstruction are crucial in selecting the appropriate treatment modality. Obstruction

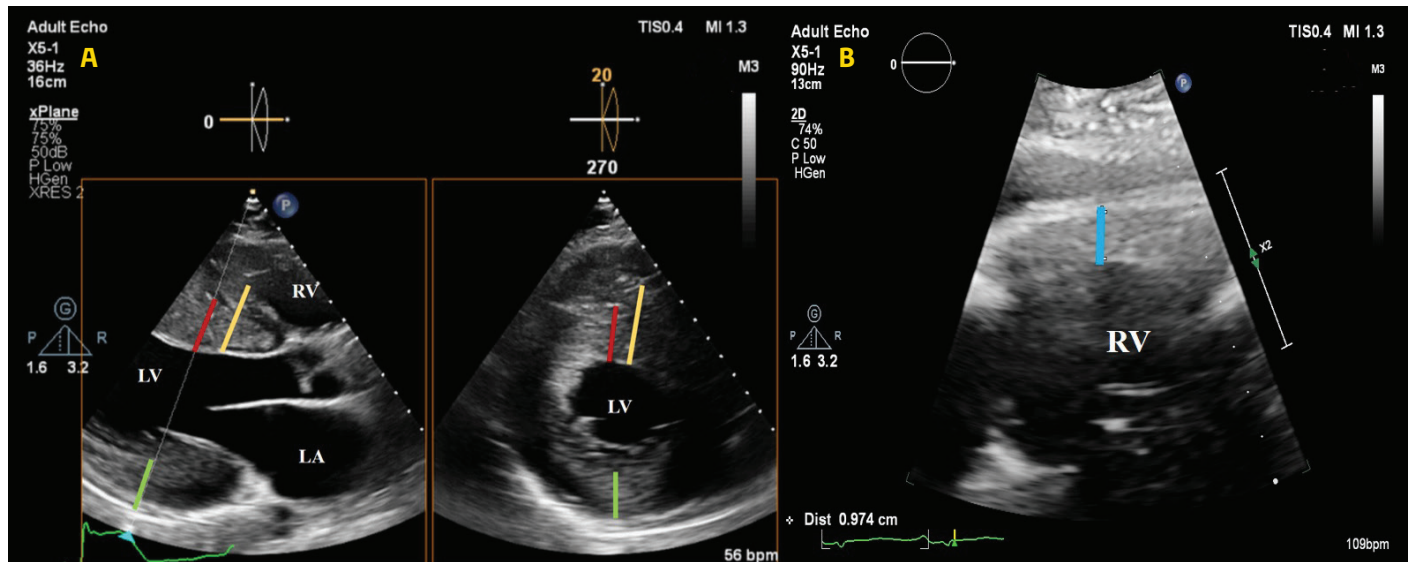


Figure 36. Evaluation of ventricular wall thickness on TTE in a patient with HCMP (TTE images of a 38-year-old male patient with a pathogenic variant in MYBPC3 gene) (A) Parasternal x-plane imaging, right panel PLAX, left panel PSAX. Red line, correct measurement of septal thickness. Yellow line, incorrect septal wall measurement including right ventricular structures. Green line, correct measurement of the posterior wall. (B) Subcostal zoom image. Blue line, RV wall thickness measurement in diastole from the point where the tricuspid leaflet reaches the right ventricular free wall. LA, left atrium; RV, right ventricle; LV, left ventricle.

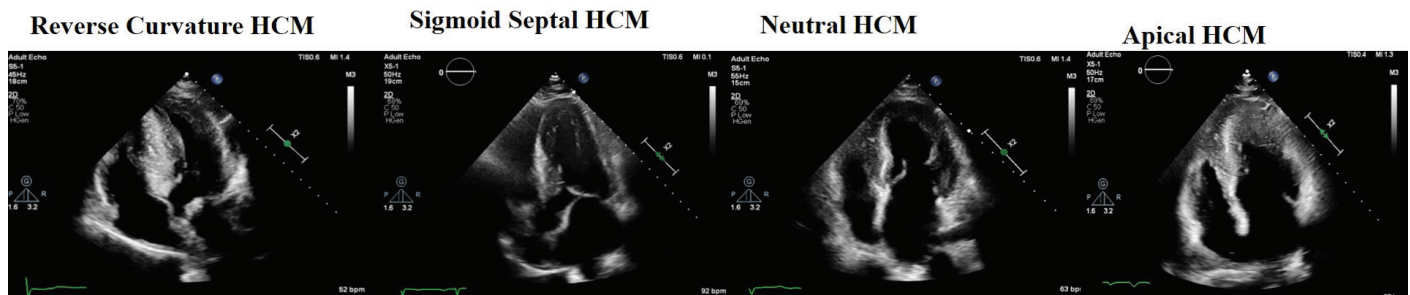
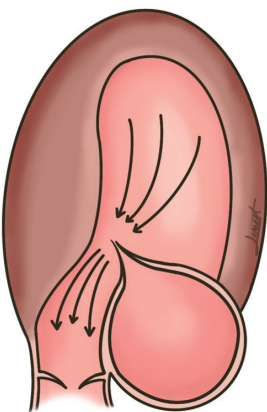


Figure 37. Common HCM phenotypes.



Organic substrates

- Septal hypertrophy
- Forward position of the mitral leaflets
- Extended, anteriorly positioned, abnormally adhered chordae tendinae
- Papillary muscle adhesion and insertion abnormalities

Figure 38. Anatomical alterations in the LV generate new hydrodynamic flow forces and trigger systolic forward motion.

typically occurs in the LVOT and, less frequently, in the mid-ventricle or apex.^{183,190} LVOT obstruction develops through various mechanisms and exhibits a dynamic pattern influenced

by afterload, preload, and LV contractility.^{1,190} The primary mechanism of LVOT obstruction is septal hypertrophy.^{190,193} However, other causative and contributing mechanisms include systolic anterior motion (SAM) of the MV, elongated or tethered chordae tendinae, and abnormalities in papillary muscle attachment and placement (Figure 38).^{1,183,193}

SAM is commonly assessed using M-mode, apical three-chamber (3C) or five-chamber (5C), parasternal short-axis (PSAX), and parasternal long-axis (PLAX) images (Video 1).^{3,190,191} In patients with unclear images on TTE, mid-esophageal long-axis or transgastric windows on TEE should be used (Video 2).^{3,190} The degree of SAM is classified based on the distance and contact time of the mitral leaflets to the septum during systole. SAM is considered severe if the mitral leaflet contacts the septum for $\geq 30\%$ of the systolic time.^{190,194} If the systolic distance between the mitral leaflet and septum is >1 cm, SAM severity is considered mild.¹⁹⁰ The first clue for assessing ventricular obstruction is turbulent flow on color Doppler in the PLAX, 3C, or 5C views.^{183,190,195} Subsequently, using pulse-wave (PW) Doppler at the site of turbulent flow, the actual location of obstruction

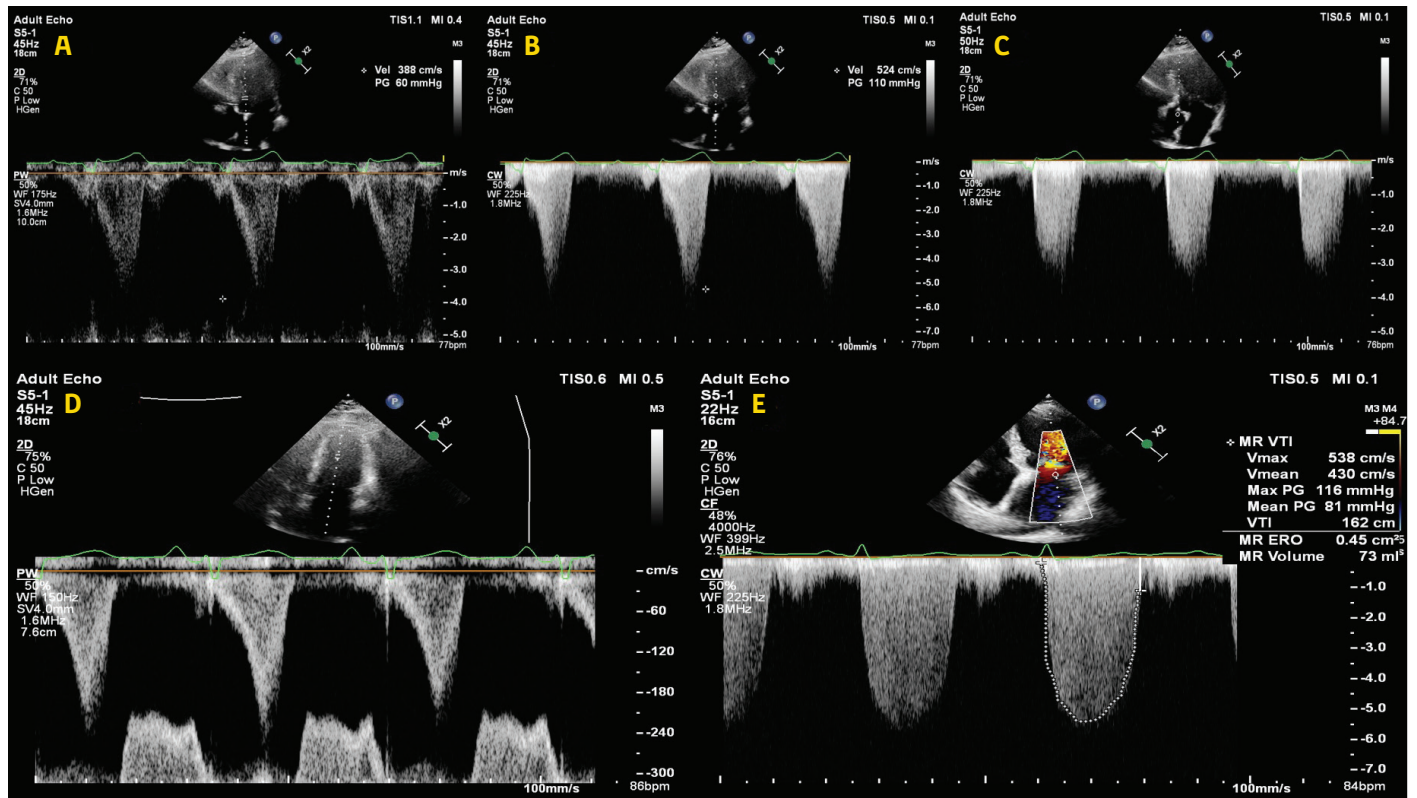


Figure 39. Evaluation of LVOTO. A-B-C Evaluation of LVOTO and aortic gradient with PW and CW doppler in a patient with SAM and bicuspid aortic stenosis. The LVOT gradient increases slowly in early systole, increases abruptly and peaks in mid-late systole, showing a 'dagger- shape' appearance (A and B), whereas the aortic stenosis gradient usually reaches its peak velocity in mid-systole (C). In a patient with mid-ventricular obstruction, the localisation of the obstruction should be determined by PW doppler (D). The mitral regurgitation jet peaks earlier, is more rounded and the peak velocity is usually $>5-6$ m/s, unlike the LVOT gradient (E).

(LVOT, apical, or mid-ventricular) is determined.^{183,190,194,195} Continuous-wave (CW) Doppler is then used to measure the peak gradient at the LVOT or obstruction site.^{183,190,194,195} In cases with concomitant aortic stenosis (AS) and MR, differentiating the LVOT gradient using CW Doppler is challenging. In such cases, the high pulse repetition frequency (PRF) feature of echocardiography helps determine the LVOT gradient using PW Doppler.^{190,195} Additionally, CW Doppler often reveals a distinctive 'dagger-shaped' appearance that distinguishes the LVOT gradient from AS and MR flow. To prevent contamination from MR in the CW Doppler examination, the probe should be shifted as far laterally as possible in the apical views, and Doppler flow should be obtained from the distal LA (Figure 39A-E).^{190,195}

Due to the dynamic nature of LVOT obstruction, patients without LVOTO at rest should be subjected to provocation using the Valsalva maneuver, squatting-to-standing, or inhalation of amyl nitrite.^{1,190,195} For an effective Valsalva maneuver, a minimum duration of 10 seconds is required (Figure 40A-B).¹⁹⁰ For squatting-to-standing to be effective, the patient should stand up approximately 3 seconds after squatting and repeat the cycle 5-6 times.^{190,195} Amyl nitrite, an inhaled vasodilator, necessitates rapid assessment a few minutes after inhalation. During all these maneuvers, the peak LVOT gradient should be measured using continuous-wave (CW) Doppler from 3C or 5C views.^{190,195} In symptomatic patients without LVOTO during

provocative tests, exercise echocardiography is recommended with a Class I indication.¹⁸³ Exercise echocardiography has been shown to be more sensitive than provocative tests in detecting labile obstruction.¹⁹⁶ The LVOT gradient, SAM, severity of MR, and estimated pulmonary artery systolic pressure should be recorded both before the exercise test and after maximal exercise.^{190,195} Assessing the response of HCM patients to medical therapy is important, so it is recommended that exercise testing be performed while patients are under medication (e.g., beta-blockers, calcium channel blockers).¹⁹⁰ Since symptoms in a significant portion of patients are triggered by meals, it is preferable not to conduct the test on an empty stomach.^{190,195}

Evaluation of Mitral Regurgitation

MR is an unfavorable prognostic factor in patients with HCM.^{1,183,197} In HCM patients, the most common mechanism of MR is SAM of the mitral anterior leaflet, which is associated with LVOTO (Figure 41A and Video 3).^{1,189,198} Approximately 10-20% of patients without LVOTO have MR that is not associated with SAM, primarily involving the mitral valve apparatus and related structures. This form of MR is classified as primary MR (Figure 41B-C).¹⁹⁸ Primary MR associated with MV anomalies is more common in obstructive s-HCM.¹⁹⁹ SAM results from LVH and the Venturi effect of elongated MV leaflets.¹⁹⁰ Because the anterior leaflet is usually pulled forward more prominently than the posterior leaflet, a gap occurs between the two leaflets during systole.^{194,195} As a result,

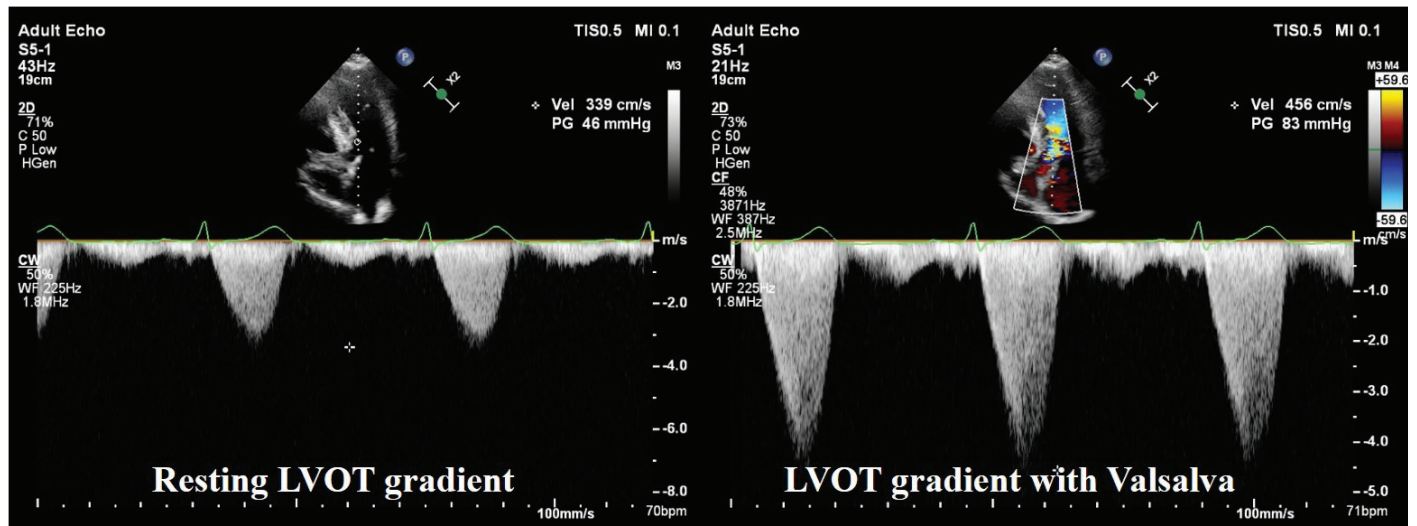


Figure 40. Evaluation of LVOTO at rest and after provocation.

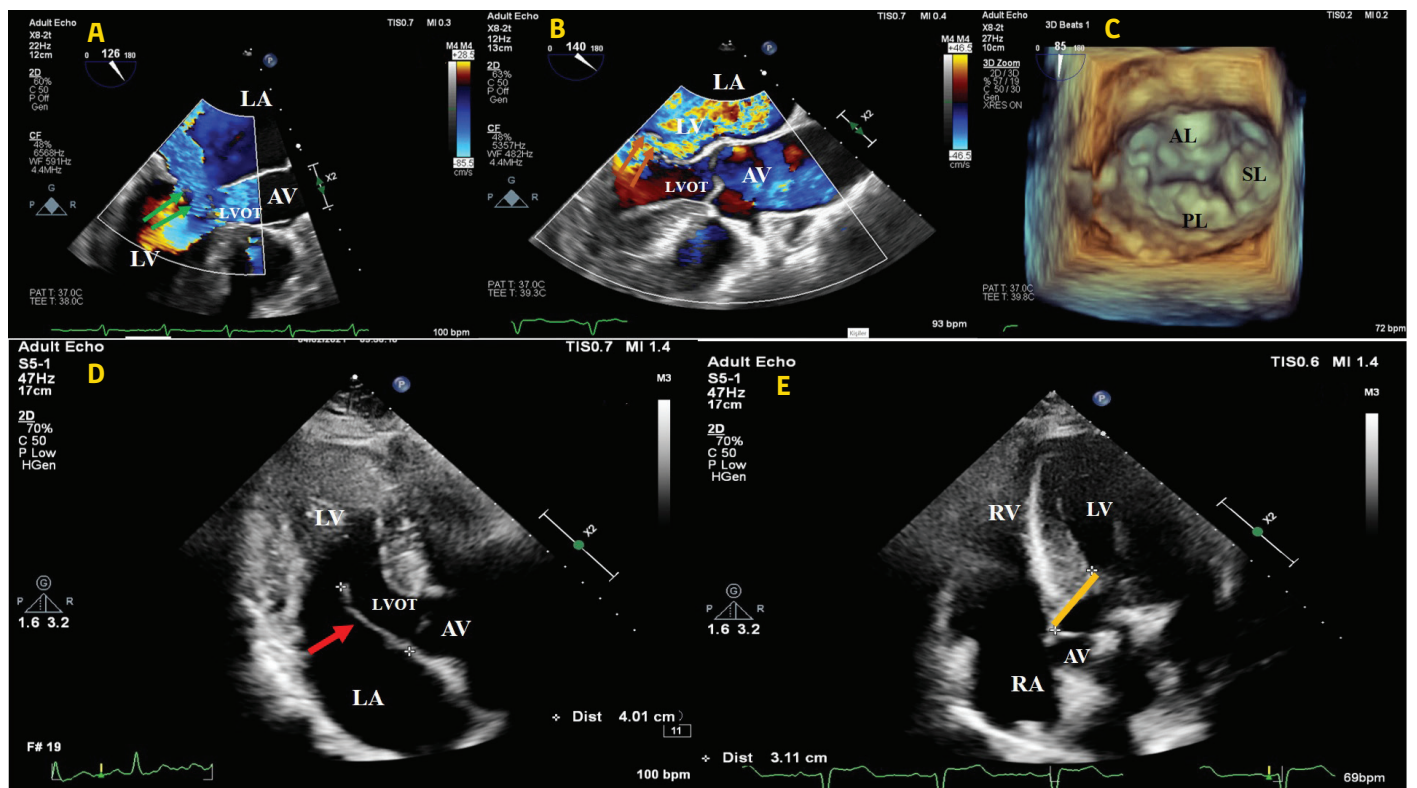


Figure 41. Mechanism of mitral regurgitation in patients with HCM. (A) Late systolic posterior eccentric MR jet associated with SAM (green arrows). (B) Anterior eccentric MR jet associated with concomitant P2 rupture in a sHCM patient with concentric hypertrophy (orange arrows). (C) sHCM patient with three separate mitral leaflets on 3D TEE. (D) Elongated anterior leaflet on apical 3C imaging (Red arrow). (E) Measurement of the distance between the aortic annulus and the SAM point on apical 5C imaging –favorable area for resection (Yellow line).

AV, aortic valve; AL, anterior leaflet; LA, left atrium; LV, left ventricle; LVOT, left ventricular outflow tract; PL, posterior leaflet; RA, right atrium; RV, right ventricle; SL, septal leaflet

SAM-associated MR typically occurs in mid-to-late systole with a predominantly posterior eccentric pattern (Figure 41A, Video 3).^{190,194,195} An anterior or central MR jet warrants evaluation for primary MV pathology (Figure 41B).^{194,197,199} Non-SAM-associated MR in HCM patients can be attributed to elongated

MV leaflets, MV prolapse, MV clefts, leaflet restriction due to calcification and thickening, chordal rupture, papillary muscle placement and attachment anomalies, and abnormalities in the MV annulus diameter, shape, and angle.^{195,197,199} TTE and TEE are recommended for evaluating the mechanism and severity of MR

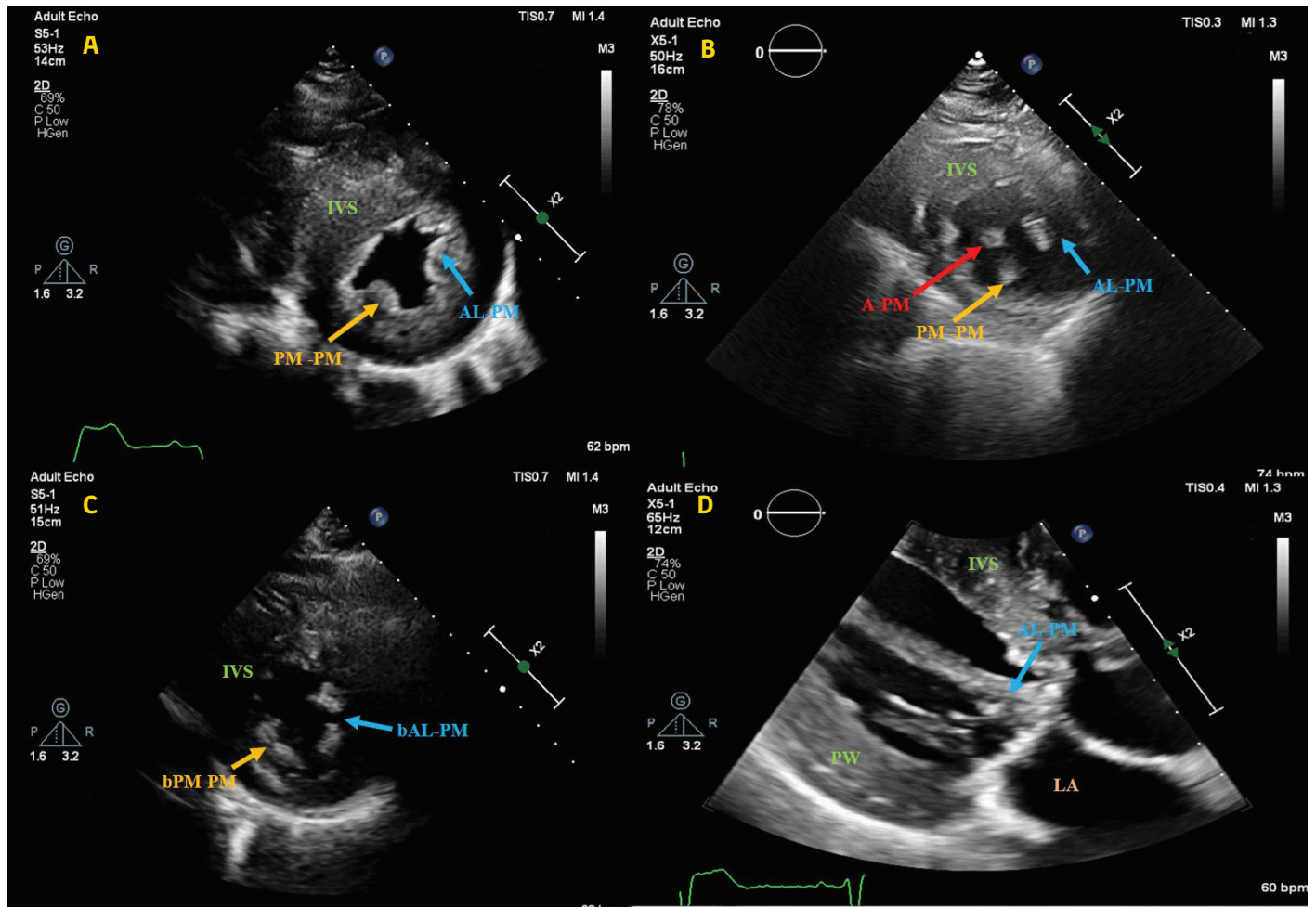


Figure 42. Papillary muscle anomalies (A) Antero-lateral and posteromedial papillary muscle hypertrophy (B) Accessory papillary muscle (red arrow) (C) Double-bifid papillary muscles (PSAX apical level) (D) Abnormal direct insertion of the anterolateral papillary muscle to the basal anterior mitral leaflet (blue arrow) without intervening chordae tendinae.

A-PM, accessory papillary muscle; **AL-PM**, anterolateral papillary muscle; **bAL-PM**, bifid antero-lateral papillary muscle; **bPM-PM**, bifid posteromedial papillary muscle; **IVS**, interventricular septum; **LA**, left atrium **PM-PM**, posteromedial papillary muscle; **PW**, posterior wall.

in HCM patients.^{190,195} In particular, TEE is crucial for determining intrinsic MV pathology in patients with anterior and central MR. To assess MR severity, a combination of 2D and 3D qualitative, semi-quantitative, and quantitative methods is recommended.^{191,195,200} In this patient group, where an eccentric MR jet is often present, caution should be exercised when using the proximal isovelocity surface area (PISA) method for quantitative assessment, as it may lead to incorrect estimation of MR severity.²⁰⁰ Instead, determining the degree of regurgitation using the 3D vena contracta area is the preferred method.^{195,200} Another important consideration is intervention for MR in patients undergoing septal myectomy. Before surgery, the mechanism of MR should be clearly determined using TTE and/or TEE. The distance between the mitral anterior leaflet and the septum causing obstruction, as well as leaflet lengths, should also be measured.¹⁹⁵ Leaflet lengths are most accurately measured through the apical 3C window (120–140°) using TTE (Figure 41D–E). In cases of SAM-associated MR, routine MV intervention is not recommended during septal myectomy because MR often regresses postoperatively in these patients.^{1,183,200} However, since multiple mechanisms, such as

annular dilation and mitral chordal anomalies, can accompany SAM, intraoperative TEE for evaluating residual MR is crucial during septal myectomy.^{190,195}

Evaluation of Papillary Muscle Anomalies

Echocardiography and CMR studies have shown that papillary muscle anomalies are more frequent in patients with HCM compared to normal individuals.^{195,201,202} More than half of patients with HCM have some form of papillary muscle anomaly.^{201–203} Some of these anomalies contribute to SAM and LVOTO.^{190,193,195} In HCM patients, papillary muscle anomalies can result from primary genetic abnormalities or arise secondary to physiological effects, such as papillary muscle hypertrophy and malposition.^{195,201,202} The commonly observed papillary muscle anomalies in HCM patients include:

a) Papillary Muscle Hypertrophy (Figure 42A): It is isolated or accompanied by septal and posterior wall hypertrophy. It is one of the causes of LVOTO or mid-ventricular obstruction. Late gadolinium enhancement on CMR is frequently present in these patients.^{183,190,201}

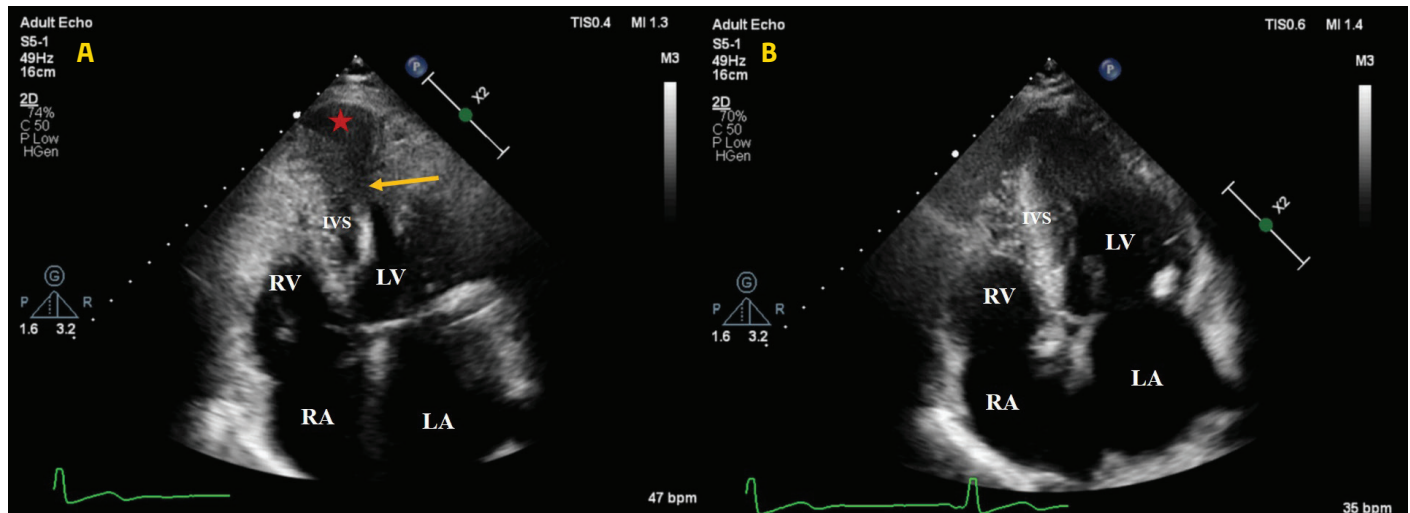


Figure 43. Apical aneurysm. (A) Concomitant apical aneurysm (Red asterisk) in a sHCM patient with mid-ventricular obstruction (yellow arrow) (B) Apical 4C image of the same patient visualized with foreshortening. The apex appears hypertrophic and the apical aneurysm is not visible.

IVS, inter ventricular septum; LA, left atrium; LV, left ventricle; RA, right atrium; RV, right ventricle.

b) Papillary Muscle Number Anomalies: HCM patients typically have more papillary muscles than other individuals. More than half of the patients have ≥ 3 papillary muscle heads. This anomaly may present as an isolated accessory papillary muscle or as a bifid anterolateral or posteromedial papillary muscle. Accessory papillary muscle (Figure 42B) is often detected as a single muscle band extending from the LV apex to the basal antero-septum or anterior wall. It generally does not cause LVOTO. Frequently observed in HCM patients, it serves as an important clue when screening family members. Bifid papillary muscle (Figure 42C) is often observed as double bifid involving both papillary muscles. In contrast to the accessory papillary muscle, SAM and LVOTO are usually present in HCM patients with bifid papillary muscle anomalies.^{195,202,203}

c) Papillary Muscle Insertion and Attachment Anomalies: The apical and anterior location of the anterolateral papillary muscle is the most common papillary muscle insertion anomaly. It causes elongation of the mitral leaflets and leads to SAM and LVOTO independently of septal hypertrophy. Papillary muscle tips may attach to the anterior or posterior leaflet, LV free wall, or septum without chordal structures. Direct attachment of the anterolateral papillary muscle to the anterior mitral leaflet (Figure 42C) is the best-known and most serious attachment anomaly. It creates a fixed obstruction in the LV cavity and leads to LVOTO, unlike classical SAM-related LVOTO.^{195,201-203}

Papillary muscle anomalies are best visualized using TTE in apical 2C, 3C, 4C, and PSAX apical views.^{190,195} In most patients, pathology can be differentiated from non-standard axis, modified images. Mid-esophageal TEE windows can be particularly helpful in distinguishing papillary muscle attachment anomalies and associated MV pathologies.^{3,190,191,204} Additionally, transgastric windows offer a good alternative for detecting papillary muscle number and localization anomalies.²⁰⁴ CMR is recommended for patients with inadequate or unclear TTE images when papillary muscle anomalies are suspected.^{13,195} Identifying the underlying papillary muscle anomaly is crucial in determining the appropriate

treatment method and assessing the benefit of treatment in patients scheduled for septal reduction therapy.

In cases where an abnormal papillary muscle is directly attached to the anterior leaflet, isolated myectomy alone is insufficient. The abnormally attached papillary muscle head must also be resected. Therefore, imaging reports for patients with HCM should include detailed information about the size, location, structure, and contribution of papillary muscles to LVOTO.

LV aneurysm is identified in approximately 5% of patients with HCM without critical coronary artery disease, most commonly located in the apical region.²⁰⁵ It typically appears as swelling or bulging of the weakened and thinned LV myocardium (Figure 43A, Video 4).^{189,205} No specific genetic mutation has been reported in these patients.¹⁸⁷ The development of aneurysms in these patients is attributed to mid-ventricular obstruction, apical hypertrophy, small vessel disease, myocardial bridging, and coronary spasm.^{206,207} A combination of these mechanisms leads to myocardial scarring and subsequent aneurysm formation due to a mismatch in oxygen supply and demand.²⁰⁵⁻²⁰⁷ Apical aneurysms range in size from 1-2 cm up to 6 cm.²⁰⁸ They rarely enlarge during follow-up and generally do not carry a significant risk of rupture.^{207,208} Current guidelines classify patients with apical aneurysms in HCM as being at high risk for sudden cardiac death (SCD).^{1,183} Additionally, anticoagulant therapy is recommended for patients with thrombus detected in the aneurysm area due to the increased risk of thrombus formation.^{1,183}

Echocardiography is crucial in the evaluation of apical aneurysms. In patients with mid-ventricular obstruction or apical hypertrophy, the apex should be carefully visualized using TTE.¹⁹⁰ Apical aneurysms in these patients are generally imaged from apical windows (Figure 43A). However, if the ultrasound beams are not perpendicular to the true apex of the left ventricle and instead pass above and anterior to the true apex, apical pathologies may not be visible, resulting in apical foreshortening. This common error during routine examinations can lead to missed diagnoses

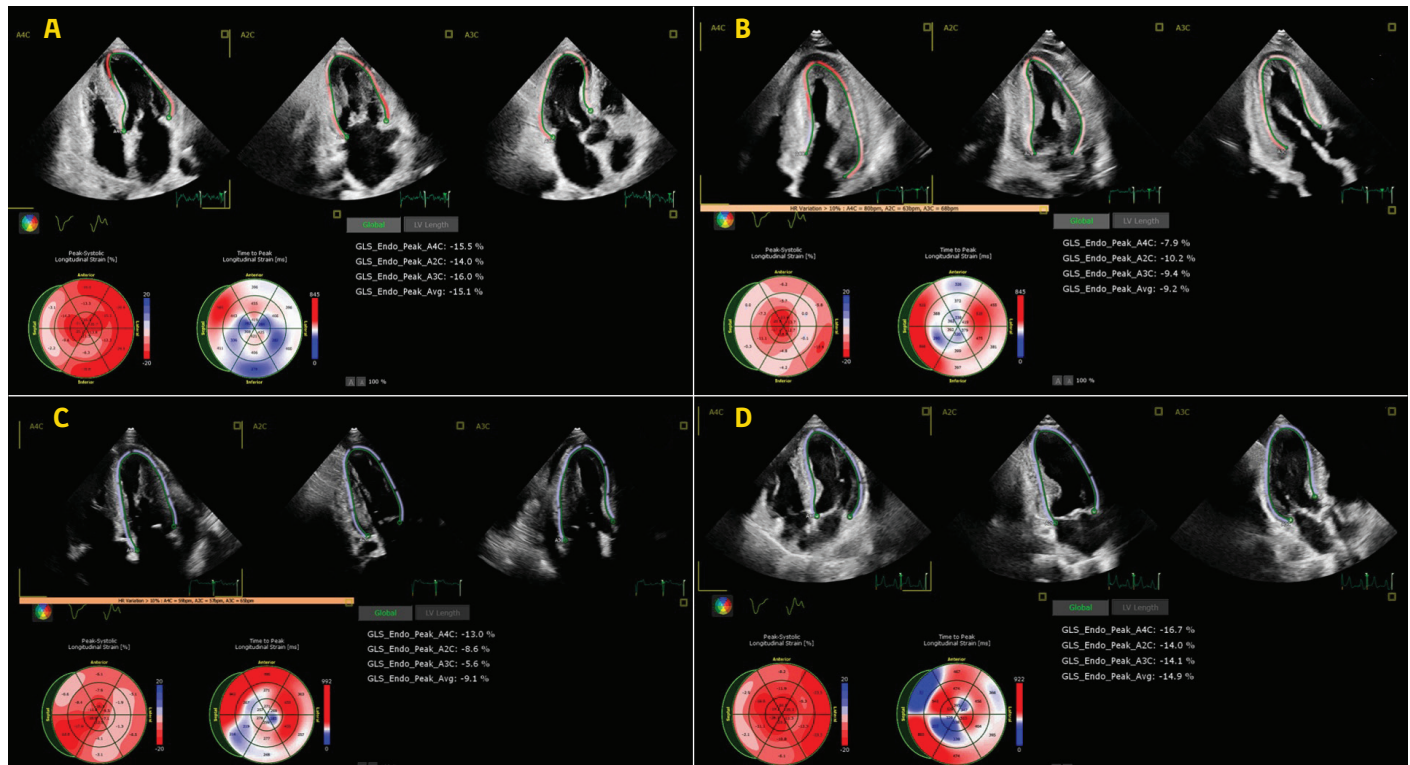


Figure 44. Specific GLS patterns in different diseases with cardiac hypertrophy. (A) sHCM patient with obvious septal involvement (B) Cardiac amyloidosis patient with apical sparing (C) Advanced Fabry patient with more prominent involvement of the basal lateral wall (D) Advanced aortic stenosis patient with patchy involvement.

of apical thrombus and aneurysm, resulting in an inaccurate calculation of EF (Figure 43B). To prevent foreshortening, the transducer should be moved more apically and laterally.^{190,195} In patients where a clear conclusion cannot be reached with TTE, contrast echocardiography may provide better visualization of the apical region and is recommended by guidelines for these patients.^{1,190,195} If TTE and contrast echocardiography images are inadequate, CMR imaging is recommended for assessing apical aneurysms and thrombi.^{1,183,195} Studies have shown that CMR is more sensitive than echocardiography in detecting apical aneurysms and thrombi in patients with HCM.^{206,209} Contrast echocardiography reveal better results in the evaluation of the LV apex in patients in whom TTE does not yield a clear diagnosis and is recommended by guidelines in these patients.^{1,190,195} If TTE and contrast echocardiography images are insufficient, evaluation with CMR is recommended.^{183,1,195} CMR has been shown to be more sensitive than echocardiography in detecting apical aneurysm and thrombus in patients with HCM.^{206,209}

Evaluation of Left Ventricular Systolic Function

The determinants of changes in systolic function in patients with HCM are LVH and fibrosis.^{190,195,210} Due to LV remodeling, global or regional abnormalities in systolic function are observed.^{195,210} As wall thickness increases, the stroke volume index decreases in patients with normal/supra-normal left ventricular ejection fraction (LVEF), primarily due to a narrowing of the LV cavity.²¹⁰ When the EF is less than 50%, overt cardiac dysfunction is present, and these patients are at high risk for adverse events.^{183,193,210} To determine EF, measurement using 3D TEE is

recommended if available.^{3,190,195} If 3D TEE is not an option, the 2D bi-plane disk method, another quantitative approach, should be used.^{190,191,195} For accurate measurements, it's important to obtain clear four-chamber (4C) and two-chamber (2C) images where myocardial borders are well defined. Images should be obtained without foreshortening and with clearly distinguishable LV myocardial borders in both systole and diastole.^{3,190,191} In some patients, obtaining clear images in systole and diastole may be challenging due to hypertrophy. In such cases, using a breath-holding maneuver while recording images can be effective.^{3,191} Selecting cycles with clear myocardial borders from recorded images ensures accurate EF measurement.

In patients with HCM, a decrease in EF is known to occur in the advanced stages of the disease.^{1,183,185} Therefore, different methods have been investigated to detect early deterioration in systolic function. Tissue Doppler myocardial imaging and 2D/3D speckle tracking echocardiography are among the most studied methods in this patient group.^{190,195} Reports indicate that decreased lateral annulus systolic velocity ($s' < 4$ cm/s) on tissue Doppler imaging may serve as an early sign of systolic dysfunction and a useful prognostic marker in these patients.^{211,212} Evaluation of volumetric LV systolic function is completed using 2D/3D speckle tracking methods, including global longitudinal strain (GLS) and circumferential strain (CSS) imaging.^{190,195} Studies have shown that GLS decreases in hypertrophic and fibrotic areas in HCM patients.^{213,214} GLS also serves as a discriminative marker for diagnosing hypertrophic diseases with specific involvement (Figure 44A-D). In HCM patients, decreased GLS values are

frequently observed at the basal levels and in the interventricular septum.^{195,213,214} Even in patients with preserved EF, GLS values below -16% have been associated with adverse outcomes.²¹⁵ Furthermore, 3D strain imaging has revealed that global circumferential strain (GSS) is reduced in hypertrophic areas but increased in non-hypertrophic regions in HCM patients.²¹⁴⁻²¹⁶ Increased endocardial GSS accompanying decreased epicardial and mid-wall GSS has also been reported.²¹⁶ Strain imaging should be acquired from apical 2C, 3C, and 4C windows, focusing on cycles where LV walls are clearly visualized.^{190,195} These advanced echocardiographic methods beyond EF assessment will play an important role in elucidating the physiological mechanisms in HCM patients and in the appropriate follow-up of genotype-positive, phenotype-negative patients.

In these patients, a detailed evaluation of diastolic functions along with systolic functions is recommended. According to current diastolic dysfunction guidelines, classification should be based on measurements of MV inflow velocities, tissue Doppler examination of the mitral lateral and septal annulus, pulmonary vein flow, estimated pulmonary artery pressure calculated from the tricuspid regurgitation jet, and LA volumetric values.¹⁵ LA diameter measurement is important in these patients due to its use in risk classification. LA anteroposterior diameter is included in the risk classification recommended by the European guidelines. LA anteroposterior diameter is measured from leading edge to leading edge in the 2D PLAX view, at the level of the sinus Valsalva, perpendicular to the long axis of the left atrium, at end-systole.¹ In all other cases, volumetric measurements of LA are recommended.^{3,191}

Conclusion

HCM is a complex congenital cardiomyopathy that exhibits diverse genotypes and phenotypes. Although s-HCM patients

are distinguished from nons-HCM patients by certain phenotypic features, basic imaging techniques and some imaging findings are similar in both groups. Echocardiography is the fundamental imaging method used at every step, from diagnosis to follow-up, prognosis determination, and treatment in patients with HCM. The major goals of echocardiographic examination are to identify prognostic indicators, distinguish HCM from other diseases with a hypertrophic phenotype, and understand the dynamically changing aspects of the disease. The primary focus of echocardiographic evaluation in these patients includes measurement of maximal wall thickness, assessment of the pathophysiology of mitral regurgitation, detection of apical aneurysm and papillary muscle abnormalities, identification of the location and degree of intraventricular obstruction, determination of systolic and diastolic functions. A comprehensive echocardiography report should contain the details required for these patients' diagnosis, medical and/or surgical treatment, and follow-up.

Acknowledgements: The echocardiographic images in the text are from the archive of the echocardiography laboratory of Başakşehir Çam and Sakura City Hospital. The image in Figure 42D is from the archive of Prof Dr Gamze Babür Güler and we thank her for her contribution. We would also like to thank Dr Levent Pay for his contribution to the drawing in Figure 38.'

Video 1. Evaluation of SAM from different TTE Windows

Video 2. Prominent SAM on mid-esophageal long axis TEE images

Video 3. PLAX colour doppler comparative imaging of mitral regurgitation associated with SAM

Video 4. Apical aneurysm in a sHKMP patient with mid-ventricular obstruction (apical 4C imaging)

Predictors of Sudden Cardiac Death in Sarcomeric Hypertrophic Cardiomyopathy: Utilization of Advanced Imaging Techniques Before and After Interventional Treatment

Predictors of Sudden Cardiac Death in Sarcomeric Hypertrophic Cardiomyopathy

Hypertrophic cardiomyopathy (HCM) is a genetic disorder inherited in an autosomal dominant manner, characterized by abnormal and asymmetric hypertrophy of the myocardium in the left ventricle.²¹⁷ Its prevalence is estimated to be between 1 in 500 and 1 in 200 in the general population.¹⁸⁹ Pathogenic single gene variants have been found in approximately 40–60% of individuals diagnosed with HCM through genetic testing. These variants are mostly situated in sarcomeric protein genes, with β -cardiac myosin (*MYH7*) and cardiac myosin-binding protein C (*MYBPC3*) being the most commonly affected.²¹⁸ However, mutations in other genes like cardiac troponin T (*TNNT2*), cardiac troponin I (*TNNI3*), α -tropomyosin (*TPM1*), cardiac α -actin (*ACTC1*), myosin light chain 2 (*MYL2*), and myosin light chain 3 (*MYL3*) may also be observed, though less frequently.²¹⁹

HCM stands as a prominent cause of sudden cardiac death (SCD) in young individuals and athletes. The annual incidence of SCD among adults with HCM is roughly 1%. Consequently, it is crucial to identify both the risk factors for SCD and individuals at high risk.^{220,221}

In 2011, the American Heart Association (AHA) devised an SCD risk calculator tool to evaluate the appropriateness of implanting an implantable cardioverter defibrillator (ICD) in HCM patients. This model factored in various elements, including a family history of SCD, recent instances of unexplained syncope, non-sustained ventricular tachycardia (NSVT), abnormal blood pressure responses during exercise, and maximal left ventricular wall thickness. Subsequently, in 2014, the European Society of Cardiology (ESC) introduced a similar risk calculator, which augmented the model with additional parameters such as age, left atrium diameter, and left ventricular outflow obstruction.^{222,223}

Lastly, the AHA guideline of 2020 identified left ventricular systolic dysfunction, the presence of a left ventricular apical aneurysm, and diffuse late gadolinium uptake (LGE) on cardiac magnetic resonance imaging (MRI) as high-risk indicators for SCD in HCM patients.¹⁸³

Left Ventricular Systolic Dysfunction

Typically, left ventricular systolic function in HCM presents as hyperdynamic. However, a decrease in left ventricular systolic function may occur due to diffuse myocardial fibrosis in patients with end-stage disease. Left ventricular systolic dysfunction is defined as an ejection fraction (EF) below 50%, as determined by transthoracic echocardiography (TTE). Its incidence is estimated to be approximately 9%.²²⁴ Patients with HCM who experience left ventricular systolic dysfunction during the disease course, face a poor prognosis. They are at heightened risk for SCD and malignant ventricular arrhythmias. The current AHA guideline recommends implantation of an implantable cardioverter defibrillator (ICD) with a class 2a indication in this patient cohort.¹⁸³

In some cases, there may be a subtle impairment of longitudinal contractile function despite a preserved EF. This can be assessed by evaluating systolic annular velocities, strain, and strain rate using tissue Doppler imaging (TDI). In 2024, a study by Lee et al.²²⁵ showed that integrating the left ventricular

global longitudinal strain (LV-GLS) value into conventional SCD risk models, as endorsed by guidelines, enhanced the prognostic effectiveness of the models. Additionally, LV-GLS emerged as an independent indicator of increased risk for SCD.

Left Ventricular Apical Aneurysm

A left ventricular apical aneurysm is found in approximately 2–5% of HCM patients.²²⁶ It is theorized to develop due to myocardial damage resulting from elevated systolic intra-cavitary pressure caused by mid-ventricular obstruction and impaired diastolic perfusion due to low stroke volume, both common occurrences in HCM. While echocardiography is typically the initial diagnostic tool, TTE may not always reliably diagnose small aneurysms. The gold standard imaging modality is cardiac MRI. However, the use of contrast agents can enhance the sensitivity of TTE.

The presence of a left ventricular apical aneurysm is associated with an increased risk of SCD and malignant ventricular arrhythmias in HCM individuals. According to the current AHA guideline, the presence of a left ventricular apical aneurysm, regardless of its size, is considered a major risk factor for SCD.¹⁸³

Left Atrium Size

The primary causes of left atrial dilatation in HCM include elevated left ventricular filling pressure, mitral regurgitation, and intrinsic atrial myopathy, believed to be instigated by sarcomeric gene mutations.^{227,228} Left atrial dilatation in HCM correlates with an elevated risk of mortality (Figure 45). In a study involving 1,491 HCM patients, a left atrial anteroposterior diameter exceeding 48 mm was identified as an independent predictor of heightened cardiovascular mortality. Similarly, left atrial volume emerged as an independent predictor of adverse cardiovascular events.²²⁹ Both left atrial dilatation and impaired left atrial reservoir function are associated with an increased risk of SCD and malignant ventricular arrhythmias in HCM.²³⁰

Compared to MRI, left atrial volume measured by TTE may be underestimated. Therefore, cardiac MRI stands as the gold standard for left atrial volume measurement.²³¹

Myocardial Fibrosis

Late gadolinium enhancement (LGE) detected on cardiac MRI serves as an indicator of myocardial fibrosis. LGE is observed in hypertrophic segments in over 50% of HCM patients. There exists a strong correlation between the extent of LGE and SCD in HCM. When LGE encompasses $\geq 15\%$ of the left ventricular mass, it is associated with a twofold increase in the risk of SCD. The assessment of myocardial fibrosis plays a crucial role, particularly in the reclassification of patients initially categorized as low-to-intermediate risk for SCD based on conventional risk models.²³²

Left Ventricular Outflow Obstruction

Left Ventricular Outflow Obstruction (LVOTO) is present in approximately two-thirds of HCM patients, either at rest or when provoked.¹³ It is a dynamic parameter influenced by preload, afterload, and left ventricular contractility. Diagnosis of LVOTO can be made by examining apical 3-chamber or apical 5-chamber views on TTE, utilizing M-mode, color Doppler, pulsed wave (PW) Doppler, and continuous wave (CW) Doppler modalities (Figure 46). The presence of LVOTO in adults with HCM is associated with

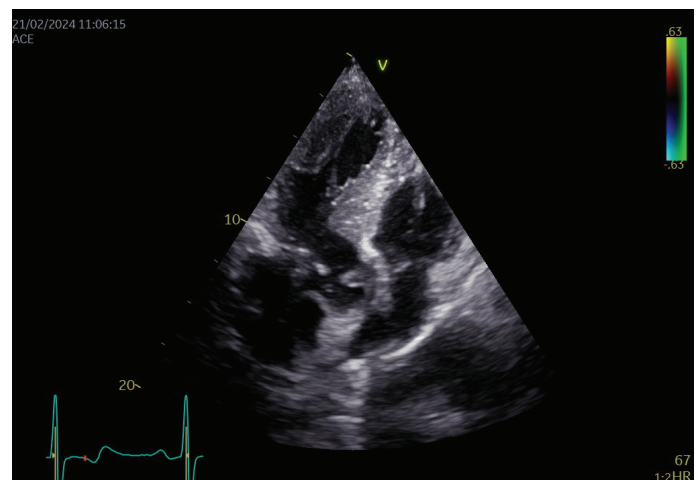


Figure 45. Left atrial dilatation.

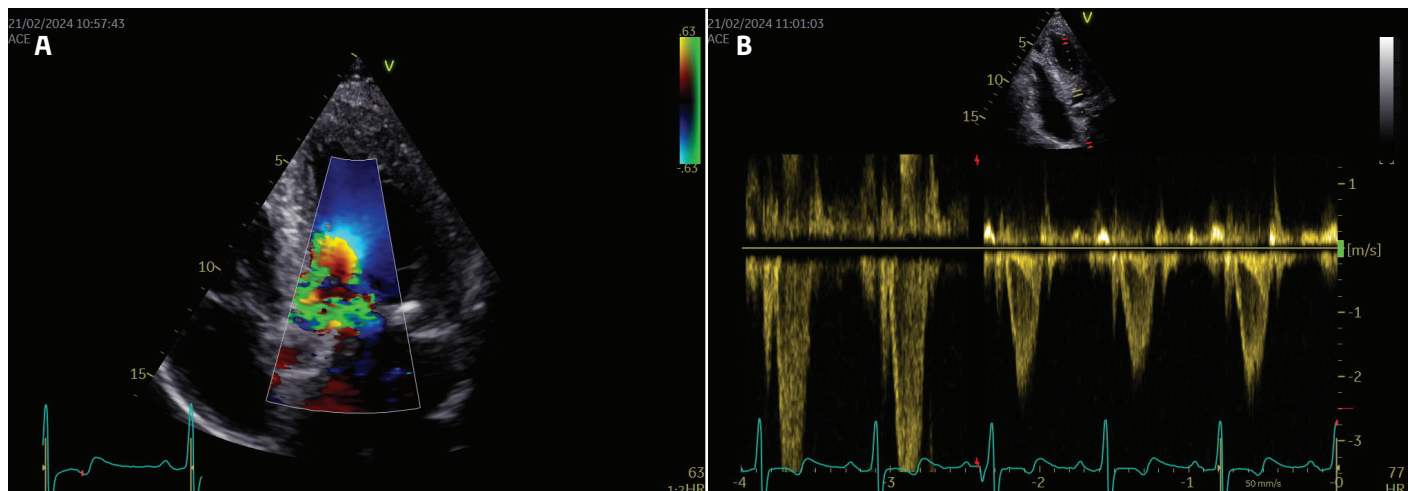


Figure 46. (A) Evaluation of left ventricular outflow obstruction with color Doppler. (B) Evaluation of left ventricular outflow obstruction with PW Doppler.

an increased risk of SCD. However, no further incremental risk is observed beyond values exceeding 30 mmHg.¹⁹³

Use of Advanced Imaging Methods Before and After Interventional Treatment

In sarcomeric hypertrophic cardiomyopathy (HCM), left ventricular outflow tract obstruction plays a crucial prognostic role. Beta-blocker therapy is the primary recommendation for symptomatic patients with a gradient of 50 mmHg or greater at rest or upon provocation. If symptoms persist or if there's intolerance or contraindications to beta-blockers, Diltiazem or Verapamil can be prescribed. Disopyramide is also recommended for patients who remain symptomatic despite therapy with the aforementioned treatments. Mavacamten is listed as a class IIa treatment in the recent European Society of Cardiology Cardiomyopathy Guideline.¹

Furthermore, septal reduction treatments are recommended with a class I indication for patients with left ventricular outflow tract gradients exceeding 50 mmHg, whose symptoms do not respond to medical treatment. Mildly symptomatic patients with an obstruction of the left ventricular outflow tract (LVOTO) of 50 mmHg or above (NYHA class II) should undergo septal reduction in experienced centers if they suffer from moderate-severe left atrial dilation, moderate-severe mitral regurgitation (MR) due to systolic anterior motion, atrial fibrillation, or pulmonary hypertension. Surgical septal myectomy or alcohol septal ablation are the two methods for reducing the septum.^{183,233} Additionally, small case studies suggest that coils can be used instead of alcohol to close

the septum, and that endocavitary/intramuscular ablation procedures can result in interventricular septum (IVS) scarring. However, due to the lack of comparative or safety studies of these methods,^{1,234,235} the guidelines recommend only alcohol septal ablation and surgical myectomy.

Imaging techniques play a crucial role in selecting and evaluating these procedures. In the following sections, we discuss the multimodality imaging methods used in the preoperative period to determine the suitability of alcohol septal ablation or septal myectomy. Additionally, we discuss intraoperative guidance and postoperative assessment of the success and complications of the procedures using multimodality imaging.

Transthoracic Echocardiography

TTE is the most common method used to measure the LVOT gradient for interventional procedures. Medical treatment is indicated for symptomatic (NYHA III-IV) patients with an LVOT gradient ≥ 50 mmHg measured at rest or during provocation (Valsalva maneuver, standing up). Interventional procedures are undertaken in patients who are refractory and/or intolerant to maximal medical treatment. TTE allows for the assessment of IVS thickness, midventricular or apical hypertrophy, and the presence of obstruction. It is recommended to measure myocardial thickness in end-diastole from a parasternal short axis view.¹ Contrast echocardiography can be useful when the image quality is suboptimal, particularly in assessing apical hypertrophy.²³⁶

TTE serves as the initial and primary imaging method, providing detailed information to guide decisions about surgical myectomy

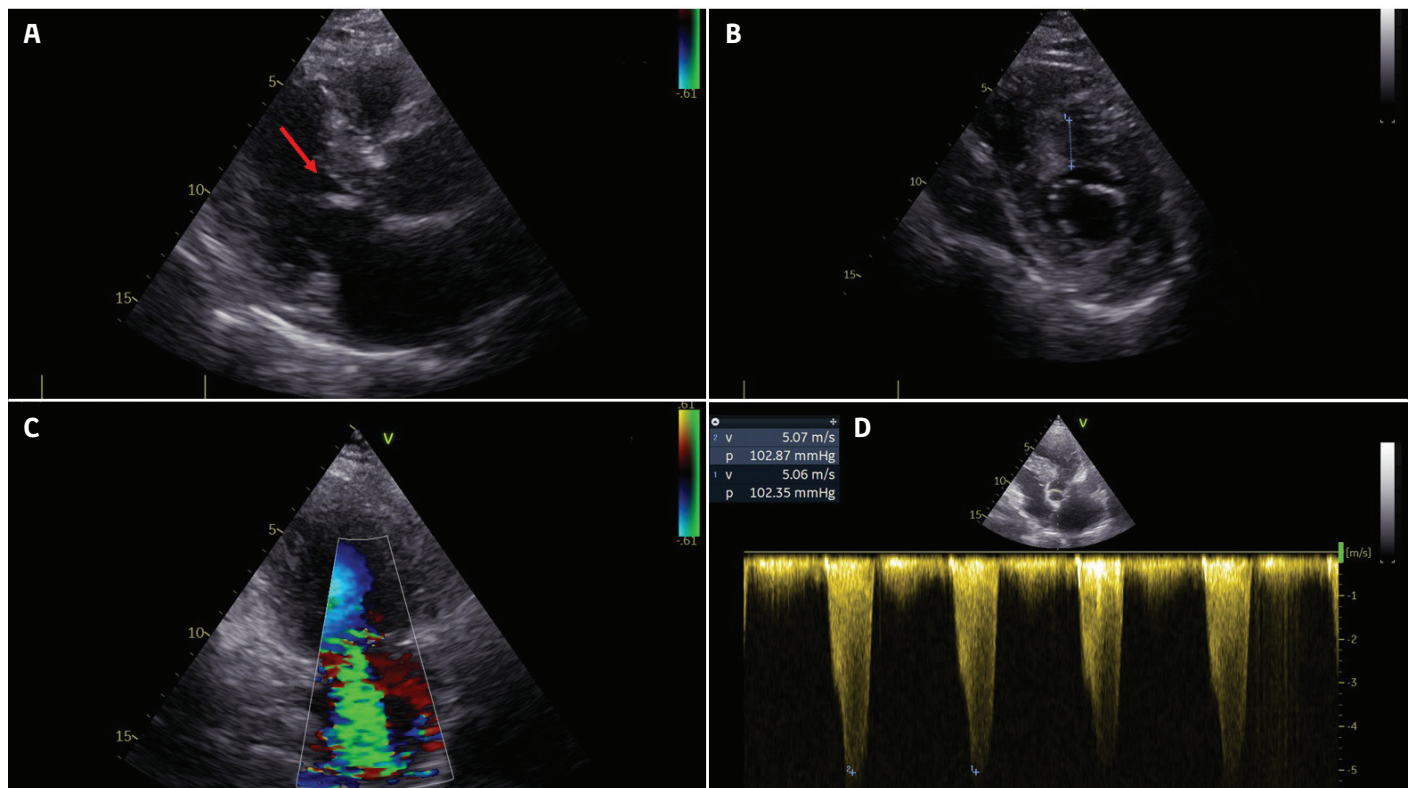


Figure 47. Transthoracic echocardiography images of the patient with a gradient of 102 mmHg in the left ventricular outflow tract. (A) The red arrow indicates anterior movement of the mitral anterior leaflet in systole. (B) Measurement of the IVS from a parasternal short-axis view of 2.1 cm. (C) Severe central mitral regurgitation.

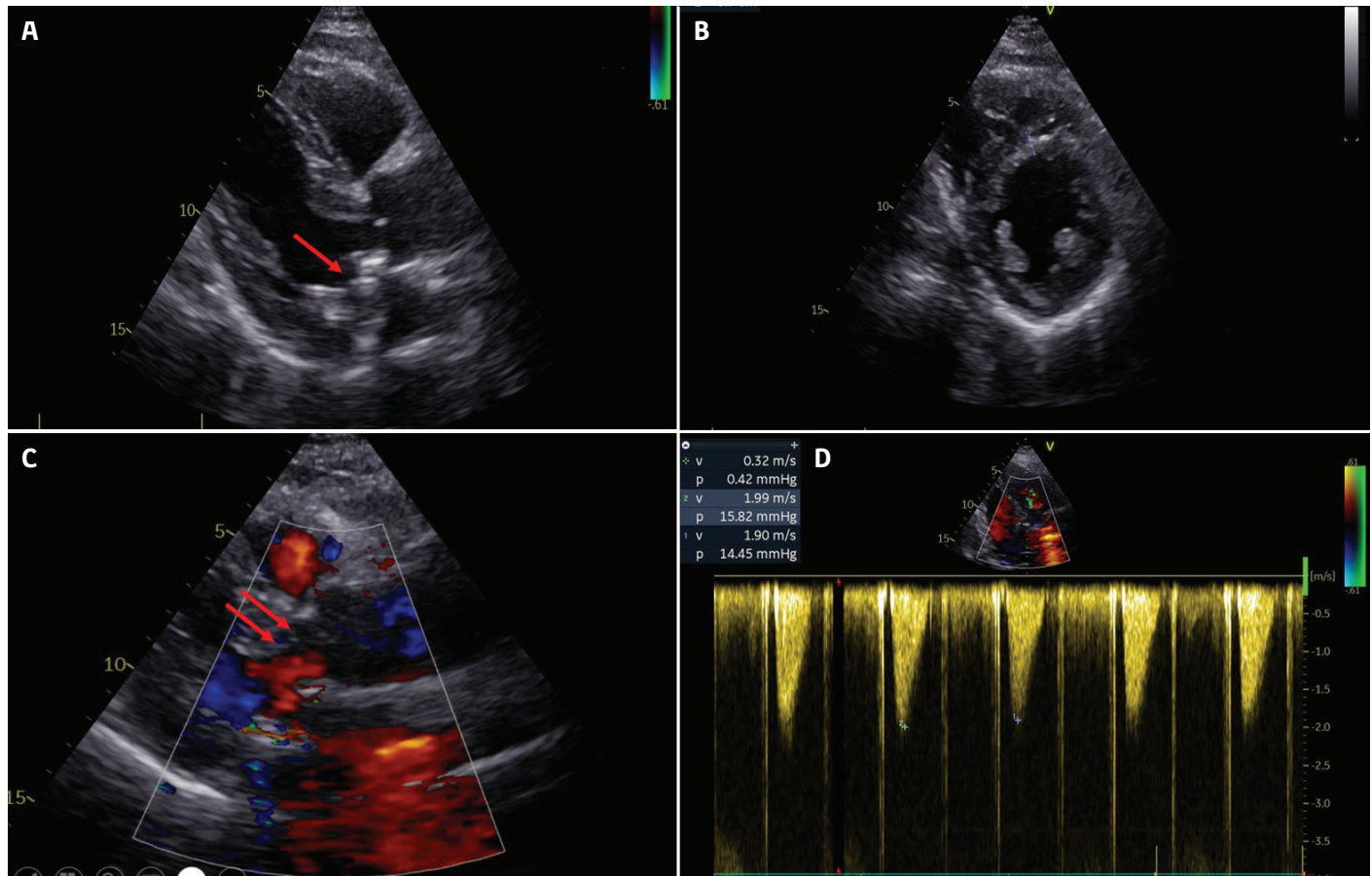


Figure 48. Transthoracic echocardiography images of a patient with HCM and severe mitral regurgitation after septal myectomy and mitral valve replacement. (A) A red arrow indicates mitral valve replacement (MVR). (B) Measurement of the IVS from a parasternal short-axis view of 0.7 cm. (C) Two red arrows indicate the disappearance of turbulence in the left ventricular outflow tract. (D) There is no gradient in the left ventricular outflow tract.

or alcohol septal ablation in the preoperative period. Surgical septal myectomy is preferred when hypertrophy is detected in the mid and apical regions of the heart, apart from the IVS base, and when papillary muscle involvement is causing obstruction in the midventricular region.

LVOTO may lead to the anterior mitral valve leaflet moving anteriorly and contacting the interventricular septum (known as SAM) during systole. While this phenomenon was previously attributed to the Venturi effect, the primary mechanism involves the sweeping of the mitral valve apparatus by the flow in the LVOT, pushing it towards the IVS.²³⁷ MR occurs due to the anterior motion of the anterior leaflet during systole. MR resulting from SAM typically manifests in mid to late systole and is oriented posteriorly or laterally. Both myectomy and alcohol septal ablation are effective in treating MR in this scenario.¹⁹⁵

Patients with HCM often present anomalies associated with the mitral valve and subvalvular apparatus. These anomalies may include an abnormally located papillary muscle, elongated leaflets, anterior displacement of the papillary muscle, mitral valve prolapse, and chordal rupture. It is crucial to thoroughly evaluate these abnormalities, particularly in the presence of centrally and anteriorly oriented MR.^{1,238}

Transesophageal echocardiography (TOE) or cardiac magnetic resonance imaging (CMR) is recommended for evaluating the mitral valve and its apparatus in patients suspected of primary valve disease when assessment by TTE is insufficiently clear.^{197,239} Dyspnea may solely result from primary valve disease. In patients with LVOTO ≥ 50 mmHg and moderate-to-severe MR resulting from anomalies of the mitral valve apparatus, advanced imaging methods should be employed if the mitral valve cannot be adequately evaluated by TTE (Figure 47). This is particularly important as septal reduction procedures will necessitate surgical myectomy along with potential mitral valve repair or replacement.

Furthermore, left atrial dilation detected by TTE serves as a prognostic indicator. The primary cause of left atrial dilation is an elevation in left ventricular filling pressure and MR due to SAM.

TTE serves as the initial imaging method for evaluating and monitoring left ventricular outflow tract obstruction (LVOTO) following septal reduction interventions. Additionally, TTE can detect potential complications such as ventricular septal defect and aortic insufficiency following septal myectomy. After septal reduction procedures, TTE plays a crucial role in assessing left ventricular systolic and diastolic function to determine the success of the intervention and prognosis (Figure 48).

Transesophageal Echocardiography

TOE is an essential imaging method in determining the course of septal reduction treatment. TOE should be conducted to identify and rule out conditions that may mimic HCM, such as a subvalvular membrane. Additionally, a TOE is necessary if primary mitral valve disease is suspected. During the intraoperative period, TOE is crucial for detecting and managing complications that may arise during septal myectomy, such as aortic regurgitation or ventricular septal defects. It also guides the surgeon throughout the procedure. Similarly, when identifying the appropriate septal branch for alcohol septal ablation, TOE must be employed to visualize the contrast or agitated saline administered and to guide the operator. A study by La Canna et al.²⁴⁰ demonstrated that three-dimensional TOE enhances the identification of the target artery for alcohol septal ablation, resulting in high long-term success rates. Consequently, TOE should be a standard component of all septal reduction procedures.

During the procedure, TOE can assess the reduction in LVOTO and determine the degree of MR. It is also valuable in evaluating the valve during repair or replacement in patients with primary mitral valve anomalies. Moreover, it enhances the success rate during septal ablation and ensures that the infarct area is minimized, thereby reducing complications like heart block. While LVOTO reduction is typically observed during the procedure, septal scar resolution may take time (usually within three months). Thus, follow-up TTE should be performed to assess LVOTO reduction. Monitoring the LVOT gradient by TTE is also recommended to detect recurrence of obstruction.¹⁸³

In patients with severe MR who are not suitable candidates for surgery, TOE can be utilized as part of a percutaneous procedure, such as Mitraclip insertion.²⁴¹

Cardiac Magnetic Resonance Imaging

Cardiac MRI serves as an imaging method that can be employed before septal reduction procedures, particularly in cases where the acoustic windows of echocardiography are suboptimal. Moreover, it can detect abnormally located papillary muscles. If a hypertrophied anterolateral muscle without chordae is directly attached to the mitral valve, this may significantly contribute to mid-cavitary hypertrophy, which warrants assessment by cardiac MRI if there is any uncertainty with TTE. Additionally, cardiac MRI is useful for evaluating mitral valve anomalies, complementing the information obtained from TOE. To ensure the success of the septal reduction procedure, it is recommended to identify hypertrophic segments before the procedure and to utilize MRI to determine the degree of fibrosis.

Cardiac Computed Tomography and Nuclear Imaging

Cardiac computed tomography can be utilized to assess left ventricular functions in situations where TTE is suboptimal and CMRI is not feasible. It is primarily advised for identifying the target septal perforator before alcohol septal ablation.²⁴² After septal reduction procedures, nuclear imaging can be employed to evaluate the procedure's success. A positive change in the perfusion pattern typically indicates a successful intervention.^{243,244}

Evaluation of the Athlete's Heart

The athlete's heart" encompasses a clinical spectrum characterized by structural, functional, and electrical alterations observed in individuals regularly engaging in prolonged high-intensity physical activity. Physiological changes induced by intense exercise in the athlete's heart may resemble or coincide with serious cardiac pathologies, such as inherited or acquired cardiomyopathies and channelopathies, which exhibit similar morphological characteristics. Given the heightened risk of sudden cardiac death (SCD) associated with these conditions, early diagnosis is of critical significance.

Evaluation of the athlete's heart typically begins with a thorough medical history, comprehensive physical examination, and electrocardiography (ECG). Following the initial assessment, echocardiography emerges as the preferred imaging modality for suspected cardiac pathology. If a definitive diagnosis remains elusive after standard echocardiographic assessment, adjunctive diagnostic modalities including exercise testing, both resting and stress echocardiography, cardiac magnetic resonance imaging, computed tomography, nuclear scintigraphy, or genetic testing may provide valuable diagnostic insights.

Cardiovascular Adaptation in Athletes

In athletes, cardiac adaptation arises from structural, functional, and electrical alterations, typically characterized by normal or mildly increased systolic and diastolic functions, along with increased left ventricular wall thickness, balanced enlargement of left and right heart chambers, increased cardiac mass, and ECG changes.²⁴⁵ These cardiac adaptations are generally moderate and fall within normal limits. The reshaping observed in athletes has numerous physiological underpinnings and is influenced by various factors such as environmental and genetic factors, as well as immutable characteristics of athletes like ethnicity, type and duration of exercise, and type of physical activity, drugs, and body surface area.²⁴⁶ Clinicians are advised to adopt a personalized approach when evaluating an athlete.

Body surface area (BSA) significantly influences cardiac dimensions. Hence, when evaluating the athlete's heart, left ventricular (LV) dimensions should be assessed relative to BSA.²⁴⁷ In female athletes, similar to males, regular physical activity induces physiological adaptation, albeit to a lesser extent compared to males. Ethnicity also contributes to this adaptation process. For instance, black athletes display more ECG changes and a higher prevalence of LV hypertrophy compared to other ethnic groups.²⁴⁸ Regarding age-related assessment, older athletes exhibit lower LV volumes and mass compared to their younger counterparts.

The effects of endurance and strength training on the athlete's heart differ significantly. Endurance sports involve aerobic, isotonic dynamic exercises, including activities like swimming or cycling.²⁴⁸ On the other hand, strength sports entail high-intensity exercises requiring more than 30% of the body's maximum contraction capacity and are not sustained solely by oxygen. Examples include martial arts, short-distance running, and weightlifting.²⁴⁹ It's worth noting that many sports incorporate a combination of strength and endurance exercises.²⁵⁰

Athletes engaged in endurance training typically exhibit eccentric LV hypertrophy, characterized by increased LV volume and diastolic wall stress, often accompanied by right ventricular (RV) dilation. Conversely, athletes performing strength training usually demonstrate concentric LV hypertrophy.²⁵¹ The "Morganroth Hypothesis," while previously considered, has limitations and has been refuted by recent

Table 13. Causes of Sudden Cardiac Death in Athletes

Structural Heart Diseases	Non-structural Heart Diseases
● Congenital ● Hypertrophic Cardiomyopathy ● Dilated Cardiomyopathy ● Arrhythmogenic Cardiomyopathy ● Coronary Artery Anomalies and Disease ● Valve Disease	● Brugada Syndrome ● Wolf-Parkinson-White Syndrome ● Hypo/Hyperthermia ● Ion channel related pathologies ● Congenital Long QT Syndrome ● Drug-induced Long QT Syndrome

Table 14. Indications for Cardiovascular Imaging in Athletes

Clinical History
Family history (sudden cardiac death/cardiomyopathy) Palpitations Chest pain Syncope
Physical Examination
Cardiac murmur Body type (Marfanoid structure)
ECG
T-wave abnormalities ST depression Pathological Q wave Left bundle branch block QRS duration >140 with intraventricular delay Right bundle branch block and left anterior hemiblock Epsilon wave Prolonged QTc (>470 ms for males, >480 ms for females) Type 1 Brugada Sinus bradycardia <30 beats/min Sinus pause >3 seconds First-degree AV block >400 ms Mobitz type 2 second-degree AV block Third-degree AV block Atrial tachyarrhythmias Ventricular arrhythmias

studies suggesting that increases in LV mass are proportional to increases in LV volume, regardless of the sporting discipline.²⁵²

The fundamental physiological characteristics of exercise training suggest classifying sports into four main groups: skill, strength, endurance, and mixed sports. In agility-demanding sports like soccer, basketball, and volleyball, as well as endurance-focused activities such as rowing and running, the combination of isometric and isotonic exercise promotes a higher occurrence of cardiac remodeling. Conversely, in power-centric sports like boxing and weightlifting, where isometric exercise predominates, cardiac remodeling is less frequent. Finally, sports emphasizing skill, such as golf, archery, and horseback riding, typically result in minimal, if any, cardiac remodeling.²⁴⁸

Sudden Cardiac Death in Athletes and Its Causes

Most sports-related SCD occur in the middle-aged group aged 35 and older, with 80% of these deaths attributed to atherosclerotic coronary artery disease (CAD).²⁵³ The prevalence of cardiovascular diseases predisposing to SCD during sports in young athletes is estimated to be 0.2-0.7%.²⁵⁴ The causes of SCD in athletes are associated with the age of onset. CAD is

the most common cause of SCD in adult athletes (aged 35 and older). Structural heart disease typically underlies SCD in younger individuals. Table 13 summarizes the causes of SCD in athletes.²⁵⁵

Clinical and ECG Findings Requiring Cardiovascular Imaging in Athletes

In athletes, pre-participation cardiovascular screening aims to detect diseases early and prevent SCD. The primary screening involves a comprehensive clinical evaluation, physical examination, and a 12-lead ECG.²⁵⁶ Following this assessment, imaging modalities are utilized in cases where suspicion arises. Table 14 outlines the indications for cardiac imaging in athletes.²⁴⁶ The athlete's heart is commonly associated with ECG changes such as sinus bradycardia, first-degree AV block, early repolarization, and voltage criteria for LV hypertrophy.

Echocardiographic Findings in Athletes

Left Ventricle

Morphological and functional echocardiographic parameters in the left heart in athletes are summarized in Table 15. In athletes, LV diameters are increased. In a study encompassing 1309 athletes, LV diameter was increased in 55% of athletes, with 14% having an LV end-diastolic diameter (EDD) >60 mm. Athletes with LV EDD above 60 mm are typically identified as endurance athletes.²⁵⁷ Threshold values for LV diameters are shown to be 70 mm for males, 66 mm for females, and 60 mm for adolescents (Table 16). LV chamber size is closely related to BSA, thus measurements are recommended to be evaluated relative to BSA. The upper limit for LV diameter in male athletes is reported to be 35 mm/m², while in female athletes, it's 40 mm/m².^{246,247}

In most athletes, the thickness of the septum and posterior wall of the LV measures below 12 mm, with few athletes showing measurements between 12 and 16 mm but not exceeding 16 mm (Figure 49). The increase in wall thickness is less common in female athletes compared to males.²⁵⁸ Additionally, black athletes tend to exhibit greater increases in wall thickness. Relative wall thickness (RWT) is used in clinical practice to characterize LV morphological remodeling. RWT is calculated by doubling the thickness of the posterior wall and dividing it by LV EDD. In athletes, this value generally does not exceed 0.42.

Most adaptations induced by physical training regress with cessation of exercise (deconditioning). However, in some cases, LV dilation has been observed to persist even after a 5-year inactive period.²⁵⁹

In athletes, LV systolic function has been reported to be normal (ejection fraction (EF) ≥52%) or mildly reduced (EF <52%), with preserved or increased diastolic function. A study by Abergel

Table 15. Morphological and Functional Echocardiographic Parameters in the Left Heart in Athletes

Parameter	Unit	Gender	Mean Value	Cut-off
LV end-diastolic diameter	mm	Female	55	70
	mm	Male	49	66
LV wall thickness	mm	Female	9.5	12
	mm	Male	10	16
LV mass	g/m ²	Female	83	117
	g/m ²	Male	103	146
LA anteroposterior diameter	mm	Female	32	45
	mm	Male	37	50
LA volume index	ml/m ²	Female	26.5	33
	ml/m ²	Male	28	36
Ejection fraction	%		55	64
E/A			1.9	1.3
e velocity septal	cm/s		13.8	10.3
s velocity septal	cm/s		13	8
LV intraventricular delay			9.5	4.5

Table 16. Right Heart Morphological and Functional Parameters in Athletes

Parameter	Unit	Gender	Mean Value	Cut-off
RV diameter basal	mm	Female	39.5	49
	mm	Male	43.5	55
RV long diameter	mm	Female	82	100
	mm	Male	89	109
RV outflow tract proximal	mm	Female	30	40
	mm	Male	32	43
RV outflow tract distal	mm	Female	21.5	29
	mm	Male	23.5	32
RA area	cm ²	Female	14.8	20
	cm ²	Male	18.9	25
TAPSE	mm		24	29

LA, Left atrium; LV, Left ventricular; RV, Right ventricular; TAPSE, Tricuspid Annular Plane Systolic Excursion

involving 286 cyclists found that 147 cyclists (51%) had an LV end-diastolic diameter (LVEDD) >60 mm, and 17 (11%) had a decrease in EF ($\leq 52\%$).²⁶⁰ When exercise echocardiography was performed in athletes with EF values below 50, it was observed that EF increased.

Regarding diastolic function, it remains preserved in athletes. Due to the increased early diastolic filling velocity at rest, the E/A ratio is above 2. The velocities of s and mitral annular e' measured by pulsed tissue Doppler imaging are found to be normal or increased.²⁶¹

Left Atrium

LA enlargement is common in athletes, proportional to biventricular enlargement and influenced by the type of training. Pelliccia et al.²⁶² reported a mild increase in LA diameter (≥ 40 mm) in 18% of athletes and significant LA dilation (≥ 45 mm) in 2%

of athletes in their study. LA volume is the preferred method to assess LA remodeling, and approximately one-fourth of athletes have a LA volume index (LAVI) above 34 ml/m².

Aorta

Measured aortic root diameters in athletes are generally normal, and dilation is observed in less than 1% of cases. Therefore, clinicians should be aware that significant aortic root dilation likely represents a pathological process. Evaluating aortic root dimensions is especially important in athletes who may resemble patients with Marfan syndrome phenotypes. Engel et al.²⁶³ examined 526 NBA players with an average height of 200.2 cm and BSA of 2.38 m. Aortic root dimensions ranged from 25 to 42 mm, with only 24 (4.6%) athletes having an aortic root diameter above 40 mm.²⁶⁴ The American Heart Association recommends

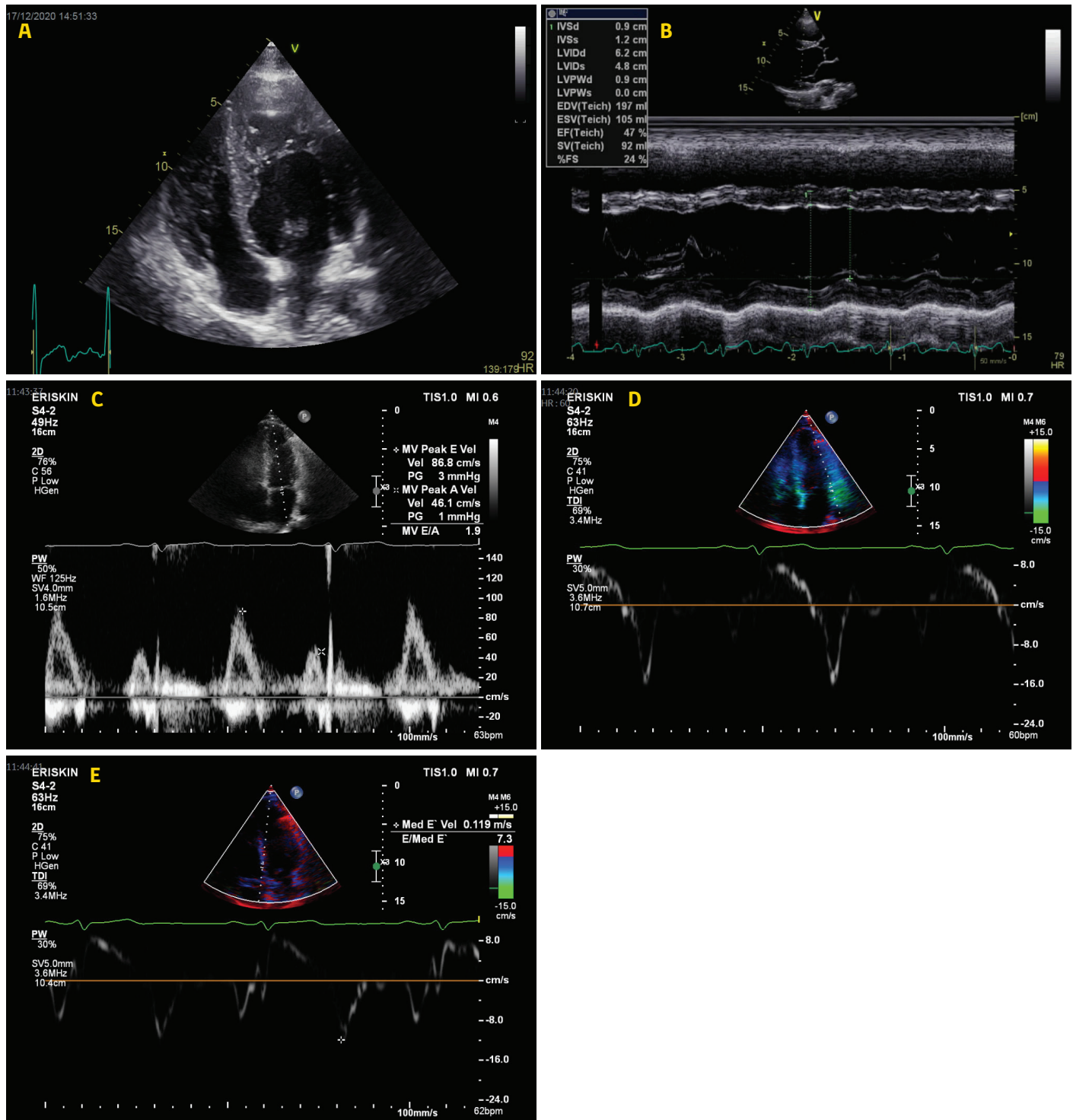


Figure 49. A 22-year-old professional basketball player. He exhibits increased left ventricular dimensions with a mildly reduced ejection fraction of 50% (A, B). Left ventricular diastolic function is normal (C-E).

close monitoring and serial imaging for tall athletes with aortic root diameters above 41 mm.²⁶⁴

Right Ventricle and Right Atrium

The right atrium and right ventricle (RV) undergo structural and functional remodeling in athletes. RV enlargement in athletes is proportional to LV enlargement.²⁶⁵ Despite RV enlargement, athletes

typically exhibit normal RV systolic function (Table 16). Assessment of the RV in athletes is important for making a differential diagnosis of arrhythmogenic right ventricular cardiomyopathy.

Strain Analyses

Advancements in strain analyses offer the opportunity to assess regional and global cardiac mechanics before a significant decline

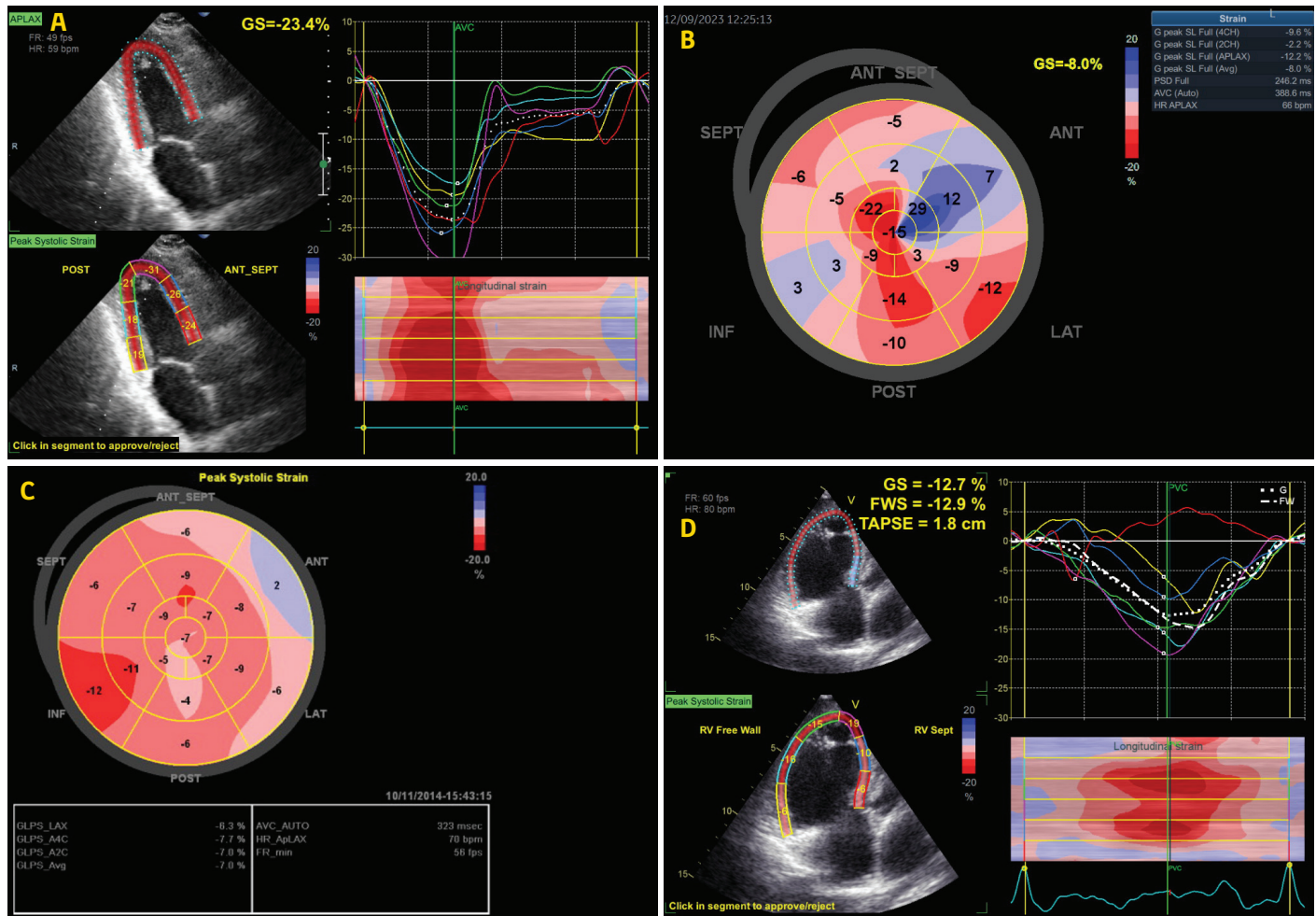


Figure 50. GLS measurements in athletes' hearts (A), a patient with hypertrophic cardiomyopathy (B), dilated cardiomyopathy (C), and right ventricular dysplasia (D).

in cardiac function occurs. This technique is highly beneficial in distinguishing cardiac remodeling in athletes from hypertrophic cardiomyopathy (HCM) (Figure 50).

Figure 50 illustrates Global longitudinal strain (GLS) measurements in athletes' hearts (A), a patient with HCM (B), dilated cardiomyopathy (DCM) (C), and RV dysplasia (D). GLS is higher than normal in athletes' hearts, but it is significantly decreased in patients with HCM, exhibiting segmental discrepancy. In DCM, GLS is globally decreased, and in RV dysplasia, RV strain is significantly decreased.

GLS values of the LV are typically reported between -16 and -22, with a mean value of -20 considered normal. The same threshold values apply to athletes. Athletes with GLS values below -15 should raise suspicion of an underlying cardiac pathology.

In a study conducted by Afonso and colleagues involving 129 participants (56 with HCM, 34 with hypertensive hypertrophy, 27 athletes, and 12 healthy controls), the utility of strain imaging as a useful diagnostic tool in the assessment of regional and global LV systolic function and in distinguishing HCM from other forms of LV hypertrophy was investigated. In patients with HCM, GLS was significantly reduced, and the global strain distribution index

(SDI) was increased compared to all other groups. Athletes were found to have similar GLS to healthy controls, and both athletes and healthy controls had lower global SDI compared to patients with HCM and hypertensive hypertrophy.²⁶⁶

The advancement of speckle tracking has facilitated the understanding of LV mechanics. LV systolic twist (LVT) and early diastolic untwist (UTR) values have been evaluated in athletes. Weiner and colleagues demonstrated the effect of endurance exercise on peak apical systolic rotation, peak systolic LVT, and early diastolic UTR in 15 male rowers after 90 days of training. This outcome could be related to exercise-induced volume expansion. Increased LVT and UTR values at rest and in response to exercise in athletes decrease after DCM and myocardial infarction. Therefore, these parameters may represent target parameters to distinguish physiological and pathological remodeling.^{267,268}

3-D Echocardiography and Strain Analysis

Assessment of LV and RV and systolic function are the most important parameters in the evaluation of athletes' hearts. However, the geometric structure of the RV complicates optimal measurement outcomes with two-dimensional evaluation. Three-dimensional (3D) echocardiography allows

for more accurate measurements of RV volumes and EF. Three-dimensional speckle tracking echocardiography is a novel technique that enables the accurate assessment of myocardial dynamics.²⁶⁹

In a study by Esposito and colleagues, 3D and speckle tracking were used to evaluate RV function in athletes. This study demonstrated a significant increase in RV GLS, primarily attributed to an increase in lateral longitudinal strain.²⁷⁰

Exercise Stress Echocardiography

Exercise stress echocardiography is a reliable and non-invasive method used to provide information about cardiac function, contractile reserve, exercise capacity, and arrhythmias. It is performed to assess global and regional cardiac function in individuals with chest pain or abnormal ECG to exclude CAD. In some endurance athletes, mild systolic dysfunction is associated with both LV and RV dilation. In these cases, exercise echocardiography allows for the evaluation of contractile reserve in dilated ventricles, indicating a physiological response with significant improvement in contraction during physical exertion.²⁷¹

Differentiation of Athlete's Heart from Cardiomyopathies **Hypertrophic Cardiomyopathy**

HCM is distinguished from athlete's heart by certain characteristics. In HCM, wall thickness is usually >15 mm. Family history is important for diagnosis in cases with thickness between 13–15 mm in the gray zone. LV cavity dimensions are generally reduced (<54 mm) or normal in HCM. Unlike in athlete's heart, LV wall thickness does not change in HCM cases with cessation of sport. Patients typically exhibit diastolic dysfunction ($E/A < 1$, decrease in e' velocity, $E/e' > 12-15$). Additionally, systolic anterior motion of the mitral valve leaflets is common in HCM

patients and can lead to LV outflow tract obstruction. The LA is often enlarged due to mitral regurgitation associated with SAM and high LV filling pressures. Typically, EF is normal or increased in HCM patients, but myocardial longitudinal velocities and deformation parameters are often reduced.²⁷²

Dilated Cardiomyopathy

DCM is defined as LV dilation accompanied by systolic dysfunction without CAD, hypertension, or valve disease. Both athlete's heart and DCM significantly overlap as they can both present with a markedly enlarged LV cavity. Diastolic dysfunction is valuable in distinguishing DCM from athlete's heart. Patients with DCM exhibit echocardiographic signs of abnormal myocardial relaxation or increased filling pressure. Additionally, while most athletes have normal strain values, they are reduced in DCM.²⁷³

Arrhythmogenic Cardiomyopathy

Arrhythmogenic cardiomyopathy (ACM) is characterized by the pathological replacement of ventricular myocardium with fibro-fatty tissue and clinically characterized by ventricular electrical instability. Recognizing this cardiomyopathy is important as individuals with ACM have a higher risk of SCD compared to sedentary individuals. Endurance athletes may have an enlarged RV that meets the dimensional criteria of ACM, making the differentiation between athlete's heart and ACM challenging. Criteria for ACM include RV enlargement, regional akinesia, dyskinesia, or RV aneurysms. In athletes, RV dilation is never accompanied by global or regional functional abnormalities. Furthermore, while harmonic dilation of the RV indicates athlete's heart, disproportionate dilation of the RV outflow tract can be observed in ACM instead of asymmetric dilation of the inlet and outlet of the RV. Systolic dysfunction (Fractional area change <33%, decreased S velocity) is seen in ACM.²⁷⁴

Hypertensive Hypertrophy and Cardiomyopathy

Hypertension (HT) stands as one of the major risk factors for cardiovascular diseases, often remaining undiagnosed or untreated for extended periods.²⁷⁵ Left ventricular (LV) systolic pressure overload, a consequence of untreated HT, leads to various LV geometric changes.²⁷⁶ Left ventricular hypertrophy (LVH) is the predominant target organ damage in HT, affecting 20% to 40% of HT patients.²⁷⁷ LVH is closely associated with an increased risk of cardiovascular morbidity and mortality. A recent study conducted in Türkiye revealed that HT accounted for 56.6% of reported cases of LVH, establishing it as the primary cause in the Turkish population.²⁷⁸

In hypertensive heart disease, LVH manifests with various remodeling patterns, predominantly concentric hypertrophy in most cases and eccentric hypertrophy in advanced stages. Persistent pressure overload contributes to the progression of diastolic dysfunction, resulting in decompensation of the remodeled left ventricle (LV) and hypertensive heart failure with preserved ejection fraction. Conversely, sustained volume overload induces LV dilatation and decompensation of concentrically remodeled LV, culminating in heart failure with reduced ejection fraction.²⁷⁹ Table 17 outlines the factors influencing LV geometry in individuals with hypertension.

For instance, concentric LVH is commonly observed in older individuals or those with diabetes mellitus (DM), whereas patients with coronary artery disease or obesity (as a state of volume overload) are more prone to eccentric LVH. Additionally, individuals of African descent with hypertension are predisposed to developing concentric LVH compared to Caucasians, while women with hypertension are more likely to exhibit concentric LVH than men.²⁷⁶ Assessing personal and family medical histories is crucial in the initial diagnosis of LV hypertrophy. The primary goal is to rule out common causes such as hypertensive hypertrophy, although it's essential to acknowledge that these conditions may coexist with primary cardiomyopathies.²⁸⁰

Electrocardiography (ECG) plays a pivotal role in the evaluation of LVH and complements other clinical and imaging findings. Hypertensive hypertrophy typically presents with elevated R-wave amplitude in the left ECG leads (I, aVL, and V4–6) and increased S-wave depth in the right ECG leads (III, aVR, V1–3). Additionally, LV wall thickening results in prolonged depolarization (elevated R wave peak time) and delayed repolarization (ST and T-wave abnormalities) in the lateral leads. ECG is also instrumental in diagnosing other causes of LVH. Inverted giant T waves in the precordial and/or inferolateral leads may indicate apical hypertrophic cardiomyopathy, while ventricular pre-excitation may be observed in storage diseases and certain mitochondrial disorders.²⁸⁰

Table 17. Factors Affecting LV Geometry in Individuals with HT

Severity, duration, and rapidity of onset of increased pressure load
Volume load
Age, race/ethnicity, and gender
Presence of concomitant coronary artery disease, diabetes mellitus, obesity, or valvular heart disease
Neurohormonal mechanisms
Changes in extracellular matrix
Genetics

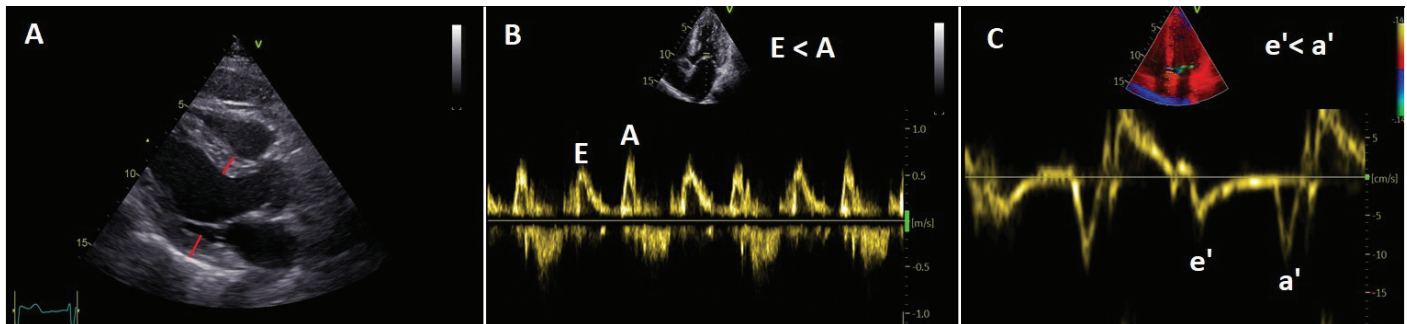


Figure 51. (A) Mild concentric hypertrophy of LVH is indicated by red lines illustrating wall thicknesses, with both the interventricular septum and posterior wall measuring 11 mm. (B) Grade 1 diastolic dysfunction is depicted in the pulse wave study. (C) Tissue Doppler study also demonstrates Grade 1 diastolic dysfunction.

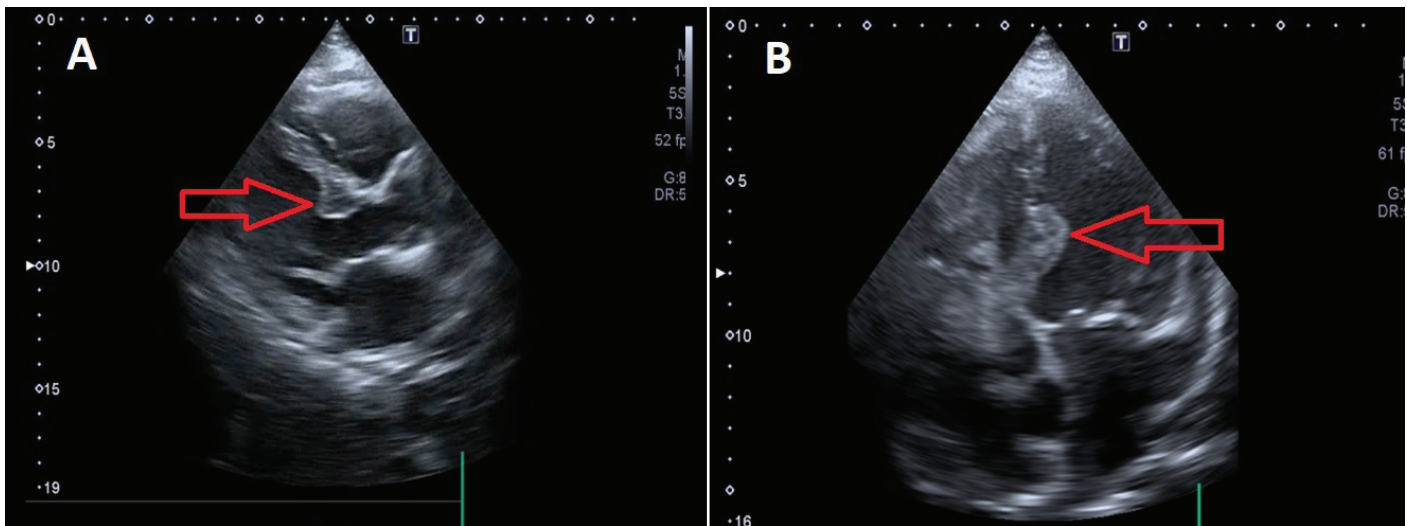


Figure 52. Ventricular septal bulge is highlighted in transthoracic echocardiography (arrows indicate the bulge).

The identification of LVH necessitates the use of multiple imaging techniques. Echocardiography serves as the initial imaging modality, offering a comprehensive assessment of systolic and diastolic performance as well as heart valves. Advanced echocardiography and strain imaging can aid in the early detection of LV dysfunction in hypertensive patients.²⁸⁰ Computed tomography enables the quantification of LV mass, volume, and wall thickness, and it helps rule out coronary artery disease in individuals with hypertension.²⁸¹ Conversely, cardiovascular magnetic resonance (CMR) is a powerful tool for accurately measuring LV and right ventricular (RV) volumes and mass, and it can characterize myocardial tissue structure, providing crucial insights into the underlying causes of LVH, including hypertensive hypertrophy.²⁸² Early identification and subsequent medical therapy may result in regression of LVH in patients with hypertension.²⁸³ Consequently, a series of imaging investigations can offer guidance on the disease's progression and the response to antihypertensive treatment. This chapter presents multimodality imaging findings in patients with hypertensive hypertrophy.

Major Echocardiographic Features of Hypertensive Hypertrophy

Echocardiography plays a crucial role in identifying the key features of LV remodeling in patients with HT. LV wall

thickening is a compensatory response to abnormal loading conditions, such as hypertension or aortic valve stenosis. As discussed earlier, an increased left ventricular wall mass (LWM) index and a relative wall thickness (RWT) greater than 0.42 signify concentric hypertrophy, while an LWM index and RWT less than or equal to 0.42 indicate eccentric hypertrophy. Concentric LV hypertrophy is typically observed in HT, with elevations in interventricular septal thickness, usually below 15 mm in the absence of other coexisting cardiomyopathies (Figure 51).^{275,276}

LVH typically presents as symmetric, although asymmetric forms have been documented in patients with HT using 2D echocardiography.²⁸⁴ The reasons behind the development of asymmetric thickening are not entirely clear. It's suggested that acute aortoseptal angulation and reduced aortic distensibility in HT patients might lead to increased LV wall stress in the basal and mid-septum, resulting in asymmetric wall thickening.²⁸² Changes in aortic configuration over time, associated with aging and duration of HT, could contribute to this phenomenon. Some studies propose that the more pronounced sympathetic innervation of the interventricular septum compared to the lateral wall might be a pathophysiological mechanism for asymmetric LVH.²⁸⁵ Additionally, differences in the location and

Table 18. Staging of Hypertensive Heart Disease	
Degree I	LV diastolic dysfunction with no LV hypertrophy
Degree II	LV diastolic dysfunction with concentric LV hypertrophy
Degree III	Clinical heart failure (increased dyspnea, pulmonary edema, etc.) with preserved ejection fraction
Degree IV	Dilated cardiomyopathy (eccentric LV hypertrophy) with heart failure and reduced ejection fraction

expression of Angiotensinogen 1 have also been hypothesized to contribute to asymmetric LVH.²⁸⁶

One of the patterns of asymmetric LVH is ventricular septal bulge (Figure 52), which is often observed in older individuals and can pose challenges in differentiation from hypertrophic cardiomyopathy (HCM).²⁸⁷ Recent studies suggest that it's not merely a variant structure but appears to be a distinct localized structural formation in response to elevated blood pressure before the onset of concentric LVH during the early stages of hypertension. Therefore, blood pressure monitoring may be warranted in patients with septal bulge and unknown hypertension history.²⁷⁷

LVH has traditionally been viewed as a pivotal indicator of HT-induced LV remodeling and hypertensive heart disease. However, recent studies employing novel imaging techniques and modalities suggest that left ventricular diastolic dysfunction (LVDD) and impairment of LV mechanical properties occur significantly before the development of LVH.^{276,288} Patients with reduced LV cavity size exhibit impaired coronary reserve and increased myocardial oxygen requirements, leading to compromised LV relaxation and heightened LV filling pressures.²⁸⁹ These processes contribute to left atrial (LA) enlargement. LVDD may be present in up to 84% of hypertensive individuals with LVH.²⁹⁰ Conversely, earlier reports suggest that 11% to 20% of HT patients may experience LVDD without exhibiting any signs of LVH.²⁹¹

Hypertensive heart disease can be categorized into four degrees²⁷⁹ based on the pathophysiological and clinical impacts of HT on the cardiac muscle (Table 18).

In the presence of hypertensive hypertrophy, the severity of LVDD can be staged using an algorithm based on the assessment of mitral inflow, primarily the E/A ratio, as previously described by Nagueh et al.¹⁵ Left atrial strain (LAS) is also recommended for further evaluation of diastolic performance. LAS alterations may manifest before the onset of LA enlargement, which is a well-established standalone indicator of cardiovascular events.²⁹²

In the majority of patients with HT, LVDD grade I or II is typically detected (Figure 51B and 51C). Grade III LVDD may be rarely observed in advanced hypertensive cardiomyopathy; however, severe LVDD is not commonly expected in patients with HT and normal left ventricular systolic function. Therefore, it is important to consider that in patients with no history of HT or those with controlled HT, and coexisting LVH and grade III diastolic dysfunction, other causes of hypertrophy such as restrictive or infiltrative cardiomyopathies should be excluded.

Over the last two decades, there has been extensive research into cardiac mechanics concerning LV structural abnormalities. Speckle-tracking echocardiographic techniques have proven

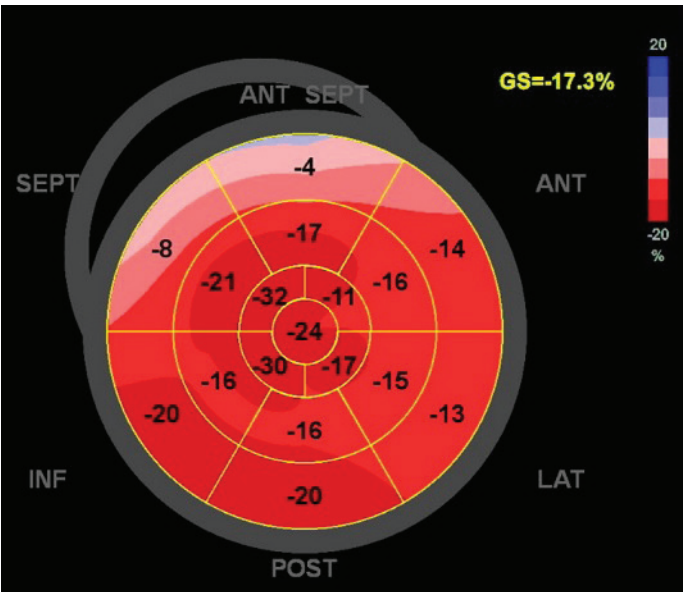


Figure 53. Strain analysis reveals marked impairment in most of the basal segments, particularly the septum, in an uncontrolled hypertensive patient. Global longitudinal strain is measured at 17.3%.

valuable in detecting the initial changes of hypertensive hypertrophy. 2D speckle echocardiography enables the assessment of global longitudinal strain (GLS), which can unveil the onset of subclinical LV systolic dysfunction in hypertensive patients.²⁹³ The basal septum is typically the first region affected by pressure overload, leading to a further decrease in GLS at this location. However, in chronic uncontrolled cases, other segments may also be affected (Figure 53). GLS serves as a useful prognostic tool in cardiomyopathies and is considered more accurate than traditional echocardiographic parameters.²⁹⁴ Basic echocardiographic features and strain patterns in different models of hypertrophy are outlined in Table 19.

In a recent study involving 200 patients, Bendiap et al.²⁹⁵ demonstrated that HT duration exceeding 10 years and uncontrolled HT correlated with a decrease in GLS. They reported that 46% of patients exhibited low GLS values (<17%), and such low GLS values were associated with prolonged HT duration and uncontrolled blood pressure among patients with HT and preserved left ventricular ejection fraction (LVEF). Several echocardiographic parameters have been linked to reduced GLS, including LV filling pressures, LA volume, RWT, concentric remodeling, and concentric LVH. These findings align with those of the study conducted by Narayanan et al.,²⁹⁶ which indicated that individuals with mild, new-onset HT and preserved LV function did not exhibit significant alterations in

Table 19. Basic Echocardiographic Features and Strain Patterns in Different Models of Hypertrophy

Cause of Left Ventricular Hypertrophy	LVEF	Diastolic Function	GLS Value	Localization of Impaired Longitudinal Strain
Arterial Hypertension	Normal or Reduced	Abnormal	Normal or Reduced	Basal Septum
Aortic Stenosis	Normal or Reduced	Abnormal	Normal or Reduced	Basal LV Segments
Athlete's Heart	Normal	Normal or Supranormal	Normal	None
Hypertrophic Cardiomyopathy	Normal / Supernormal or Reduced	Abnormal	Reduced	The site of hypertrophy, mostly interventricular septum
Cardiac Amyloidosis	Normal or Reduced	Abnormal	Reduced	Apical Sparing (regional variance in longitudinal strain from base to apex)
Fabry Disease	Normal or Reduced	Abnormal	Reduced	Basal Posterior–lateral Wall

LVEF, left ventricular ejection fraction; GLS, Global longitudinal strain.

GLS. Additionally, Galderisi et al.²⁹⁷ reported that the extent of GLS was strongly correlated with LVDD, irrespective of changes in afterload and the degree of LVH.

LV torsion, the twisting motion of the heart, has garnered attention in studies involving HT patients. Interestingly, Camelli et al.²⁹⁸ noted increased LV torsion dynamics in patients exhibiting concentric remodeling and concentric hypertrophy during the initial stages. They suggested that in hypertrophy characterized by thick LV walls, epicardial fibers became more prominent, and the transmural gradient of myofibers increased, resulting in enhanced LV torsion. However, in advanced hypertensive heart disease, LV geometry changes, adopting a spherical shape. Consequently, the oblique architecture of LV loop fibers is lost, impairing LV torsion. Thus, enhanced LV torsion appears to serve as a compensatory mechanism in the early phases, but this hyper-torsion is irreversibly lost in the more advanced stages of eccentric hypertrophy.

Computed Tomography in Hypertensive Hypertrophy

While CMR is often considered the gold standard for measuring LV mass and functional parameters, CT imaging also plays a valuable role in providing anatomical and functional assessment of the LV chambers and tissue characterization of the LV myocardium, complementing echocardiographic and CMR evaluations.^{281,299} CT can measure biventricular wall thickness, allowing for the detection of asymmetrical hypertrophy and variations in wall thickness across different segments. Moreover, there exists a strong correlation and linear relationship between cardiac CT and CMR in evaluating LV volumes, ejection fraction, and mass.³⁰⁰

Additionally, CT is effective in excluding coronary artery disease in patients with HT. Furthermore, it can aid in evaluating secondary causes of hypertension, including both hormonal (e.g., hyperaldosteronism, pheochromocytoma) and non-hormonal (e.g., aortic coarctation, renal artery stenosis) disorders. Accurate diagnosis of secondary causes of HT is crucial, as many of these conditions are treatable, leading to improved symptoms or resolution of HT.

However, it is important to note that during CT examination, concerns remain regarding radiation exposure and the use of nephrotoxic iodinated contrast media. Nevertheless, CT can be particularly useful in cases where echocardiography results

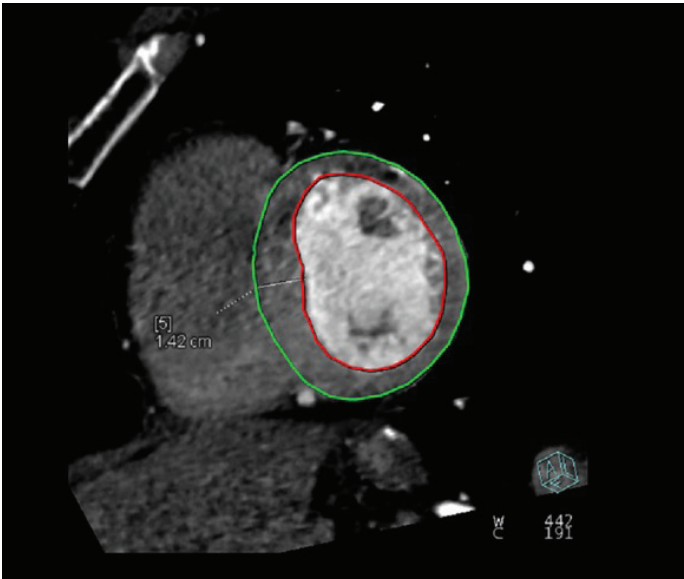


Figure 54. A reconstructed end-diastolic computed tomographic view of the left ventricular short axis reveals left ventricular hypertrophy attributable to hypertension.

are inconclusive or suboptimal, or when CMR is contraindicated due to factors such as the presence of intracardiac devices, pacemakers, or defibrillators. Figure 54 depicts a short axis CT image illustrating asymmetrical LVH due to HT.

Nuclear Imaging

Radionuclide scanning, utilizing single photon emission computed tomography or positron emission tomography, is often utilized in patients with HT; however, its role in evaluating hypertensive LVH is limited. In this patient population, coronary artery disease stands as the primary cause of mortality, with coronary microcirculatory abnormalities associated with LVH playing a significant role in the pathogenesis of complications linked to LVH.³⁰¹

Given that HT patients often exhibit nonspecific ECG abnormalities in the presence of LVH, treadmill exercise stress testing is less practical. Therefore, myocardial perfusion scintigraphy during physical or pharmacological stress emerges as a favorable choice for assessing coronary artery disease in patients with HT and LVH.

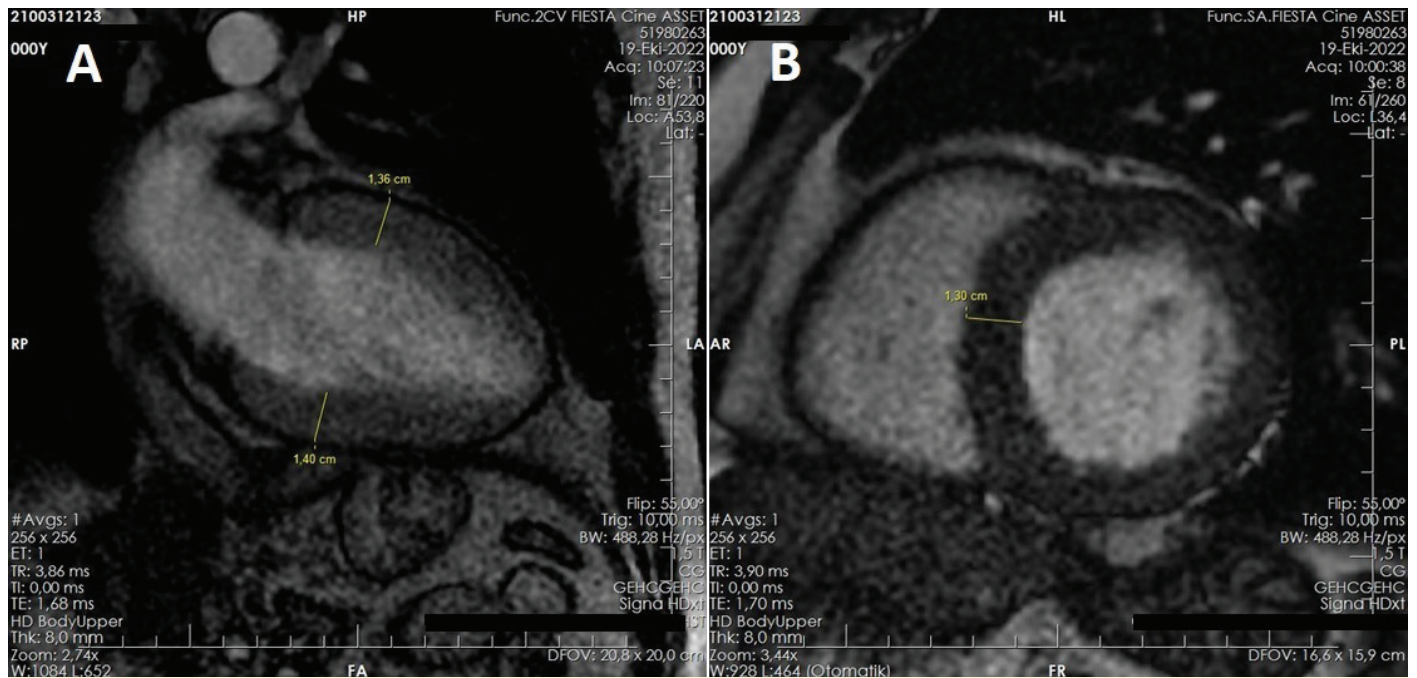


Figure 55. CMR images of a patient with mild to moderate concentric left ventricular hypertrophy related to hypertensive HT. (A) Two-chamber long-axis view. (B) Short-axis cine SSFP study.

Magnetic Resonance in Hypertensive Hypertrophy

CMR has been employed in prior studies investigating antihypertensive drugs, demonstrating regression of LV mass.³⁰² As previously highlighted, CMR stands as the gold-standard modality for evaluating LV structure and tissue characteristics. However, its consideration as a first-choice option in HT patients raises questions regarding cost-effectiveness and necessity.³⁰³

Steady-state free precession (SSFP) imaging allows for the assessment of LV function, chamber size, wall thickness, LV mass, and both local and global wall motion.³⁰⁴ Additionally, SSFP cine images enable the evaluation of LA volumes, which are essential in assessing diastolic functions, particularly in long-axis views. CMR facilitates the calculation of atrial filling, peak diastolic filling rate, and time to peak diastolic filling based on SSFP cine images.³⁰⁵

Strain imaging with CMR proves valuable for both global and local evaluation of LV function, with reduced circumferential strain found to be associated with increased blood pressure.³⁰⁶ Furthermore, advanced tissue characterization techniques such as T1 mapping, T2 mapping, and T2-weighted sequences can be employed to exclude other causes of LVH.³⁰⁷

A significant advantage of CMR lies in its ability to provide absolute quantification of fibrosis using late gadolinium enhancement (LGE). Around half of HT individuals with LVH exhibit LGE with a non-specific distribution.³⁰⁸ Additionally, the extent of LGE has been reported to correlate with the severity of diastolic dysfunction.³⁰⁹

CMR facilitates the evaluation not only of myocardial cells but also of the interstitial space. This assessment holds significance

in HT patients, as the majority of changes in HT occur in this space, which cannot be depicted by echocardiography.^{310,311} Despite the recent guideline from the Society of Cardiac Magnetic Resonance not recommending CMR for the evaluation of HT-related hypertrophy,³¹² it is important to note that if LVH is disproportionate to the degree of HT, other causes of LVH should be assessed using CMR. Figure 55 illustrates a patient with mild to moderate concentric LVH related to HT.

Differential Diagnosis of Hypertensive Hypertrophy

Many echocardiographic findings can help distinguish between physiological and pathological hypertrophy, as well as differentiate between various forms of hypertrophy. If echocardiographic findings are unclear, multimodal imaging may be necessary. The diagnosis of hypertensive hypertrophy does not appear difficult in the presence of mild LVH and clinical findings associated with HT.³¹⁴ The majority of the HT population typically exhibits a symmetrical concentric mild LVH pattern. However, identifying hypertensive heart disease and other cardiomyopathies can be challenging when the wall thickness falls within the range of 12 to 16 mm. Patients with HT may have coexisting cardiomyopathy, requiring additional time to be spent on the differential diagnosis of HT, especially in those with moderate to severe LVH or an asymmetrical LVH pattern.

Hypertrophic cardiomyopathy is the primary consideration in the differential diagnosis of LVH associated with hypertensive heart disease. In HCM, the distribution of hypertrophy throughout the LV walls and segments can vary significantly among patients, resulting in various patterns of LVH.³¹³ HCM typically affects the interventricular septum more than other LV walls, and asymmetric septal hypertrophy is often

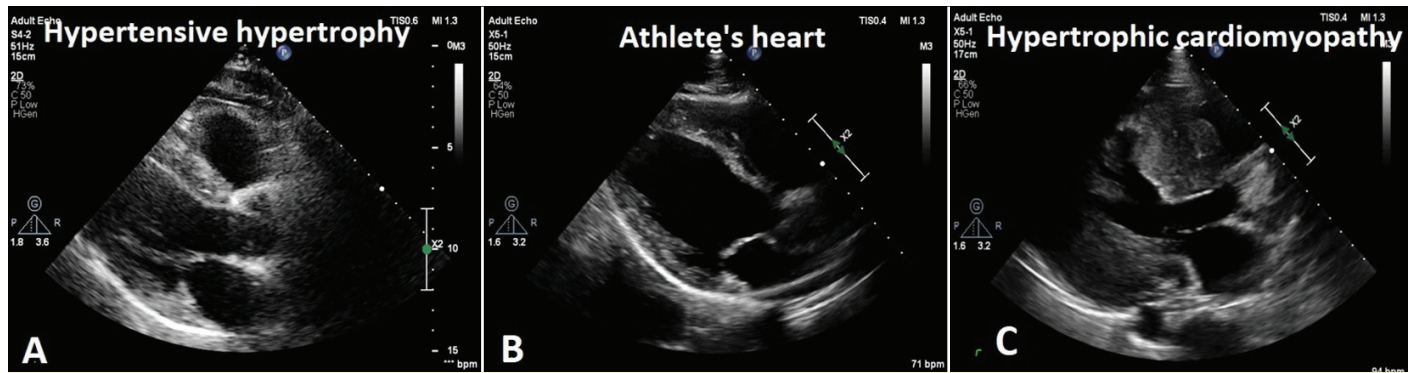


Figure 56. Transthoracic parasternal echocardiographic view of (A) Hypertensive hypertrophy with mild concentric LV geometry, (B) Athlete's heart with eccentric LV hypertrophy, and (C) Hypertrophic cardiomyopathy with massive LV hypertrophy.

considered a key diagnostic feature to distinguish HCM from LVH associated with HT. However, making this distinction can be challenging.

In an older study, Wicker et al.³¹⁴ reported a 5% prevalence of asymmetric septal hypertrophy on 2D echocardiography in patients with HT. Their definition of LV asymmetry was based on a septal thickness 1.3 times greater than the free LV wall, without a specific absolute end-diastolic wall thickness threshold. A more recent study by Rodrigues et al.²⁸² observed a higher prevalence of hypertensive LV asymmetry using CMR. They found that asymmetrical end-diastolic wall thickness of 15 mm or 1.5-fold the opposing myocardial segment occurred in at least one segment in one-fifth of their purely HT cohort.

Patients with asymmetric hypertensive heart disease, particularly in older age groups, have also been noted to have more acute aortoseptal angulation and less aortic distensibility. This study highlights the frequent morphological overlap between hypertensive heart disease and HCM, especially considering the 15 mm septal thickness threshold recommended by the European HCM guidelines.¹

Cardiac mechanics play a crucial role in differentiating between LVH due to HT and HCM. Unlike hypertensive LVH, patients with HCM often exhibit reduced regional radial and circumferential strain measured by 2D speckle tracking imaging, along with the detection of LV dyssynchrony despite normal global LV systolic function.³¹⁵ Conversely, GLS tends to be relatively preserved in HT-related LVH.

Diagnosing HCM can be challenging, particularly in cases with mild wall thickening (13–14 mm). Therefore, caution is warranted when diagnosing HCM solely based on wall thickness, especially in the presence of concomitant HT. CMR proves to be highly valuable in such scenarios. Additionally, CMR may serve as the primary method for confirming HCM, especially when LVH is confined to specific regions such as the anterolateral free wall, posterior septum, or apex, which may be difficult to visualize using echocardiography.³¹⁶ Furthermore, CMR with LGE imaging can aid in the differential diagnosis of LVH. The prevalence of LGE, indicative of focal replacement fibrosis, is low in patients with HT, whereas it has been reported in approximately 72% of patients with HCM.³⁰⁸

CMR can also identify risk factors for sudden cardiac death, such as apical aneurysms, which may be small and undetectable by echocardiography. Secondary findings, such as an elongated mitral valve and anomalous papillary muscle insertion into the mitral valve, may favor obstructive HCM. Conversely, the absence of systolic anterior motion of the mitral valve may serve as a helpful discriminator, favoring hypertensive heart disease.

Athlete's heart typically manifests as a physiological hypertrophy, characterized by eccentric LVH with maximal wall thickness <14mm. It is often accompanied by balanced biventricular dilatation, normal LVEF, normal diastolic functions (or supernormal), and preserved GLS. The evaluation of LV diastolic function appears to be a crucial factor in distinguishing between physiological LVH secondary to exercise adaptation and hypertensive heart disease. An important feature of athlete's heart is the regression of hypertrophy after a period of complete detraining.

Hypertensive heart disease-related LVH, HCM, and athlete's heart are depicted in Figure 56.

Cardiac amyloidosis represents another common cause of LVH, typically characterized by symmetric wall thickness followed by the development of restrictive ventricular filling patterns and involvement of the right heart. Additionally, distinctive echocardiographic features of cardiac amyloidosis include the presence of pericardial effusion and thickening of the atrioventricular valves, setting it apart from hypertensive hypertrophy. Signs of cardiac deformation such as decreased global myocardial GLS and increased relative apical sparing are often observed. Moreover, global diffuse LGE with high T1 mapping values can be detected on CMR.³¹⁷

Fabry's disease is a rare cause of concentric LVH. In addition to concentric LV remodeling or hypertrophy, disproportionate hypertrophy of the papillary muscles may be detected. Although LVEF may be preserved, myocardial strain is often impaired, typically showing regional reduction in the basal and mid inferolateral segments, along with right ventricular hypertrophy. Consequently, LGE can be observed in the lateral wall. Lipid accumulation resulting from alpha-galactosidase-A deficiency is associated with a reduction in native T1, leading to lower T1 mapping values, along with enhanced T2 values in the presence of edema.⁴³

As a result, multimodality imaging, including CMR, plays an incremental role in excluding mimickers of hypertensive heart disease. These pathologies are discussed in separate chapters.

Conclusion and Future Perspectives

Hypertensive hypertrophy is a pathological cardiac hypertrophy secondary to pressure overload. In most patients with HT, LVDD is the initial expression of heart disease, but LVH typically develops in cases of uncontrolled HT. Other cardiomyopathies may accompany HT-associated LVH, and identifying cardiomyopathies can be challenging when wall thickness is in the 12–16 mm range (considered the grey area).

Recent advances in cardiac imaging, including basic and advanced echocardiography, CT, nuclear medicine, and CMR, allow for a more accurate evaluation of ventricular volumes, thickness, systolic and diastolic function, and tissue structure. Echocardiography is the most practical imaging modality for evaluating HT-related LVH. Speckle tracking echocardiography can detect subclinical myocardial dysfunction by measuring intrinsic myocardial deformation.

CMR is considered the gold standard modality for assessing cardiac volumes, LV mass, and function. Although current guidelines do not initially recommend the use of CMR for HT patients, it can provide valuable data, especially when LVH is disproportionate to the degree of HT. CMR can offer a direct measure of fibrosis using either LGE or T1 mapping and can be utilized to exclude other causes of LVH.

Despite the incremental role of multimodality imaging, it's essential to integrate data acquired from imaging modalities with clinical history, ECG, and laboratory findings to reach a correct diagnosis.

Recent advancements in imaging modalities, such as new CMR sequences and advanced speckle-tracking software, along with the growing utilization of artificial intelligence, have the potential to assist clinicians in better differentiating the causes of hypertrophy by integrating clinical and imaging data.

Acknowledgement: The CT and CMR images are obtained from the archives of Türker Acar MD and Ahmet Barutçu MD.

Cardiac Involvement in AL Amyloidosis

Cardiac amyloidosis (CA) is a progressive form of infiltrative cardiomyopathy caused by the extracellular deposition of misfolded amyloid fibrils in the myocardium.^{318,319} Based on the accumulating protein precursors, there are two main types of CA. The first is amyloid light chain (AL-CA) amyloidosis, which results from the deposition of monoclonal immunoglobulin light chains produced by bone marrow plasma cells. The second is amyloid transthyretin (ATTR-CA) amyloidosis, caused by the deposition of transthyretin, a serum transport protein for thyroid hormone and retinol, primarily synthesized by the liver.⁷⁵ ATTR amyloidosis is further classified into wild-type (wtATTR) and hereditary/variant (vATTR) subtypes.²⁰

AL-CA is a hematologic emergency that affects fewer than 50 people per million and usually involves multiple organs. It is characterized by a rapidly progressive clinical course; if left untreated, the median survival is less than six months. Although it can occur at younger ages, AL-CA typically becomes symptomatic after age 40, generally between ages 50 and 70. Cardiac involvement occurs in up to 75% of AL-CA patients, depending on the diagnostic criteria, and the most commonly affected organ is the heart. Renal involvement occurs in 58% of patients and may present with nephrotic-range proteinuria, varying degrees of renal failure, and peripheral edema.^{321,322}

Peripheral neuropathy, autonomic dysfunction, and gastrointestinal complaints may be the initial findings in some patients. Periorbital ecchymosis and macroglossia are pathognomonic but occur in only 10% of patients.³²³ Compared to ATTR, carpal tunnel syndrome is less common in AL-CA. Amyloid accumulation in small coronary vessels can lead to microvascular dysfunction and angina.³²⁴ Multiple myeloma can be identified in 10–15% of patients, but most patients have fewer than 20% plasma cells in bone marrow biopsies. An important clue for cardiologists is severe hypotension after the initiation of angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blocker (ARB) therapy, or clinical worsening after the initiation of β -blockade.³²⁵ Severe cardiac involvement at diagnosis often prevents patients from receiving optimal treatment and results in a survival of 6–12 months.³²⁶

The fundamental pathophysiology involves the deterioration of the tetrameric structure of the transthyretin protein. In ATTRm (mutant), this occurs due to various gene mutations, and in ATTRwt (wild-type), it results from aging. This deterioration decomposes the protein into monomers, which then misfold and accumulate in organs. ATTRwt is more common, with a prevalence of up to 10% in elderly patients with heart failure with preserved ejection fraction (HFpEF) and up to 16% in elderly patients with aortic stenosis.

The most common extracardiac involvement in ATTRwt is carpal tunnel syndrome, which may occur years before cardiac manifestations. Additionally, biceps tendon rupture, spinal canal narrowing, and hearing loss can be detected. Sensory/autonomic polyneuropathy often accompanies mutations identified in ATTRm amyloidosis.^{327,328}

Different types of cardiac amyloidosis have different clinical courses, prognoses, and treatment approaches (Table 20).

Cardiac amyloidosis presents diagnostic difficulties. It is a rare disease and can be challenging to differentiate from other common causes of left ventricular (LV) hypertrophy, such as hypertension,

Table 20. Main types and clinical features of cardiac amyloidosis modified from source³²⁵

Type	Precursor Protein	Underlying disorder	Organ involvement	Sex and age	Typical clinical presentation
AL	Immunoglobulin light chain	Plasma cell dyscrasia	Renal Heart Liver Autonomic nervous system Peripheral nerve System	Either sex, >50	Heart failure with multiorgan involvement such as nephrotic syndrome, autonomic dysfunction, orthostatic hypotension, peripheral neuropathy, macroglossia and periorbital purpura, severe hypotension after ACEI/ARB
ATTR wt	Wild-type transthyretin	Aging	Heart	Male>Female >70	Slowly progressive fatigue, exercise intolerance, weight loss and gastrointestinal complaints, left and right sided congestive heart failure with normal systolic function and diastolic dysfunction, arrhythmias. History of carpal tunnel syndrome
ATTR m	Mutant transthyretin	TTR gene mutation	Nervous system Heart	Male>Female >40	Symptoms of slowly progressive heart failure with peripheral or autonomic neuropathy (As in ATTRwt). Family history of neurological disease

Table 21. Cardiac amyloidosis 'red flag' findings are adapted from the table in reference.³²⁹

Possible family history	LV wall thickness $\geq 12\text{mm}$ + At least one of these
HFpEF in ≥ 65 years	
Severe aortic stenosis in ≥ 65 years	
Normotensive or hypotensive while previously hypertensive	
Autonomic dysfunction	
Peripheral neuropathy	
Proteinuria	
Skin bruising	
Bilateral carpal tunnel syndrome	
Biceps tendon rupture	
Low QRS voltage discordant with hypertrophy	
Pseudo Q wave on ECG	
AV conduction disturbance	
Reduction of LV GLS with apical sparing	
Subendocardial/transmural LGE or increased ECV in CMR	

chronic renal failure, hypertrophic cardiomyopathy, and aortic stenosis. Low awareness of the disease adds to the challenge. However, the most important factor in diagnosis is clinical suspicion. The presence of certain clinical findings (red flags) in patients with LV hypertrophy should alert the clinician to conduct further examinations (Table 21).

Recent advances in cardiac imaging, diagnosis, and treatment have led to the increased recognition of cardiac amyloidosis and have improved its management.^{319,330}

Electrocardiography

The typical Electrocardiography (ECG) in cardiac amyloidosis is characterized by low QRS voltage due to amyloid infiltration and is observed in approximately 50–60% of AL–CA cases and 20% of ATTR–CA cases. Therefore, the diagnosis of CA cannot be ruled out in the presence of normal or elevated voltage on the ECG.^{331,332}

The combination of pericardial effusion and concentric LV wall thickening, along with low or normal QRS voltages, should raise the clinician's suspicion of cardiac amyloidosis.³³³

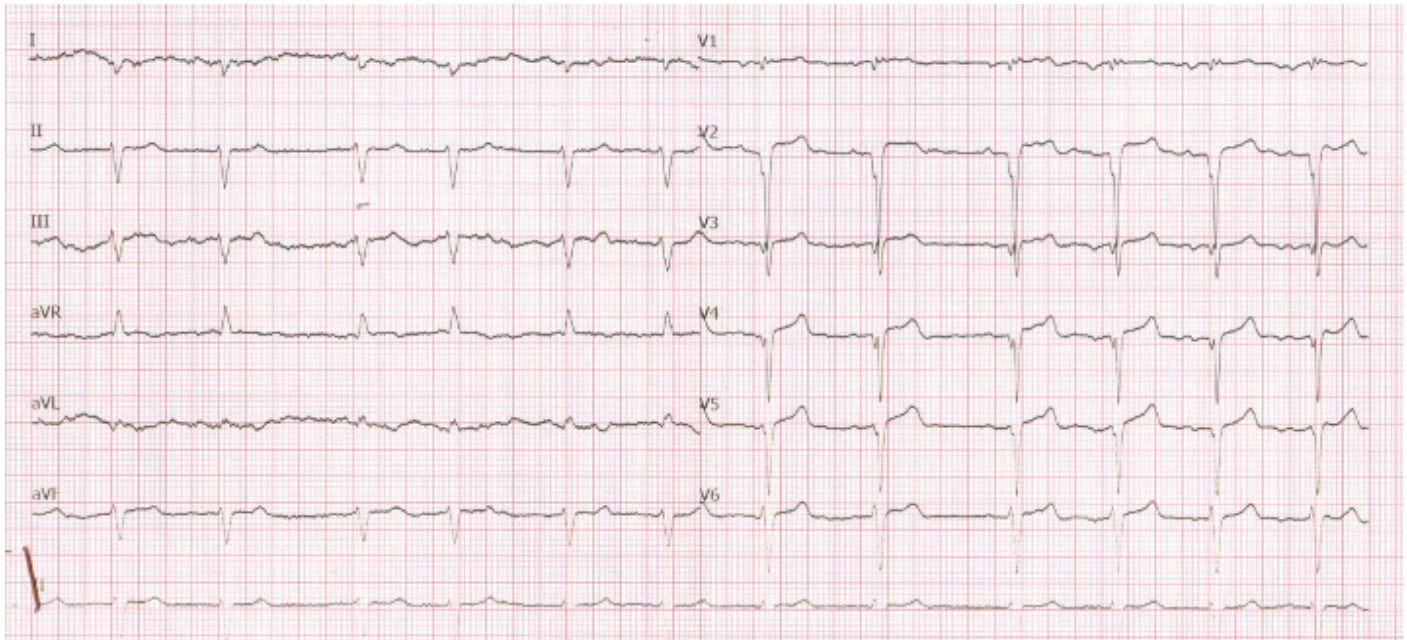


Figure 57. Pseudoinfarct pattern in the anterior face leads on electrocardiography.

Particularly, the ratio of QRS voltage to echocardiographic LV wall thickness is important in diagnosing cardiac amyloidosis (relative increased wall thickness).³¹⁸ Increased LV wall thickness in the presence of a low-voltage ECG pattern may distinguish cardiac amyloidosis from hypertensive or hypertrophic cardiomyopathy.³³⁰ Pseudoinfarct patterns are present in approximately 50–70% of patients,^{332,334} often leading to unnecessary coronary angiography (Figure 57).

Prolonged QRS duration and conduction abnormalities affecting the sinus node and His–Purkinje systems are also common. Atrial fibrillation (AF) frequently occurs, with the highest prevalence in ATTRwt patients (40%), and lower rates in ATTRm (11%) and AL (9%) patients.^{325,334} The P wave may reflect prolonged atrial conduction or atrial dilation. Amyloid fibril infiltration into the conduction system can lead to sinus node dysfunction, AV block, AF with a slow ventricular response, and may necessitate permanent pacing.³²⁸ The presence of atrioventricular block in patients with left ventricular hypertrophy should raise suspicion.³²⁵ These patients may present with syncope or presyncope.

Sudden cardiac death (SCD) in patients with AL amyloidosis is usually due to electromechanical dissociation rather than a primary arrhythmic event.³³⁵ For patients with a high burden of Non sustained ventricular tachycardia or sustained ventricular tachycardia on telemetry monitoring and for those awaiting cardiac transplantation, a careful risk–benefit analysis for ICD is recommended.³³⁶ ICD implantation should be individualized for secondary prevention.

Echocardiographic Imaging

Echocardiography plays a crucial role in the non-invasive diagnosis of cardiac amyloidosis due to its widespread use in evaluating structure and function in patients with cardiac symptoms.

Infiltration of amyloid fibrils among cardiomyocytes leads to concentric wall thickening in the LV, resulting in impaired LV relaxation and progressive diastolic dysfunction, reflecting the disease's course. Although the left ventricular ejection fraction (LVEF) usually appears normal, it declines as the disease progresses.³³⁷ In advanced cases, the LV exhibits a restrictive filling pattern.³³⁸

Echocardiographic findings, known as 'red flags,' suspicious for cardiac amyloidosis:³³⁷

- * Increased wall thickness of the LV (≥ 1.2 cm) or both ventricles without evidence of LV overload.³³⁷

The measurement of hypertrophy requires great care. Measurement of the interventricular septum (IVS) might be difficult because of the moderator band, supraventricular crest, and trabeculations in the right ventricle (RV). It is possible to verify wall thickness using the parasternal short-axis view. RV wall thickness is best measured through the subcostal window. Two-dimensional or M-mode echocardiographic measurements should be taken at the end of diastole, when the valve is fully open, at the level of the anterior tricuspid leaflet tip, 1 cm below the tricuspid annulus, and a measurement >5 mm is considered RV hypertrophy.

While the LV is symmetrically hypertrophic in AL amyloidosis, it is asymmetrically hypertrophic in ATTR amyloidosis, with a prominent appearance of the sigmoid septum. Sigmoid septum is observed in 70% of cases, while reverse septal curvature is seen in 30%. ATTR amyloidosis results in greater deterioration of LV systolic and diastolic function compared to AL amyloidosis. It also leads to a greater increase in both LV and RV masses (Figure 58).

- * Increased echogenicity of the myocardium (granular sparkling)

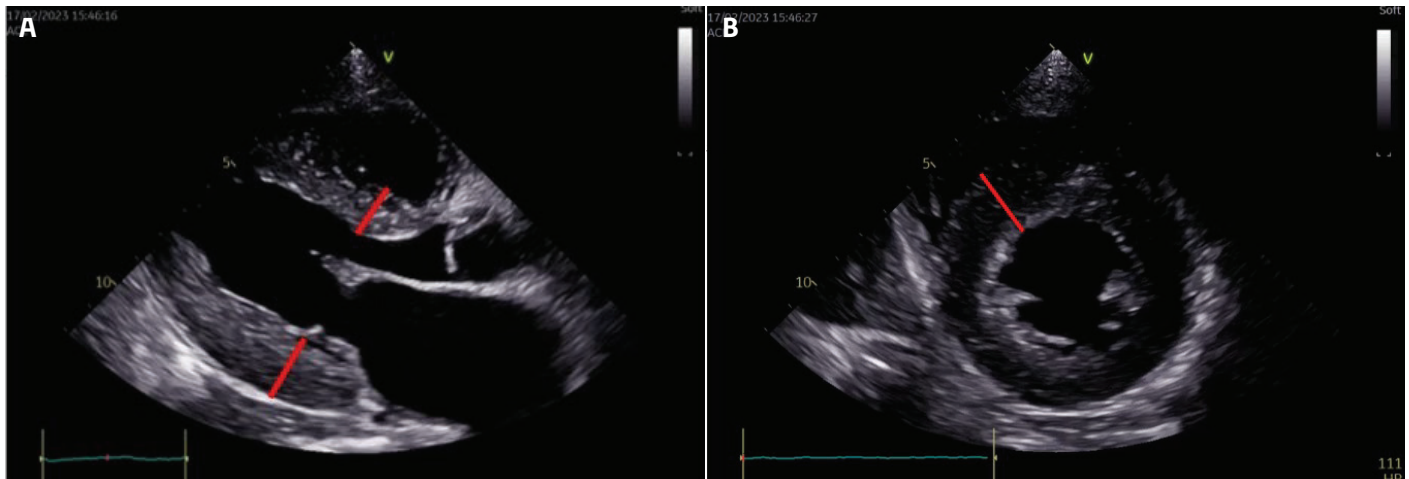


Figure 58. (A) Typical echocardiographic findings in cardiac amyloidosis. (B) Typical echocardiographic findings in cardiac amyloidosis.

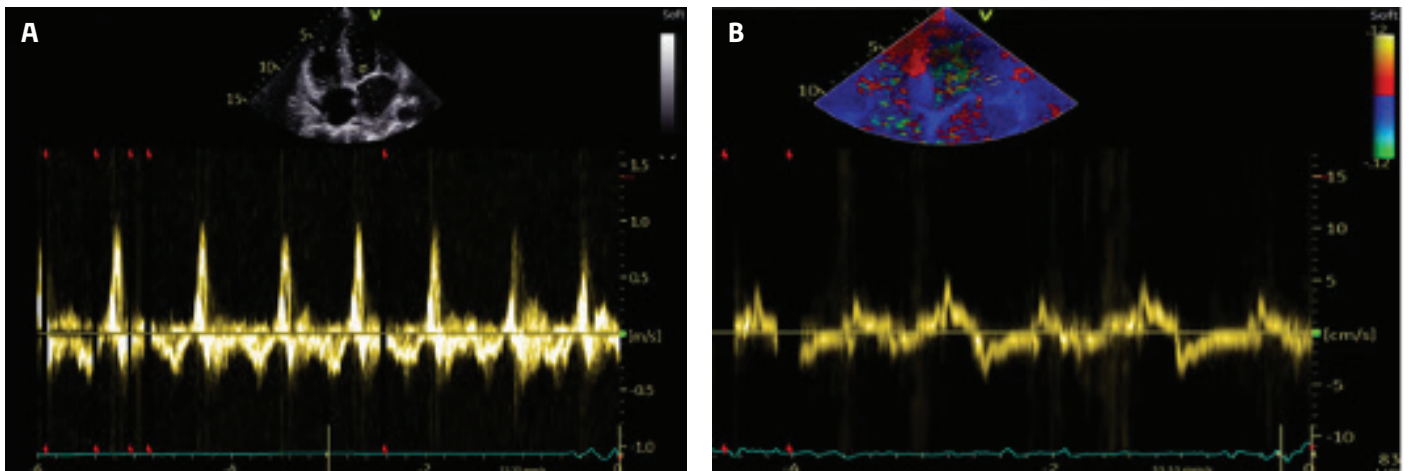


Figure 59. (A) Restrictive pattern on mitral Doppler recording in a patient with AL-CA. (B) Decreased s', e', a' velocities on tissue Doppler examination ("5-5-5" finding).

- * Biatrial enlargement
- * Increased atrial septal thickness (>0.5 cm), disappearance of the "drop-out" zone,
- * Increased concentric LV wall thickness with normal or low-voltage criteria on associated ECG
- * Diffuse valve thickening
- * Diastolic dysfunction (>grade I I) (E/A ratio >1.5) with elevated LV filling pressures and reduced E wave deceleration time (<150 msec).
- * Mitral annular septal and lateral all tissue Doppler s', e', and a' velocities generally very low (<5 cm/sec) (the "5-5-5" sign) (Figure 59)
- * Pericardial or pleural effusions
- * Preserved ejection fraction with low stroke volume index
- * Paradoxical, low-flow, low-gradient severe aortic stenosis
- * 'Apical sparing' "Cherry-on-the-top" sign; reduced global longitudinal strain (GLS) with apical sparing (< -15%); the apical segmental strain values are greater than those in the basal and mid segments.³³⁷ Apical longitudinal strain/mid +

basal segment >1 is a characteristic finding for CA (sensitivity 93%, specificity 82%) and helps distinguish cardiac amyloidosis from other forms of cardiac hypertrophy.³³⁸ While longitudinal systolic functions are generally impaired in the early period, radial thickening and circumferential shortening are still preserved (Figure 60).^{318,339,340}

Another quantitative measure of LV contractility in cardiac amyloidosis is the myocardial contraction fraction (MCF), which is the ratio of stroke volume to myocardial volume. MCF is an index of myocardial volumetric shortening and is highly correlated with LV longitudinal strain.³⁴¹

The stroke volume index has prognostic significance similar to that of LV stroke in AL cardiac amyloidosis, independent of biomarkers.³¹⁸

Pulmonary artery systolic pressure, estimated from the peak velocity of the tricuspid valve regurgitant jet, may indicate moderate pulmonary hypertension (estimated pulmonary artery pressure of 40 to 50 mmHg). This elevation is almost certainly due to markedly increased LV diastolic pressure. The

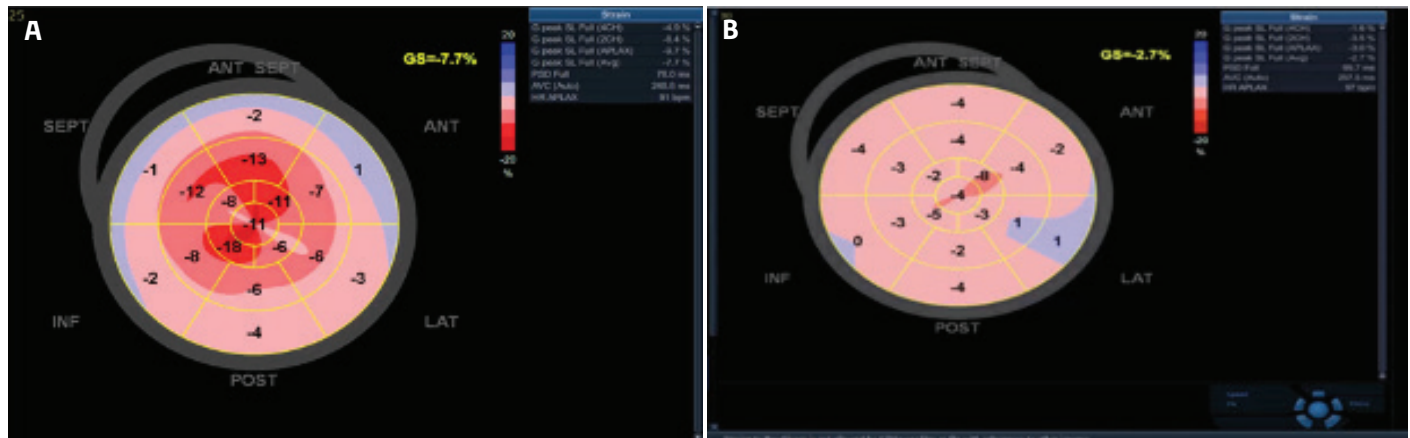


Figure 60. (A) Reduced left ventricular global longitudinal strain in the AL-KA patient along with relatively preserved apical strain (cherry on the top sign). (B) Significantly decreased global longitudinal strain in the late diagnosed AL-KA patient.

RV is affected by a combination of increased afterload from pulmonary hypertension and amyloid infiltration, resulting in reduced excursion of the tricuspid annular systolic plane (TAPSE ≤ 18 mm), decreased tissue Doppler systolic velocity, and reduced longitudinal strain.^{318,342}

The reservoir and pump functions of the left atrium (LA), assessed by strain, are impaired independently of LA dimensions. This impairment demonstrates the contribution of both elevated LV filling pressures and direct atrial amyloid infiltration (as documented by CMR studies) to LA dysfunction. LA dysfunction leads to the formation of atrial and atrial appendage thrombi, even in normal sinus rhythm (atrial standstill), exposing the patient to a high risk of embolic strokes.^{318,343,344}

Cardiac Magnetic Resonance

Cardiac magnetic resonance (CMR) plays a central role in the non-invasive diagnosis of CA due to its ability to provide high-resolution tissue characterization alongside morphological and functional assessment. However, CMR is particularly valuable for clinicians in two clinical scenarios:

1. Differentiating CA from other cardiomyopathic processes with increased wall thickness.
2. Detecting early cardiac involvement in patients with potential evidence of systemic amyloidosis.

A comprehensive CMR evaluation for CA includes assessing the LV and RV and atria using cine imaging, as well as evaluating the native T1 signal, late gadolinium enhancement (LGE), and measuring extracellular volume (ECV). T1 mapping is a quantitative method that measures signals directly from the myocardium both pre-contrast (native T1) and post-contrast ECV. T1 mapping before and after contrast administration quantitatively measures the contrast change between the cardiac blood pool and the enhanced ECV, thus allowing the degree of infiltration to be determined.

Conventional LGE imaging techniques may present challenges in imaging and evaluating CA. However, with the PSIR (phase-sensitive inversion recovery) technique, LGE is significantly more specific and sensitive than echocardiographic or CMR functional assessment.

Cine Imaging

Cine CMR is used for the morphologic and functional evaluation of ventricular and atrial tissue. Two-, three-, and four-chamber, as well as short-axis images, are analyzed according to guideline recommendations. Measurements include wall thickness, myocardial structure, and thickening of other cardiac structures, such as the interatrial septum, valves, and atrial wall. Pericardial effusion, atrial thrombus, (LV and RV volumes, and LVEF are also examined.

LV hypertrophy is the main finding in cardiac amyloidosis. A septum/posterior wall thickness ratio of ≤ 1.5 is considered symmetric concentric hypertrophy, while a ratio >1.5 is defined as asymmetric hypertrophy.

In a CMR study involving ATTR and AL patients, asymmetric septal hypertrophy (70% with a sigmoid septum and 30% with a reverse septal contour) was observed in 79% of ATTR patients, while symmetrical hypertrophy was seen in only 18%. ATTR amyloidosis without hypertrophy was detected in 3% of the patients. In the AL patient group, symmetrical hypertrophy was found in 68% of the patients, asymmetric hypertrophy (sigmoid septal contour) in 14%, and AL-CA without hypertrophy in 18%. In amyloid patients, it should be noted that LV hypertrophy may only present as a sigmoid septum, although this is less common in AL-CA (Figure 61A,B).³⁴⁵

Late Gadolinium Enhancement (LGE Imaging)

Many LGE distribution patterns have been described using gadolinium-based contrast agents in the diagnosis of CA. However, subendocardial and transmural involvement predominates.³⁴⁹ Both patterns are present in AL and ATTR cardiac amyloidosis, but subendocardial LGE is more common in AL, while transmural LGE is more common in ATTR. LGE is initially basal but shows a biventricular transmural distribution in advanced disease.³¹⁸

In a recent meta-analysis, CMR-based LGE for diagnosing CA was found to have an estimated sensitivity and specificity of 85% and 92%, respectively. LGE is detected in 100% of patients in the LV and in 96% of patients in the RV. It is also

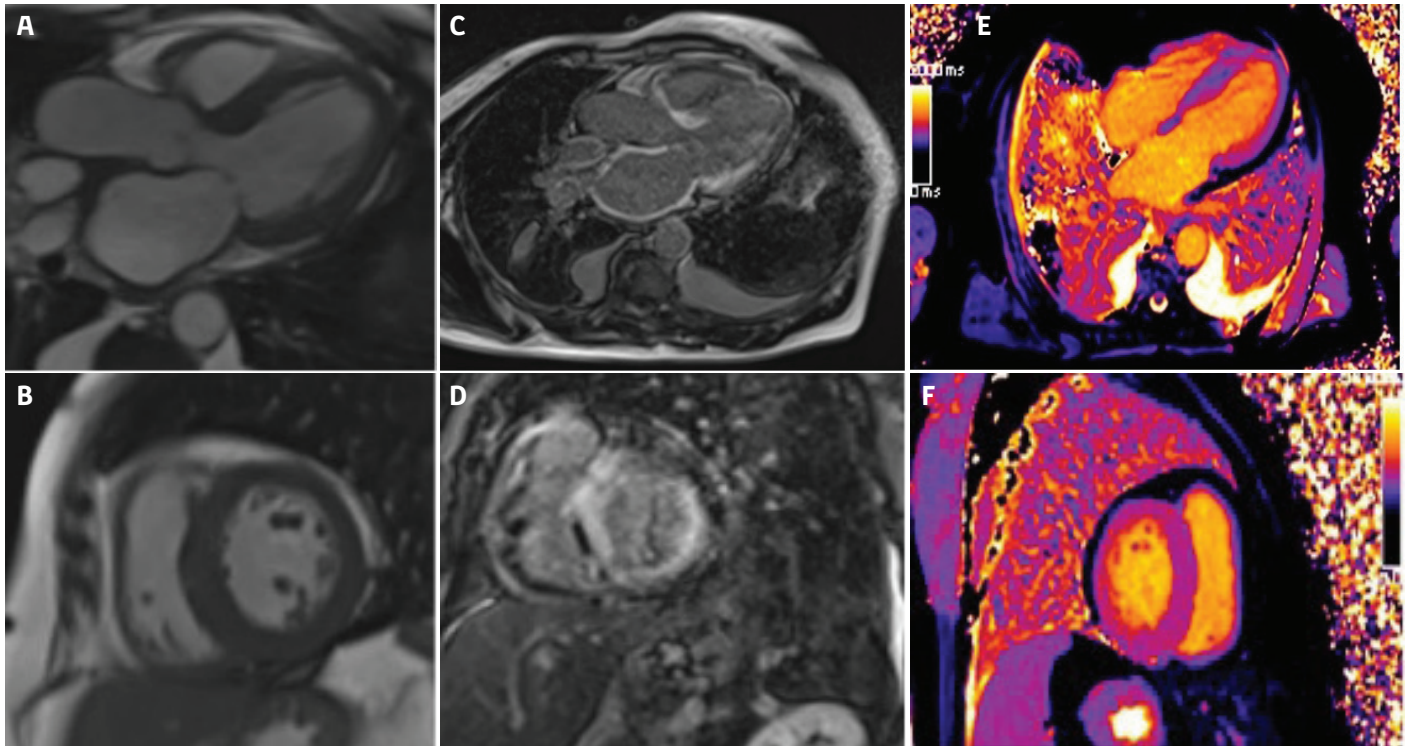


Figure 61. Marked LV and RV hypertrophy in AL-CA patients (A,B). LV subendocardial LGE and LGE in the interatrial septum (C) and transmural LGE (D). Increased native T1 values (E,F).

an important predictor of mortality. Transmural involvement is associated with a poor prognosis; the 24-month survival rate is 45% in AL-CA patients and 65% in ATTR-CA patients (Figure 61C,D).^{350,351}

T1 Mapping and Measurement of Extracellular Volume

T1 mapping measures the T1 signal of each pixel and/or voxel in an image. Compared with normal tissue, native T1 values (before gadolinium contrast medium) are higher in areas of amyloid deposition or extensive fibrosis, reflecting changes in both the myocyte and extracellular space. Native T1 times are prolonged in CA, correlating with the degree of systolic and diastolic dysfunction. The sensitivity of T1 prolongation in detecting CA is 92%, while the specificity is 91%.³⁴⁶

In patients with contraindications to contrast media, native T1 provides valuable information, although its reproducibility is low, particularly in devices with a magnetic field strength of 1.5 T.

Postcontrast T1 mapping and ECV calculation can be performed more reliably and reproducibly than absolute T1 following gadolinium application. Amyloidosis is an interstitial disease, and in patients with AL and ATTR cardiac amyloidosis, increased myocardial mass and wall thickness are combined with significantly elevated ECV (generally >40%). ECV >40% is considered a red flag,³²⁵ but it does not distinguish between subtypes of cardiac amyloidosis. ECV is elevated even in the absence of cardiac LGE enhancement, underscoring its potential role as an early marker of the disease.

There is evidence that both native T1 and ECV can be used to monitor changes in amyloid burden and to predict prognosis.³¹⁸

While native T1 signal is higher in AL patients, ECV values have been found to be higher in ATTR patients.³⁴⁷ Recent studies have shown that higher native T1 may be associated with worse prognosis in AL CA,³⁴⁸ but this relationship has not been demonstrated in ATTR amyloidosis.⁴⁴ Alternatively, T1-derived ECV has been linked to prognosis in both AL and ATTR cardiac amyloidosis (Figure 61E,F).^{348,345}

T2 Mapping

Advanced techniques, such as T2 mapping and perfusion, are used to evaluate the phenotype of CA, including myocardial edema and coronary microvascular dysfunction. Myocardial blood flow and coronary flow reserve are significantly reduced in patients with CA despite the absence of epicardial coronary artery disease.⁷⁹ It is not yet known whether coronary microvascular dysfunction improves after successful anti-amyloid therapy.

T2 mapping, a measure of myocardial edema, adds a third dimension to tissue characterization and is an independent predictor of prognosis in patients with AL CA.³⁵²

Using a combination of CMR features, the possibility of identifying the type of CA (ATTR or AL) can be assessed, but this is typically not sufficient to distinguish AL from ATTR cardiac amyloidosis.^{347,353} The combination of bone scintigraphy and free light chain (FLC) is superior to echocardiography and CMR in differentiating the type of CA.⁷⁵ To optimize diagnostic accuracy, CMR characteristics must be integrated with ECG, clinical, biomarker, and additional imaging findings.

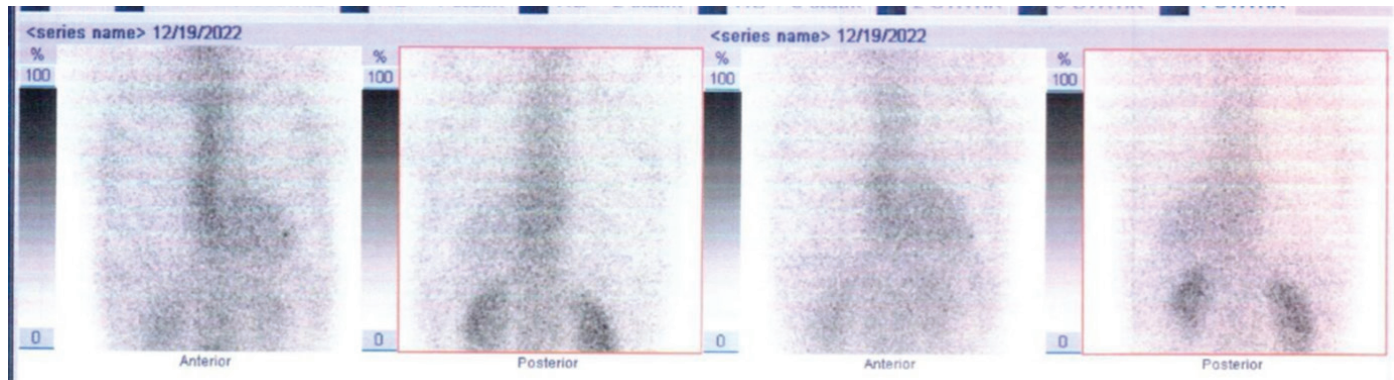


Figure 62. Perugini grade 2 uptake by Tc-99m PYP scintigraphy. H/CL ratio=1.52

Radionuclide Imaging

Radionuclide imaging plays a unique role among imaging modalities for the non-invasive diagnosis of CA. Scintigraphic imaging with technetium (Tc-99m)-labeled bone scintigraphy agents is a non-invasive diagnostic method with high sensitivity and specificity for diagnosing ATTR amyloidosis and distinguishing it from AL amyloidosis.⁷⁵ Tc-99m-labeled pyrophosphate (PYP), Tc-99m-labeled 3,3-diphosphono-1,2-propanocarboxylic acid (DPD), and Tc-99m-labeled hydroxymethylene diphosphonate (HDMP) are used for bone scintigraphy in diagnosing ATTR-CA, depending on local availability. Cardiac uptake of the diphosphonate radiotracers is highly sensitive, though not entirely specific, for (ATTR-CA).^{75,354}

I-123 metaiodobenzylguanidine scintigraphy can be used to identify sympathetic denervation and autonomic dysfunction observed in CA. Additionally, F-18 Florbetapir, F-18 Florbetaben, F-18 Flutemetamol, C11 Pittsburgh compound, and F-18 Sodium Fluoride, all positron emission tomography agents, are radiopharmaceuticals used to evaluate systemic and cardiac amyloidosis. However, they cannot be used routinely due to limited literature data and their limited availability.

While the diagnosis of ATTR-CA previously required an endomyocardial biopsy (EMB), the radionuclide imaging technique has transformed the diagnostic algorithm and clinical practice. All three radiopharmaceuticals (Tc-99m-labeled pyrophosphate, DPD, and HDMP) are known for their high sensitivity in detecting cardiac involvement in ATTR amyloidosis. However, Tc-99m methylenediphosphonate is not recommended for use in CA due to its low myocardial uptake.

The data obtained from this method are combined with echocardiography and CMR findings to differentiate AL-CA from other causes of LV hypertrophy, such as Fabry disease and hypertrophic cardiomyopathy. In hypertrophic ventricles unrelated to ATTR, accumulation is absent or minimal. While grade 0 or 1 involvement is observed in 80% of AL amyloid patients, grade 2 or 3 involvement can be seen in 20%.³⁵⁵

Therefore, to diagnose ATTR-CA, it is crucial to exclude AL amyloidosis in patients with grade 2 and 3 involvement. Grade 2 and 3 involvement in the absence of monoclonal protein in serum and urine indicates 100% specificity and positive

predictive value for ATTR-CA without the need for additional histological diagnosis.

Tc-99m-PYP/DPD/HDMP images are evaluated using visual and semi-quantitative methods. Visual grading is based on Perugini's study and ranges from grade 0 (no involvement) to grade 3:

Grade 0: No cardiac involvement.

Grade 1: Mild cardiac involvement (less than bone involvement).

Grade 2: Moderate cardiac involvement (equal to bone involvement).

Grade 3: High cardiac involvement (greater than bone involvement).⁷⁰

For Tc-99m PYP at 3 hours and for Tc-99m DPD/HDMP scintigraphy at 2-3 hours, semi-quantitative grading is performed by comparing myocardial involvement to bone involvement, using the ribs as a reference. The heart-to-contralateral (H/CL) ratio is calculated by comparing the mean uptake in the heart region of interest (ROI) to the mean uptake in the contralateral thorax (CL) ROI.

An H/CL ratio >1.5 on the 1-hour images distinguishes ATTR from AL-CA with a sensitivity of 97% and specificity close to 100%, provided that no monoclonal protein is detected in serum and urine.⁷⁵ However, it is crucial to ensure that the area of uptake detected on planar images is not confined to the blood pool but also involves the myocardium. For this purpose, SPECT or SPECT/CT is recommended (Figure 62).³¹⁸

A heart/CL ratio of ≥ 1.3 at the end of the 3rd hour on Tc-99m PYP images has been recommended to definitively distinguish ATTR from AL cardiac amyloidosis.

It is recommended to use the report format of the ASNC/AHA/ASE/EANM/HFSA/ISA/SCMR/SNMMI consensus recommendations on multimodality imaging in CA.

1. ATTR does not support amyloidosis: Visual semiquantitative score 0 or H/CL <1

2. ATTR strongly favours amyloidosis: Visual semiquantitative score 2-3 or H/CL >1.5

3. Suspicious for ATTR: Visual semiquantitative score: $1 < \text{H/CL} < 1.5$

Tc-99m PYP/DPD/HMDP uptake (false positivity) may also be seen in other causes of myocardial injury, including pericarditis, acute or subacute myocardial infarction, and chemotherapy- or drug-related myocardial toxicity. In patients with a history of extensive myocardial infarction, the H/CL ratio may be falsely low, as myocardial uptake is limited to the non-infarcted region. Careful evaluation of these imaging studies using SPECT is recommended.

Diagnosis: Laboratory Tests and Pathology

In cases of continued clinical suspicion, EMB is the gold standard method for diagnosing and accurately typing CA with positive monoclonal protein. EMB is a highly sensitive and 100% specific method.³²⁹ Congo red staining will show amyloid deposits as red under bright light and apple-green birefringence under polarized light, which should be followed by immunohistochemistry.

Due to the invasive nature of the procedure, EMB carries a risk of complications, and special expertise is required for interpreting the histological examination. Because of these risks, biopsies of other extracardiac tissues (e.g., subdermal adipose tissue, labial, rectal, renal tissue) are frequently performed to diagnose amyloidosis.³⁵⁶

In AL amyloidosis, the definitive diagnosis is made in close cooperation with hematologists, and bone marrow biopsy is essential to determine plasma cell dyscrasia. AL amyloidosis cannot be diagnosed without a tissue biopsy showing light-chain amyloid deposits from some organ or region (not necessarily the heart). However, insufficient amyloid deposition in relevant tissues may yield negative results, and negative results cannot exclude CA. Performing a tissue biopsy from the symptomatic organ will increase the probability of diagnosis.

To detect monoclonal protein, all three tests must be performed:

1. serum kappa/lambda FLC ratio analysis,
2. serum protein immunofixation and
3. urine protein immunofixation.

While the kappa/lambda ratio is normally between 0.26 and 1.65, a plasma cell disease producing monoclonal light chains leads to altered κ/λ ratios. It's important to consider that the normal κ/λ ratio can also increase in patients with kidney disease. In patients with a glomerular filtration rate (GFR) of 45-59 mL/min/1.73 m², the normal range is 0.46-2.62; in those with a GFR of 30-44 mL/min/1.73 m², the normal range is 0.48-3.38; and for patients with a GFR <30 mL/min/1.73 m², a range of 0.54-3.30 is considered normal.³⁵⁷

Abnormal N-terminal prohormone brain natriuretic peptide (NT-proBNP) levels are often disproportionately elevated due to the toxicity of precursor proteins. Troponins exhibit moderate chronic elevation, fluctuating within a certain range without significant rise or fall. They are usually slightly elevated in ATTR patients, but higher levels are observed in AL amyloidosis patients due to the cardiotoxic effect of light chains. Both troponin and NT-proBNP have prognostic implications in AL-CA and ATTR-CA and can also be used for monitoring treatment response.³⁵⁸

It should be noted that AL cardiac amyloidosis can sometimes lead to grade 1 or even higher degrees of cardiac involvement on bone scintigraphy. Importantly, heart and/or tissue biopsy is required in all cases (i.e., low-grade involvement and positive light chains) to exclude AL-CA and rarer forms of amyloidosis (e.g., AA, AApoA1). Although the presence of monoclonal protein suggests AL amyloidosis, tissue biopsy is crucial because other possible causes may include monoclonal gammopathy of undetermined significance (MGUS) combined with ATTR or MGUS combined with other types of amyloidosis (e.g., AApoA1 or AA) (Figure 63).

Prognosis and Imaging at Follow-Up

CA is not simply an infiltrative disease; it may be better described as a "toxic-infiltrative cardiomyopathy." The specific treatment of cardiac AL amyloidosis should be undertaken in specialized centers by multidisciplinary teams that include oncohematology and cardiology specialists. AL amyloidosis has a rapidly progressive clinical course, and survival is less than six months if left untreated. After diagnosis, staging is necessary to assess treatment appropriateness and prognosis. Staging for AL amyloidosis is based on the Mayo Clinic system, which uses troponin, NT-proBNP, serum FLC, and the performance scale.

Although no study has yet established the optimal follow-up regimen, patients with CA should be considered for 6-month visits, which should include an ECG and comprehensive blood tests (including NT-proBNP and troponin). Annual echocardiography and 24-hour Holter ECG monitoring are also recommended.

The reduction in FLC following anti-plasma cell therapy, known as a hematological response, is typically followed by a reduction in NT-proBNP and troponin within 6 to 12 months, termed an organ-specific response. This response is associated with improved heart failure symptoms and prolonged survival.

Transthoracic echocardiography (TTE) is recommended to monitor disease progression or treatment response and to assess LA size and function. Transesophageal echocardiography (TOE) is recommended to evaluate the left atrial appendage (LAA) for anticoagulation management. CMR is recommended to assess LV wall thickness, LV mass, and especially changes in ECV to monitor treatment response and disease progression.

Currently, serial SPECT 99m Tc-PYP/DPD/HMDP scintigraphy is not recommended for assessing treatment response or disease progression. In one study, basal longitudinal strain values were found to be independent predictors of cardiac involvement, clinical outcomes, and survival in patients with AL amyloidosis.³⁵⁹ Interestingly, the prognosis of patients with the most significant reduction in LGS is much worse, regardless of the Mayo scoring system. Changes in LGS over time can be used to assess treatment response. At the end of one year of treatment, the patient group with a 2% increase in LGS or greater and FLC transformation has the best prognosis.³⁶⁰

In CMR studies, the presence of LV LGE, prolongation of native T1 time, and an increase in ECV have been identified as the strongest prognostic parameters (HR: 2.69, HR: 2.19, HR: 3.95, respectively). It has been reported that a reduction in ECV can be used to evaluate treatment response in both AL-CA and ATTR-CA.³⁶¹

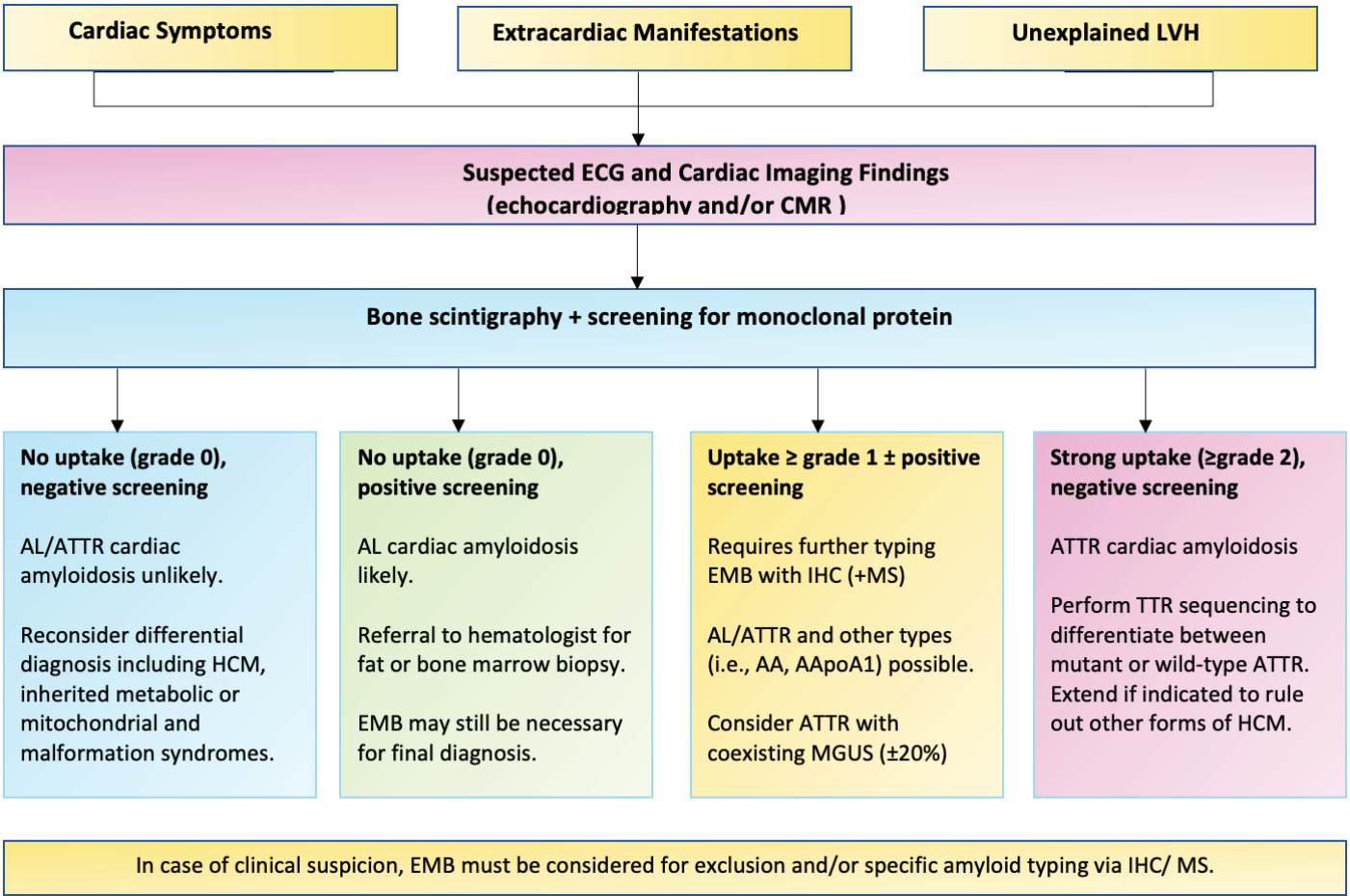


Figure 63. Diagnostic algorithm for AL amyloidosis.³²⁵
HFpEF, heart failure with preserved ejection fraction; AF, atrial fibrillation; SVT, supraventricular tachycardia; LVH, left ventricular hypertrophy; HCM, hypertrophic cardiomyopathy; AS, aortic stenosis; ECG, electrocardiogram; CMR, cardiac magnetic resonance; AL, amyloid light chain; ATTR, amyloid transthyretin; EMB, endomyocardial biopsy; IHC, immunohistochemistry; MS, mass spectrometry; AA, amyloid serum A protein; AApoA1, amyloid apolipoprotein A1; MGUS, monoclonal gammopathy of unknown significance, TTR, transthyretin.

Conclusion

AL amyloidosis is a hematological emergency that often presents as a multisystemic disease, most commonly with cardiac involvement. The diagnosis and treatment of amyloidosis should be approached with a multidisciplinary team. While clinical suspicion is the first step in diagnosis, ECG and imaging findings reveal crucial red flags. Echocardiography is the most important imaging modality for diagnosis, treatment response evaluation, and prognosis assessment. Both ventricles, the interatrial septum, and valves are evaluated for thickening, as are diastolic functions and the pericardium. Tissue Doppler examination and strain analysis provide essential information for diagnosing CA.

Although CMR is not routinely included in the diagnostic algorithm, detecting hypertrophy on cine images, prolongation

of native T1 times, subendocardial-diffuse LGE involvement, and ECV $\geq 40\%$ are vital for diagnosing and monitoring AL amyloidosis. Every patient with suspected CA should be treated as having AL-CA until proven otherwise, and the presence of monoclonal gammopathy should be immediately investigated and evaluated through simultaneous bone scintigraphy. Tissue diagnosis should be performed on the recommendation of a hematologist for every patient in whom the presence of monoclonal gammopathy cannot be excluded by serum/urine immunofixation examination and FLC analysis. Tissue diagnosis is essential for diagnosing AL-CA (typically via bone marrow biopsy).

Recent advances in imaging and the emergence of treatment options for ATTR amyloid have led to increased awareness of amyloidosis among physicians.

Cardiac Involvement in Transthyretin Amyloidosis

Cardiac amyloidosis (CA) is a form of cardiomyopathy characterized by the buildup of misfolded proteins, referred to as amyloid fibrils, in the myocardium. The primary origins of CA typically involve two precursor proteins: amyloid immunoglobulin light chain (AL-CA) and transthyretin (ATTR-CA). In AL-CA, the misfolded protein usually stems from a monoclonal immunoglobulin light chain produced by plasma cells in the bone marrow. Conversely, in ATTR-CA, the misfolded protein is transthyretin (TTR), primarily synthesized by the liver, where it acts as a serum transport protein for thyroid hormone and retinol.⁷⁵

ATTR amyloidosis is further categorized into two main types: wild type (ATTRwt) and hereditary (ATTRv), depending on whether mutations are present in the gene encoding the TTR protein. In ATTR-CA, the homotetrameric structure of the TTR protein is disrupted, leading to the formation of amyloid deposits due to misfolding after separation into monomers and dimers. Various gene mutations in ATTRv destabilize the tetrameric structure, encouraging a propensity to separate into monomers and consequent misfolding. In the case of ATTRwt, aging-related breakdowns in homeostatic mechanisms, oxidative changes in protein structures, and disruptions in repair mechanisms contribute to the natural breakdown and misfolding of TTR, resulting in its accumulation in organs.^{362,363}

Different types of cardiac amyloidosis exhibit significant variability in clinical presentations, prognosis, and treatment strategies. AL-CA is characterized by a rapidly progressive clinical course, with an average survival of less than 6 months if left untreated.³²⁶ In contrast, ATTRv displays variable organ involvement depending on the specific mutation detected, often manifesting as cardiomyopathy and/or sensory/autonomic polyneuropathy. Furthermore, ATTR amyloidosis demonstrates age-related penetrance.

In AL amyloidosis, cardiac involvement is prevalent, observed in up to 75% of cases, although this figure varies based on diagnostic criteria. Conversely, cardiac manifestation is a dominant clinical feature in almost all cases of ATTRwt amyloidosis.³²⁰ The most frequently detected mutations in ATTRv include Val30Met, Val122Ile, and Glu89Gln, among which variants Val122Ile, Leu111Met, and Ile68Leu exhibit predominant cardiac involvement.^{364,365}

In ATTRwt, carpal tunnel syndrome (CTS) is the most common extracardiac involvement, often presenting as an initial symptom that may precede cardiac symptoms by several years. Additionally, issues such as biceps tendon rupture and hearing impairment may also be identified. While polyneuropathy can occur during the course of ATTRwt, it is more closely associated with ATTRv.^{327,366}

Diagnosing cardiac amyloidosis remains challenging due to various factors, including the rarity of the disease, its clinical overlap with more common conditions causing myocardial thickening (such as hypertension, chronic kidney failure, hypertrophic cardiomyopathy, and aortic stenosis), and a lack of established diagnostic algorithms. Studies employing advanced diagnostic techniques have revealed that ATTRwt is identified in 10% to 16% of patients with severe aortic stenosis undergoing interventional treatment or being treated for heart failure.^{328,367}

The critical initial step in diagnosing cardiac amyloidosis is maintaining a high level of suspicion. Clinicians rely on specific clinical findings, often referred to as "red-flag" signs, to guide their suspicions. Detection of left ventricular hypertrophy (LVH) alongside these red-flag signs initiates

Cardiac red flags	Extra-cardiac red flags
•Left ventricular hypertrophy •Atrial fibrillation •Impaired diastolic function (grade 2 or worse) •Symptoms of heart failure •Presence of low flow-low gradient severe aortic stenosis •Apical sparing pattern in strain imaging •Low voltage findings on ECG that are inconsistent with hypertrophy •Pseudo-infarct pattern on ECG •Extensive subendocardial or transmural LGE on cardiac MRI, increased T1, and increased extracellular volume fraction •Persistent mild elevation of troponin •Elevated natriuretic peptide levels	•Bilateral carpal tunnel syndrome •Spinal stenosis •Spontaneous biceps tendon rupture •Peripheral neuropathy •Autonomic dysfunction •Orthostatic hypotension •Intolerance to antihypertensive medications •Hearing loss •Renal dysfunction •Becoming spontaneously normotensive or hypotensive with a history of hypertension •Skin findings •Gastrointestinal findings

Figure 64. Red-flag signs of cardiac amyloidosis.
***Modified from reference 319 and 396.**

the diagnostic algorithm, prompting further testing. These red-flag signs are summarized in Figure 64.³¹⁹

Once cardiac amyloidosis is suspected, diagnosis typically proceeds using non-invasive imaging methods. Although endomyocardial biopsy has long been considered the gold standard for diagnosing cardiac amyloidosis, advancements in echocardiographic imaging techniques, the utilization of cardiac magnetic resonance imaging (CMR), and improvements in correlating nuclear imaging with biopsy results have shifted the emphasis toward non-invasive assessments in diagnosis. The diagnostic algorithm for cardiac amyloidosis is outlined in Figure 65.¹

Echocardiography in Transthyretin Amyloidosis

While echocardiographic descriptions of cardiac amyloidosis have been documented since the 1970s, the significance and utility of echocardiography have garnered greater attention in recent years, reflecting increased interest in the disease.³⁶⁸ Compared to other imaging modalities, echocardiography enjoys widespread use, enabling swift assessment of left ventricular wall thickness alongside simultaneous evaluation of cardiac dimensions and function. This versatility facilitates the assessment of multiple parameters crucial for diagnosis, including diastolic filling patterns, which are affected in ATTR-CA.³⁶⁹ The echocardiographic findings in cardiac amyloidosis are summarized in Figure 66.

The primary diagnostic hallmark in ATTR-CA is increased wall thickness. When left ventricular thickness reaches ≥ 12 mm or biventricular hypertrophy is observed (defined as right ventricular hypertrophy with a wall thickness of > 5 mm in the subcostal window) without evidence of loading conditions, suspicion for CA is warranted.³⁶⁸ This thickening represents a form of "pseudo-hypertrophy" stemming from progressive infiltration of amyloid into the extracellular space, rather than true cardiomyocyte

hypertrophy (Figure 67). This characteristic discrepancy between low-voltage QRS complexes on electrocardiography (ECG) and increased wall thickness on echocardiography serves as a crucial criterion for distinguishing cardiac amyloidosis from other causes of hypertrophy.³⁴⁷

Additional echocardiographic findings that may raise suspicion for ATTR-CA include thickening of the interatrial septum (>5 mm), thickening of valve structures, biatrial dilatation, and the presence of pericardial and pleural effusions.^{368,369} Unexplained right ventricular (RV) hypertrophy and RV systolic dysfunction also provide additional clues for amyloidosis. Reduced tricuspid annular plane systolic excursion (TAPSE) and tissue Doppler (s') values correlate with disease severity and indicate a poor prognosis. Dilatation and reduced collapsibility in the inferior vena cava due to increased right atrial pressure are not uncommon findings in CA patients (Figure 66f).⁶⁴

Doppler echocardiography serves as another valuable tool in assessing ATTR-CA, providing crucial insights into diastolic function and left ventricular (LV) filling pressures. Infiltration of the myocardium by amyloid fibrils leads to abnormal LV relaxation and progressive diastolic dysfunction. The extent of diastolic dysfunction often mirrors the disease's progression, with more severe forms typically emerging in advanced stages.

Pulsed-wave (PW) Doppler assessment of mitral flow can detect Grade I diastolic dysfunction in early disease stages, with most patients progressing to Grade II or III by the time of diagnosis.⁶⁴ Severe diastolic dysfunction is marked by an elevated ratio of early to late diastolic mitral flow velocity ($E/A > 1.5$) and a shortened E-wave deceleration time (<150 ms). Tissue Doppler imaging (TDI) of the mitral annulus provides crucial information regarding longitudinal function, with septal and lateral annular velocities

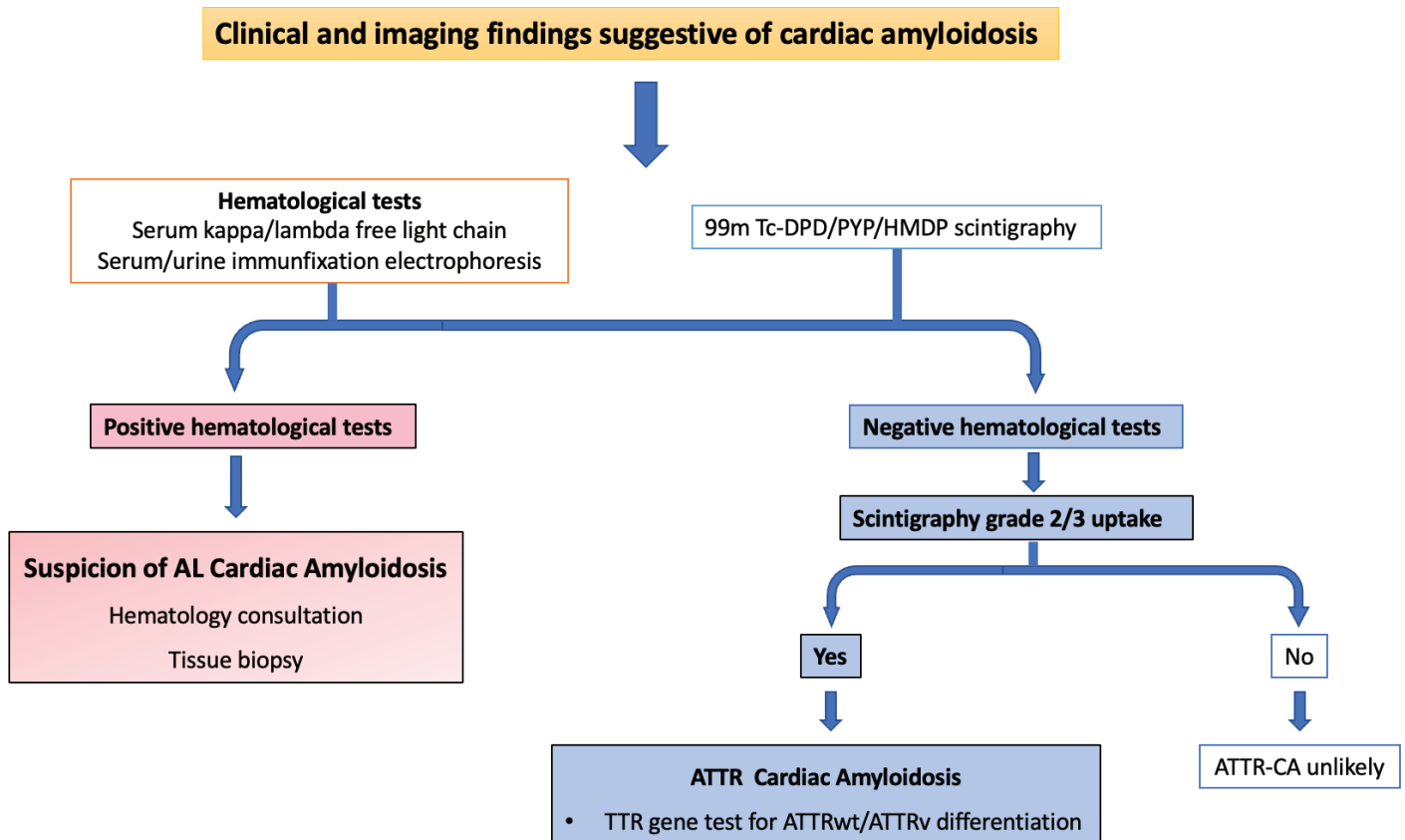


Figure 65. Diagnostic algorithm for cardiac amyloidosis.

*Modified from reference 1 and 396.

typically registering very low (<5 cm/s) in TDI examinations (Figure 66E). Impairment of longitudinal systolic function can be discerned even in the disease's earliest stages, potentially aiding in early diagnosis. An elevated ratio of the mitral E wave to mitral annulus motion velocity ($E/e' > 14$) indicates increased LV filling pressure.^{64,368}

Pulsed-wave Doppler examination of the pulmonary vein reveals a progressive reduction in the S wave coupled with a concurrent increase in the D wave, reflecting high left atrial pressure—a trend that becomes more apparent as the disease advances. These characteristics often become evident after an increase in wall thickness, but in some cases, diastolic parameters may exhibit impairment before hypertrophy occurs, enabling early detection. Increased end-diastolic pressures and frequently associated biatrial dilatation are also notable features of the disease.

Strain echocardiography, a method for evaluating myocardial deformation, is crucial in the diagnostic assessment of cardiac amyloidosis via echocardiography. According to prevailing theories on the pathophysiology of ATTR-CA, amyloid fibril accumulation typically progresses from the base to the apex of the heart, impacting longitudinal ventricular functions.³⁴⁷ However, this concept lacks robust support from evidence-based studies. Consequently, it remains unclear why longitudinal function is often the first parameter affected and how the pattern known as "apical sparing" (Figure 68) manifests in ATTR-CA. It's noteworthy that apical sparing may also occur in other conditions featuring left ventricular hypertrophy, with

its accuracy heavily dependent on the examined cohort. Therefore, the sensitivity and specificity of this finding may vary.^{368,370}

The apical/mid-basal longitudinal strain ratio, when exceeding 1, demonstrates a sensitivity of 93% and specificity of 82% in distinguishing cardiac amyloidosis from other causes of left ventricular hypertrophy.⁶⁴ In patients with ATTR-CA, unlike AL-CA, valve dysfunctions are not uncommon. Particularly in older patients, mitral and tricuspid valve regurgitations are frequently observed due to senile degeneration and concomitant atrial fibrillation.³⁷¹ Additionally, there is a well-established correlation between aortic stenosis and ATTR-CA. Indeed, in a study that screened patients undergoing transcatheter aortic valve implantation (TAVI), ATTR-CA was detected in approximately 16% of cases. The likelihood of ATTR-CA is even higher in low-flow, low-gradient aortic valve stenosis (Figure 69).³⁶⁷ Therefore, echocardiographic assessment should not only focus on ventricular size and functions but also comprehensively evaluate valve functions.

In addition to conventional measurements, alternative methods are utilized in the echocardiographic assessment of ATTR-CA. One such method is the septal-apical/basal longitudinal strain ratio (SAB), where a threshold value >2.1 is deemed significant for CA.³⁷² Furthermore, the ejection fraction (LVEF) to global longitudinal strain (GLS) ratio (EFSR), which represents the ratio of LVEF to GLS, has been identified as a helpful parameter in distinguishing ATTR-CA from hypertrophic cardiomyopathy (HCM)

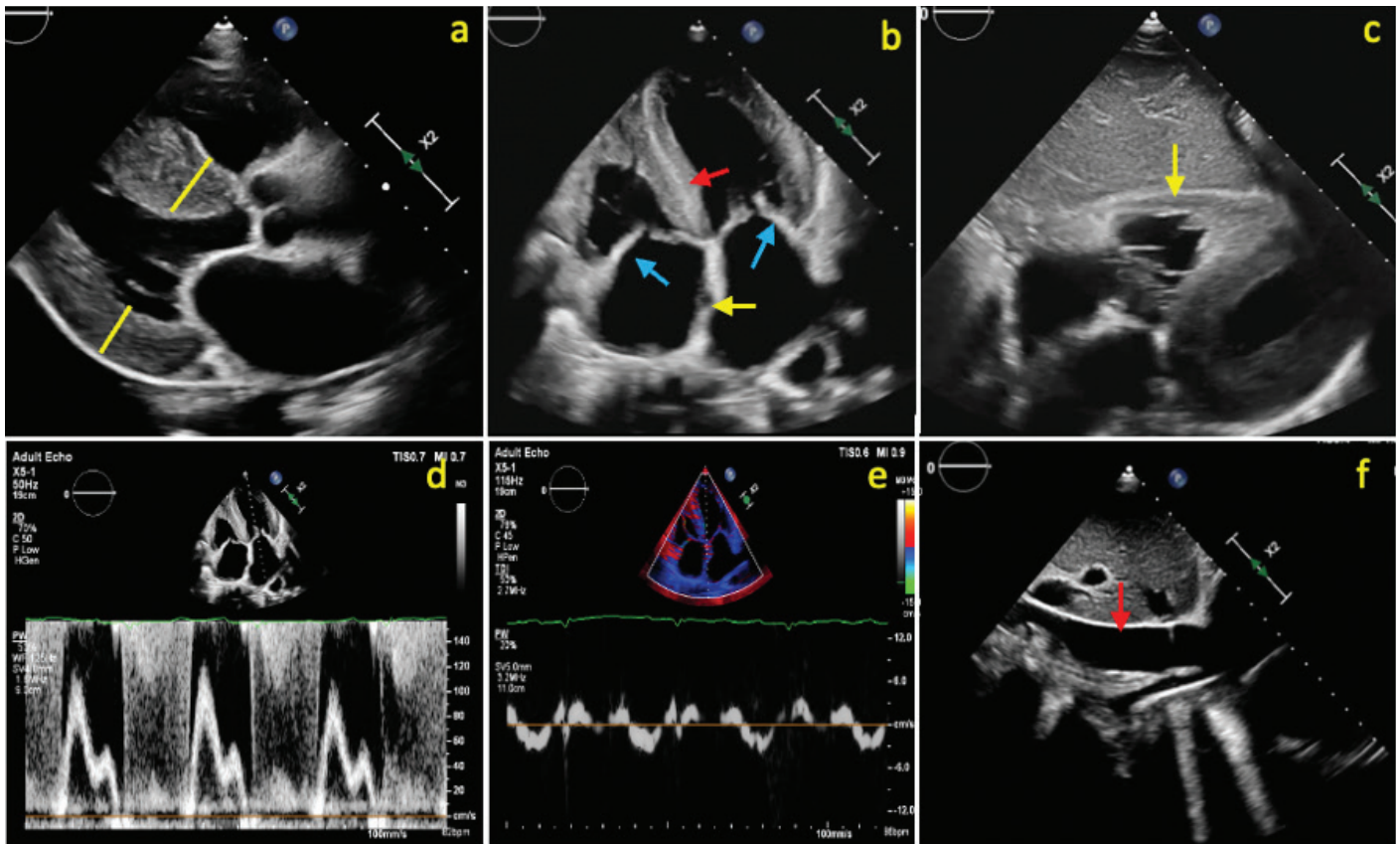


Figure 66. Typical morphological features of cardiac amyloidosis. Transthoracic echocardiographic images in the parasternal long axis (a), apical 4-chamber (b), and subcostal (c) views. (a) Concentric hypertrophy of non-dilated left ventricular walls (yellow lines in a), (b) thickened interatrial septum with a granular sparkling pattern (red arrow in b) and involvement of atrioventricular valves (blue arrows in b), (c) right ventricular hypertrophy (yellow arrow in c), (d) restrictive pattern in mitral inflow showing E and A waves ($E/A > 2$), (e) decreased diastolic functions on tissue Doppler imaging (septal $e' < 4$ cm/s), (f) dilatation and impaired collapsibility in the inferior vena cava (red arrow in f).

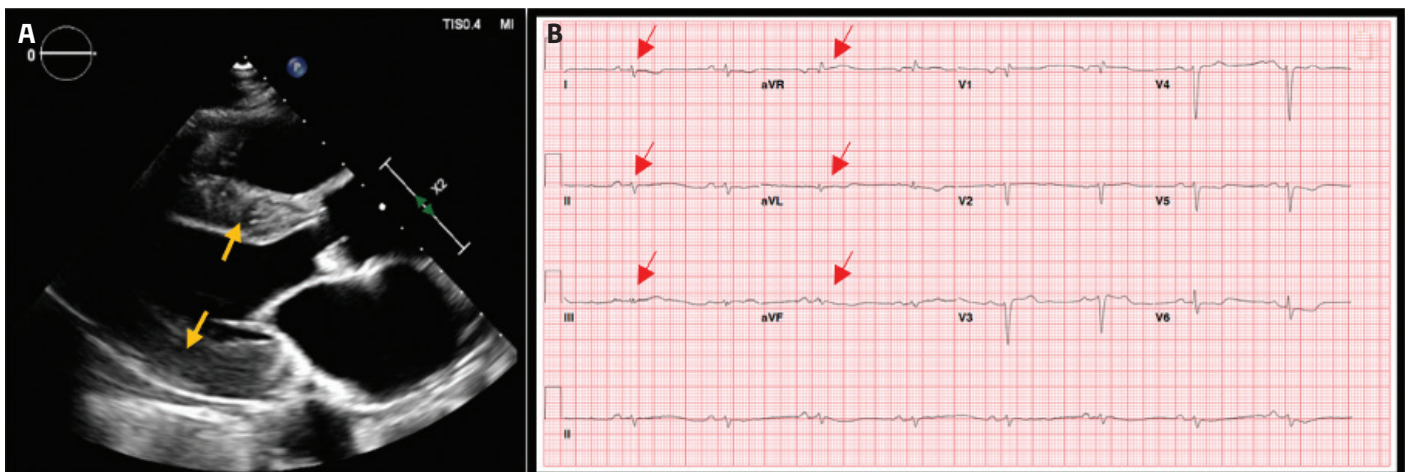


Figure 67. Pseudo-hypertrophy evidenced by low voltage on ECG, inconsistent with left ventricular hypertrophy in an ATTR-CA patient. (A) Concentric left ventricular hypertrophy (yellow arrows), (B) Low voltage in limb leads (red arrows).

and hypertensive heart disease.³⁷³ In another study involving patients with ATTR-CA, the myocardial contraction fraction (MCF), obtained by the ratio of stroke volume to myocardial mass, has been recognized as a diagnostically useful parameter.³⁷⁴

Several echocardiographic scoring algorithms recommended for diagnosing ATTR-CA are available. In patients with LV wall thickening, the Increased Wall Thickness (IWT) score, which incorporates parameters such as relative wall thickness (RWT),

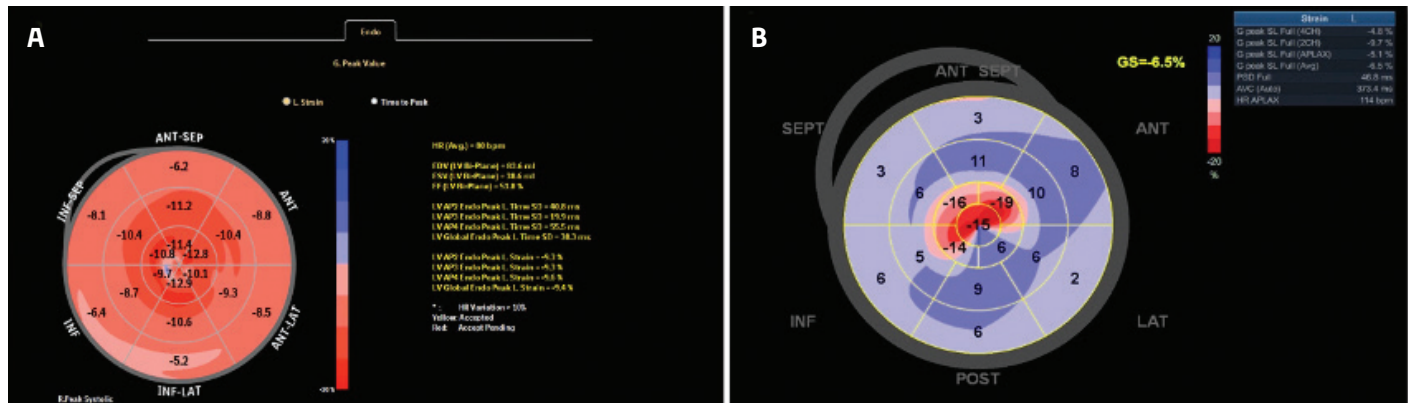


Figure 68. Presence of apical sparing sign along with low global longitudinal strain in two different ATTR-CA patients, one with ATTRv (A) and the other with ATTRwt (B).

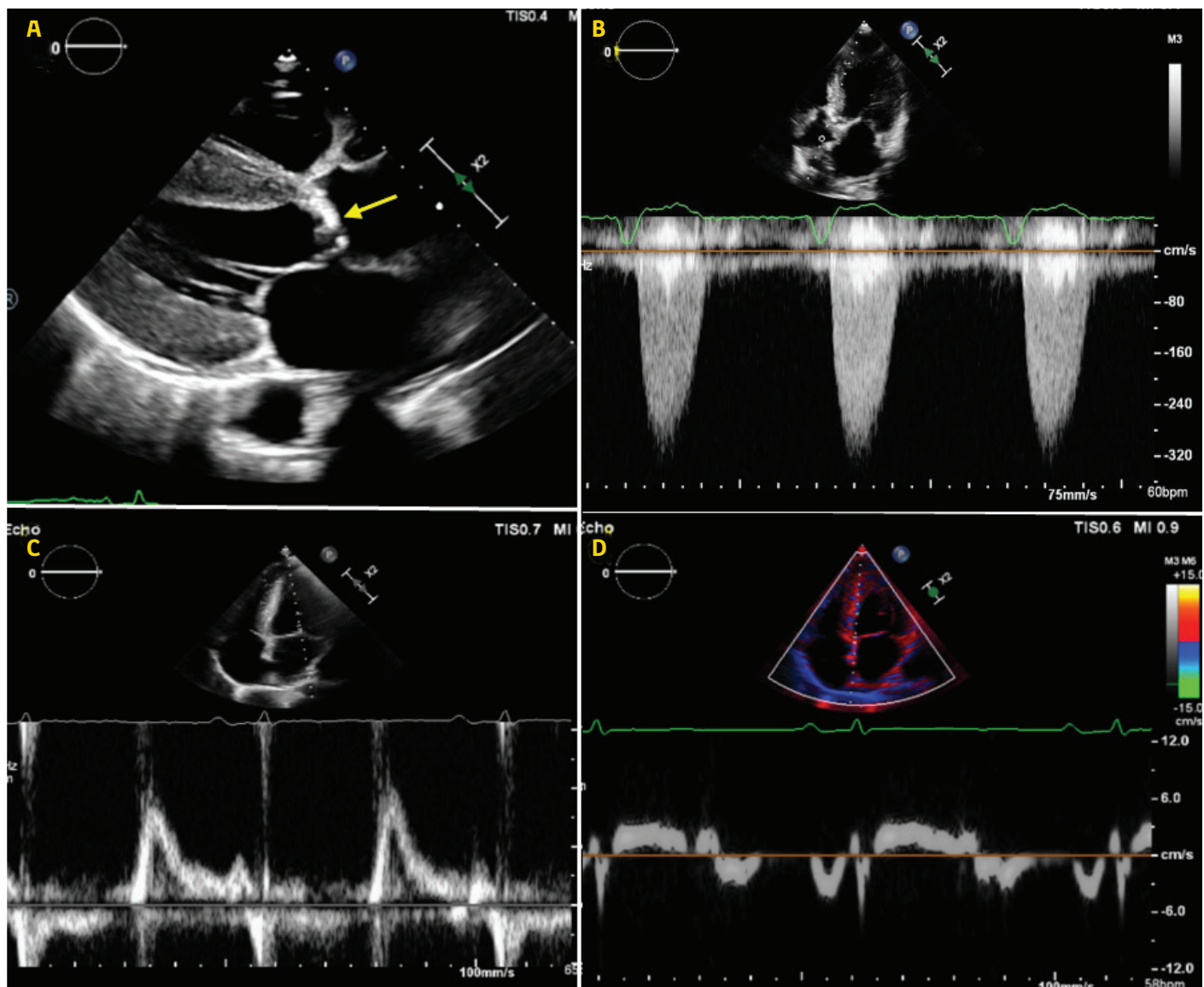


Figure 69. Low flow and low gradient severe aortic stenosis with in an ATTRwt-CA patient. (A) Concentric left ventricular hypertrophy and aortic valve calcification (yellow arrow) are observed in the parasternal long-axis image. (B) CW- Doppler flow across the aortic valve (aortic valve gradient 57/29 mmHg, aortic valve area 0.7 cm²). (C) Restrictive filling pattern in mitral Doppler flow. (D) Decreased diastolic function is demonstrated in tissue Doppler imaging.

Table 22. Diagnostic Echocardiography Scores in ATTR-CA

A- IWT Score

Parameter	Cut-off value	Points*
Relative wall thickness	> 0.6	3
E/e'	> 11	1
TAPSE, mm	≤ 19	2
LS (4-chamber), %	≥ -13	1
SAB	> 2.9	3

LS, Longitudinal strain; SAB, Septal-Apical/Basal Strain Ratio; TAPSE, Tricuspid Annular Plane Systolic Excursion.
A score of ≥ 8 points is considered significant.

B- ATTR-CM Score

Parameter	Cut-off value	Points*
Age, years	60-69	2
	70-79	3
	≥ 80	4
Gender	Male	2
Relative wall thickness	> 0.57	2
Posterior wall thickness, mm	≥ 12	1
LVEF, %	< 60	1
Hypertension	If present	-1

LVEF, Left Ventricular Ejection Fraction.
A score of ≥ 6 points is considered significant.

E/e', TAPSE, GLS, and septal longitudinal systolic apex-basal strain ratio (SAB), offers high diagnostic accuracy for ATTR-CA (Table 22A).³⁷² In a recent study involving patients with non-dilated hypertrophic ventricles, the presence of an additional echocardiographic red-flag sign was found to indicate a 29% likelihood of cardiac amyloidosis. Thus, the presence of a restrictive filling pattern, granular sparkling, pericardial effusion, interatrial septal thickening (>5 mm), thickening of atrioventricular valves (>5 mm), and the presence of the apical sparing pattern in strain assessment in patients with hypertrophic and non-dilated left ventricles with preserved ejection fraction (HFpEF) raises serious suspicion for the diagnosis of CA.³⁷⁵

Moreover, the ATTR-Cardiomyopathy (ATTR-CM) score, which considers factors such as age, gender, relative wall thickness, posterior wall thickness, LVEF, and the presence of hypertension, serves as a useful method for identifying the presence of CA in patients with HFpEF (Table 22B).³⁷⁶ Additionally, there is a growing interest in machine learning tools to assist in distinguishing the causes of LVH.^{377,378}

Despite the importance of all these evaluation parameters, it's crucial to note that the threshold for hypertrophy, typically set at 12 mm, can vary depending on gender and the presence of additional diseases. In reality, this threshold value offers high sensitivity but low specificity for diagnosing cardiac amyloidosis. Therefore, when assessing patients with increased wall thickness, it's essential to consider other echocardiographic findings highlighted above. Particularly when interpreting echocardiographic results, clinicians should take into account other clinical red-flag indicators.

The term "granular sparkling" in the myocardium has long been associated with amyloidosis. However, it should be avoided due to its lack of specificity. "Sparkling" is a marker indicating decreased longitudinal function not only in cardiac amyloidosis but also in many other conditions, including hypertensive heart disease, chronic kidney disease, HCM, and Pompe disease.³⁷⁹

Data regarding the prognostic value of echocardiography are limited. However, the relationship between CMR markers, particularly the correlation between extracellular volume (ECV) and amyloid load, offers significant prognostic insights.³⁸⁰

Some echocardiographic parameters have been investigated for their association with ECV and are believed to provide valuable prognostic information. In certain cross-sectional studies, GLS and E/e' values have demonstrated a strong correlation with ECV, suggesting their potential role in prognosis determination.

In patients with ATTR-CA, the MCF, derived from the ratio of stroke volume to myocardial mass, has been identified as a diagnostically useful parameter.³⁸¹ Additionally, in this study, the presence of atrioventricular valve infiltration was found to have adverse effects on survival. Similarly, in AL-CA, GLS and stroke volume index have been shown to predict survival.³⁶⁰ The role of echocardiographic parameters in typing and prognosis of cardiac amyloidosis is described in Table 23.

Cardiac MRI in Transthyretin Amyloidosis

CMR has recently experienced a notable increase in prevalence and utilization, offering comprehensive insights into both the anatomical structure and hemodynamics of the heart. CMR provides detailed information on the presence, location, and distribution of hypertrophy, facilitating the visualization of cardiac amyloid infiltration through late gadolinium enhancement (LGE) imaging, and quantifying cardiac amyloid load using T1 mapping and ECV assessment. In this context, CMR plays a crucial role in functional and tissue characterization, boasting approximately 85-90% sensitivity and specificity for diagnosing cardiac amyloidosis (CA).³¹⁹ Even higher sensitivity can be attained through the utilization of native T1 mapping and ECV fraction. While CMR cannot offer a definitive classification for cardiac amyloidosis, certain parameters may aid in distinguishing ATTR-CA from AL-CA (Table 24).³⁵³ Illustrative CMR findings in CA patients are depicted in Figure 70.

Cine Imaging

Cine CMR is a method utilized to evaluate myocardial morphology as well as global and regional heart function. Typically, CA is characterized based on concentric and symmetric left ventricular thickening using this method. However, in a CMR study involving patients with ATTR-CA, it was found that 79% exhibited asymmetric hypertrophy, with only 18% classified as having concentric hypertrophy. Among those with asymmetric hypertrophy, the majority had sigmoidal septum morphology (55%), and nearly one-fourth of ATTR-CA patients (24%) displayed the traditionally accepted reverse septal contour characteristic of HCM.³⁴⁵ Therefore, it's crucial to note that the presence of asymmetric hypertrophy does not exclude the possibility of cardiac amyloidosis.

Obstruction of the left ventricular outflow tract and systolic anterior motion (SAM) of the mitral anterior leaflet are rare but

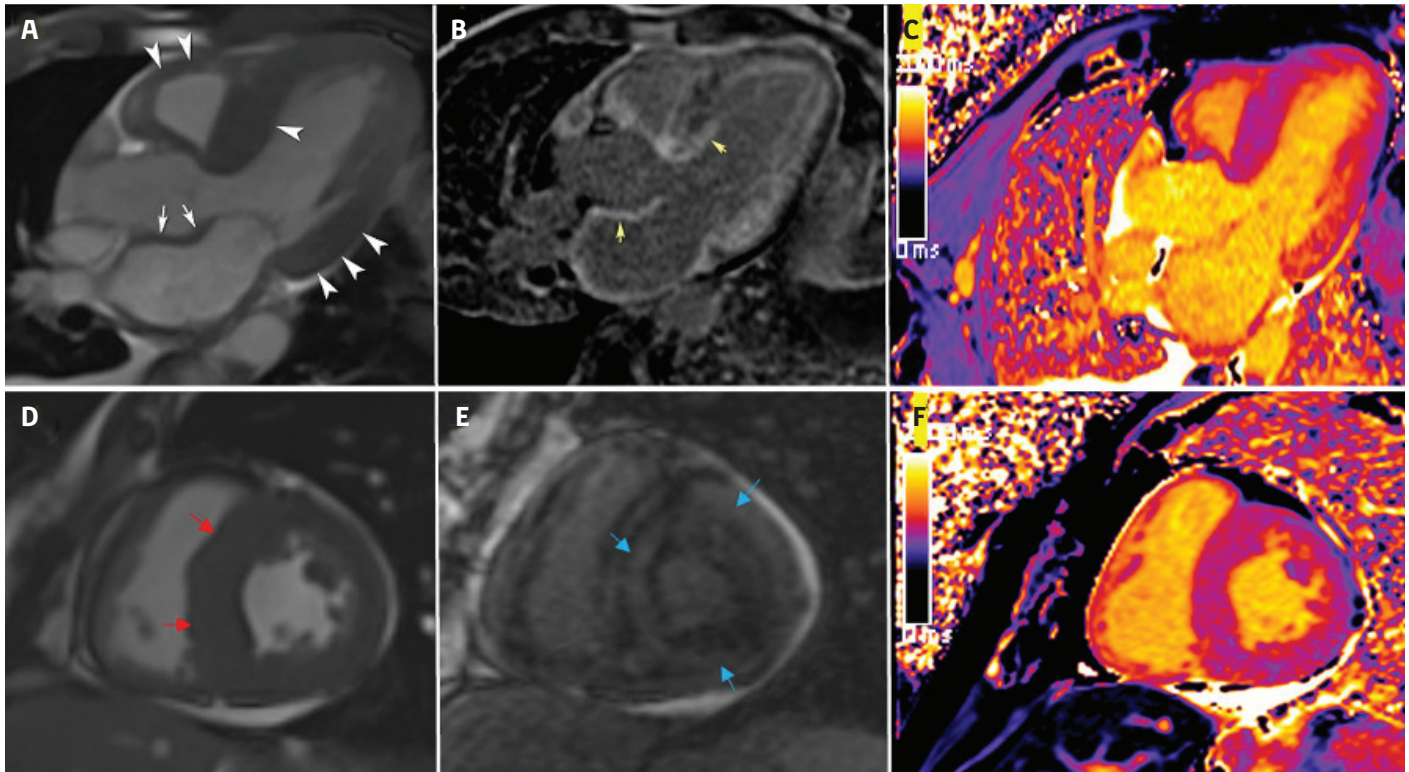


Figure 70. CMR images of two different cardiac amyloidosis patients are shown. In AL-CA patient, marked biventricular and interatrial septum hypertrophy is observed (white arrows) (A), along with widespread subendocardial LGE in the left ventricle and LGE in the interatrial septum (yellow arrows) (B), and increased native T1 values (C). In ATTRv-CA patient, left ventricular hypertrophy is indicated (red arrows) (D), along with transmural LGE in the left ventricle (blue arrows) (e), and increased native T1 values (F). (Images belong to Prof. Dr. Aysel Türkvatan Cansever.)

more commonly observed in ATTR patients than in AL patients, often occurring in conjunction with morphological subtypes such as sigmoid septum and reverse septal contours.³⁴⁵ Although left ventricular hypertrophy is more pronounced in ATTR patients compared to AL patients, the prevalence rates for various morphological phenotypes do not significantly differ between ATTRv and ATTRwt patients.^{345,370} In addition to left ventricular involvement, thickening of the right ventricle, atrial walls, and interatrial septum are commonly observed.³⁸² Thickening of the interatrial septum or right atrial wall may be specific to cardiac amyloidosis when it exceeds 6 mm.³⁷⁰ While cine CMR morphological and functional assessments may be useful for diagnosing cardiac amyloidosis, the identified features are not specific and exhibit varying prevalence rates. Among extracardiac findings, pleural and pericardial effusions are present in 48% and 35% of patients, respectively.³⁵³ Accumulation of abdominal fluid (ascites) suggesting right heart failure is more frequently observed in advanced stages of cardiac amyloidosis.

Late Gadolinium Enhancement Imaging

LGE imaging utilizing gadolinium-based contrast agents is a fundamental technique in diagnosing CA. The typical LGE pattern in cardiac amyloidosis involves an area extending to the global subendocardial region, unrelated to the coronary artery region.¹³⁷ However, transmural or patchy LGE may also be observed in patients with CA. LGE involvement demonstrates a diagnostic sensitivity

of 86% and specificity of 92% for cardiac amyloidosis.³⁵¹ While LGE is more common in ATTR than in AL, it cannot differentiate between subtypes of CA.³⁴⁵ Notably, LGE can also be identified in the atria, atrioventricular valves, and right ventricle.³⁷⁰

LGE findings in CA patients may vary during the disease course. This variation often occurs in stages, beginning with no LGE initially, followed by the appearance of subendocardial LGE as a typical pattern, and progressing to the development of transmural LGE. Transmural LGE indicates a poor prognosis in patients with CA.³⁵⁰ Additionally, LGE associated with amyloid accumulation in CMR is often observed in the basal regions of the myocardium, supporting the apical sparing pattern seen in strain echocardiography.³⁸³

T1 Mapping and Extracellular Volume

T1 mapping involves measuring the T1 signal of each pixel and/or voxel in an image. Native T1 values, obtained before the administration of contrast agents, are typically higher in areas of amyloid accumulation or widespread fibrosis compared to normal tissues. These values characterize the extracellular space, reflecting changes in myocytes and the extracellular environment. Notably, native T1 is significantly increased in cardiac amyloidosis and demonstrates a strong correlation with ventricular functions.³⁸⁴ High native T1 values exhibit a sensitivity of 92% and specificity of 91% in detecting cardiac amyloidosis.³⁴⁶ Additionally, native T1 values are useful in revealing early amyloid involvement in ATTRv gene carriers.³⁸⁴

Table 23. Role of Echocardiographic Parameters in Typing and Prognosis of Cardiac Amyloidosis.³⁶⁵

Echocardiographic parameters	ATTR- CA		AL-CA	
	Diagnosis	Prognosis	Diagnosis	Prognosis
Left ventricular wall thickening	++	+	+	+
Right ventricular wall thickening	++	+	++	+
Pericardial effusion	+	+	++	++
Apical sparing pattern	+++	N/A	+++	N/A
Reduced GLS	+	+++	+	+++
Increased E/e' ratio	++	++	++	++
Biatrial dilation	++	++	++	++
Low-flow, low-gradient severe aortic stenosis	++	+	N/A	N/A
Right ventricular systolic dysfunction (FAC, s')	N/A	+++	N/A	+++
Mitral regurgitation (Carpentier type 1/3a)	++	+++	+	++
Tricuspid regurgitation (Carpentier type 1/3a)	++	+++	+	++
Left ventricular ejection fraction / GLS ratio	+++	N/A	+++	N/A
Myocardial contraction fraction ratio	+++	+	+++	+

ATTR-CA, Transthyretin cardiac amyloidosis; AL-CA, Amyloid immunoglobulin light chain; FAC, Fractional area change; RV, Right ventricle; GLS, Global longitudinal strain.

Table 24. CMR Findings Used in Differentiating ATTR and AL Cardiac Amyloidosis

	ATTR-CA	AL-CA
Degree of hypertrophy	++	+
Presence of asymmetric hypertrophy	++	+
LGE pattern	More transmural More common RV involvement	More subendocardial
ECV values	++	+
Native T1 values	+	++
T2 values	+	++

ATTR-CA, Transthyretin Cardiac Amyloidosis; AL-CA, Immunoglobulin Light Chain Cardiac Amyloidosis; LGE, Late Gadolinium Enhancement; ECV, Extracellular Volume.

It's important to note that native T1 signals provide valuable insights even in patients who do not receive gadolinium-based contrast agents. However, their repeatability may be low across different devices or magnetic field strengths (e.g., 1.5-T versus 3.0-T).³⁸⁵

Post-contrast T1 mapping and ECV estimation are typically performed following gadolinium administration, with ECV providing more reliable measurements than absolute T1 values.³⁸⁶ ECV values are notably elevated in CA and can correlate with the severity of the condition, although they do not differentiate between CA subtypes.³⁸⁷ Interestingly, native T1 signal is higher in AL-CA patients compared to ATTR-CA patients, while ECV values are higher in ATTR-CA cases.³⁴⁷ This discrepancy is believed to stem from an additional mechanism in AL-CA, possibly related to direct tissue toxicity from light chains, leading to an increase in native T1, a phenomenon not observed in ATTR-CA.³⁷⁰

T2 Mapping

Myocardial T2 signal serves as an important method for indicating the presence of edema. However, the clinical application of T2-weighted CMR images is constrained by issues related to image quality, repeatability, and objectivity.

To address these challenges, myocardial T2 mapping between myocardial regions is employed.³⁸⁸ Nonetheless, the utilization of T2 mapping in patients with cardiac amyloidosis remains limited. Studies have indicated significantly elevated myocardial T2 values, particularly in patients with AL, as compared to those with ATTR.^{352,389} Furthermore, T2 values can serve as prognostic indicators for patients with AL, offering insights into the mechanisms underlying myocardial damage and amyloid infiltration characteristic of cardiac amyloidosis.

The presence of LGE in patients with CA serves as a significant predictor of mortality. Specifically, in patients with transmural LGE, the overall survival at 24 months is notably worse for both AL-CA and ATTR-CA.³⁵⁰ As a prognostic indicator, ECV demonstrates greater strength when compared to native or post-contrast T1 mapping alone.³⁴⁸ Quantifying ECV proves highly beneficial for monitoring amyloid burden and assessing response to treatment.

Nuclear Imaging in Transthyretin Amyloidosis

The clinical significance of radionuclide molecular imaging has markedly increased in recent years, becoming an integral

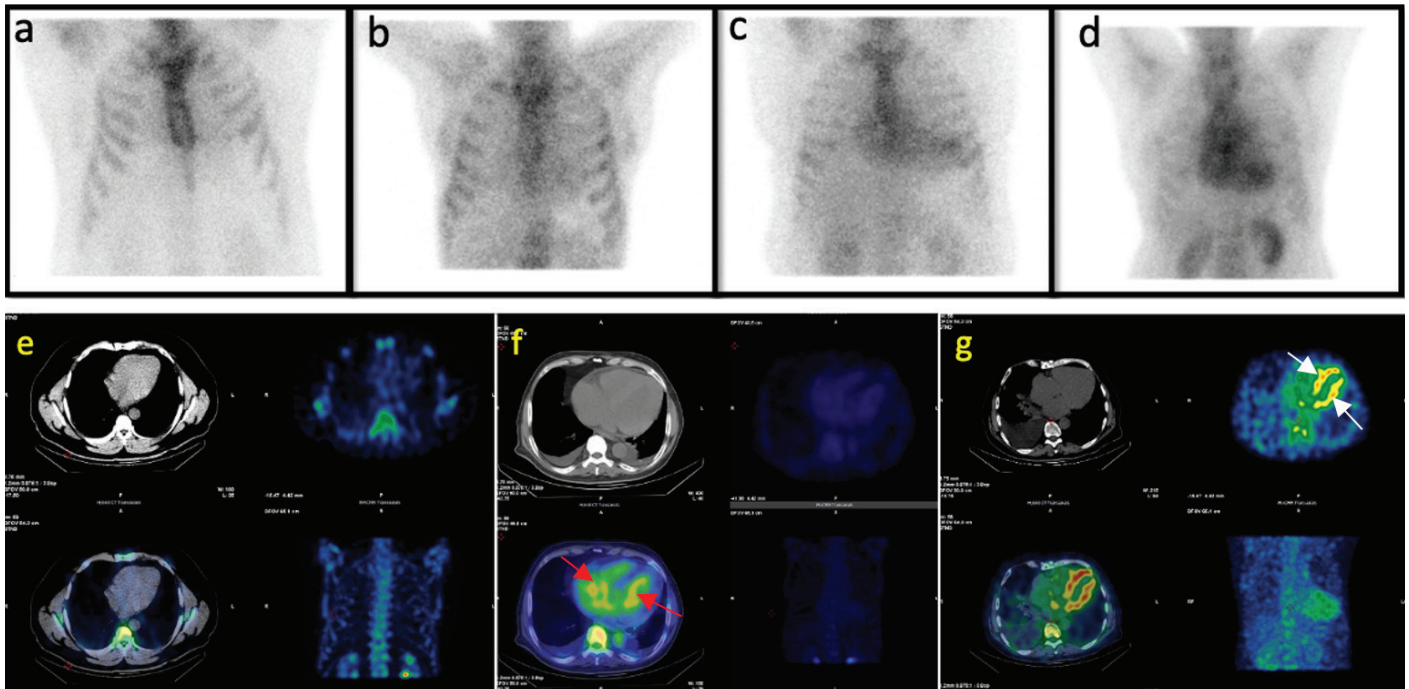


Figure 71. Perugini levels with Tc-99m PYP scintigraphy and SPECT/CT images. a) Grade 0, b) Grade 1, c) Grade 2, d) Grade 3 demonstrate different levels of involvement. e) SPECT/CT image of a patient without detected involvement in planar imaging, f) SPECT/CT image of a patient with Grade 2 involvement in planar imaging showing the involvement in the blood pool rather than the myocardium (red arrows), g) SPECT/CT image of a patient with Grade 3 involvement in planar imaging confirming myocardial involvement (white arrows) in the diagnosis of ATTRwt. (Images belong to Prof. Dr. Burcu Esen Akkaş.)

component of the diagnostic algorithm for CA. In 1983, the utilization of technetium-99m-labeled pyrophosphate (Tc-99m PYP) in patients with cardiac amyloidosis confirmed by biopsy was first demonstrated, revealing myocardial involvement through bone scintigraphy.³⁹⁰ A study conducted in 2005 further showcased the high sensitivity of bone scintigraphy using technetium-99m-3,3-Diphosphono-1-2-Propanodicarboxylic Acid (Tc-99m DPD) in ATTR-CA and overall specificity for CA.⁷⁰

To differentiate ATTR-CA patients from those with AL or non-amyloid heart failure, radioisotopes such as Tc-99m PYP, Tc-99m DPD, and Tc-99m hydroxymethylene diphosphonate are employed. Furthermore, intense myocardial involvement observed with nuclear radioisotopes serves as an independent determinant of poor prognosis in patients with ATTR-CA.

In planar images, the visual assessment of cardiac involvement is conducted using the Perugini scoring system.⁷⁰ According to this scoring system, a score of 0 indicates no cardiac involvement, 1 denotes mild involvement (less than the bone), 2 signifies moderate involvement (equal to the bone), and 3 represents high involvement (more than the bone) (Figure 71).⁷⁰

Utilizing Tc-99m PYP planar imaging for semi-quantitative assessment, a ratio of heart to contralateral lung involvement exceeding 1.5 (H/CL) at 1 hour, with concurrent exclusion of monoclonal gammopathy, has demonstrated 97% sensitivity and nearly 100% specificity in distinguishing ATTR from AL CA.^{72,75} In a multicenter study, when compared to the Perugini score and H/CL ratio at 3 hours, 1-hour imaging metrics were

found to be more sensitive and less specific, yet demonstrated similar overall accuracy for diagnosing ATTR CA.⁷⁵ The researchers proposed a cutoff value of >1.3 for the 3-hour planar imaging detection of ATTR CA. While 1-hour imaging is associated with higher sensitivity, 3-hour imaging is linked to higher specificity.⁷²

Furthermore, it is crucial to ensure that the region identified for involvement on planar images is localized not only in the blood pool but also in the myocardium, necessitating the addition of single-photon emission computed tomography (SPECT) or, ideally, SPECT/CT to the imaging protocol to minimize false-positive results associated with blood pool uptake.³¹⁸ The exact mechanisms underlying myocardial tracer uptake in the bones of ATTR patients remain unknown, but it is speculated that calcium-mediated mechanisms may be involved, albeit not definitively determined.⁶⁶

The diagnosis of ATTR-CA is typically established when there is evidence of echocardiography or CMR suggestive of cardiac amyloidosis, absence of monoclonal protein (confirmed by serum/urine immunofixation and serum free light chain test), and Perugini grade 2 or 3 detected on bone scintigraphy.^{1,75} However, relying solely on bone scintigraphy for evaluation may not be entirely accurate; in fact, approximately 40% of AL-CA patients may exhibit scintigraphy positivity. Even in 10% of AL-CA patients, Perugini grade 2 or 3 involvements can be observed.³⁹⁰

In patients with evidence of amyloidosis on MRI or echocardiography, and grade 2 or 3 cardiac uptake on radionuclide scintigraphy, along with the presence of monoclonal protein in any of the aforementioned tests, consideration should be

given to differential diagnosis between ATTR-CA and AL-CA. Histological confirmation through endomyocardial biopsy is generally required for the definitive diagnosis of amyloid type.

The utilization of bone scintigraphy for screening ATTR-CA in specific populations has yielded intriguing findings. ATTR-CA has been diagnosed in 13.3% of elderly adult patients with preserved ejection fraction heart failure (PEHF), 16% of patients undergoing TAVI, and 10% of patients with carpal tunnel syndrome using ^{99m}Tc-PYP/DPD/HMDP imaging.^{72,328,391}

Another crucial role of nuclear imaging is to exclude other cardiomyopathies in patients with biventricular thickening or left ventricular hypertrophy. In patients exhibiting widespread cardiac uptake on radionuclide scintigraphy, the aforementioned biventricular thickening can be confidently attributed to the cause of CA. However, the reverse is not true, as radionuclide scintigraphy cannot reliably rule out CA, given that only 60% of AL-CA cases yield a negative scintigraphy result. Additionally, while radionuclide scintigraphy exhibits high sensitivity in ATTR-CA, rare ATTRv variants such as S77Y and Y114C may demonstrate lower uptake on bone scintigraphy than expected in early-stage ATTR patients. Therefore, in patients with the mentioned TTR variants, if other imaging methods such as echocardiography and MRI strongly suspect ATTR-CA, CA cannot be conclusively ruled out based solely on bone scintigraphy and should still be considered.³⁹⁰

Positron emission tomography (PET) scans utilizing amyloid-specific substances like ¹¹C-PiB and ¹⁸F-florbetapir have demonstrated utility in the diagnosis of CA.³⁹² Initially developed for imaging amyloid fibrils in the brain, ¹⁸F-florbetapir presents as a promising agent for the early diagnosis of CA and the quantification of cardiac and extracardiac amyloid loads.³⁹³ This agent binds to both AL and ATTR accumulations, albeit with reported higher affinity for AL.³⁹⁴ Similarly, ¹¹C-PiB has exhibited high selectivity for cardiac tissue in both AL and ATTR.^{395,396}

However, the clinical utilization of these PET agents remains considerably limited, necessitating further research in this domain.

Conclusion

TTR cardiac amyloidosis has emerged as a more frequently diagnosed disease in recent years, primarily due to heightened awareness and the demographic shift towards an aging population. The advancements in multiple imaging techniques outlined above have empowered clinicians to diagnose ATTR-CA using non-invasive methods, thereby reducing reliance on endomyocardial biopsy. While clinical findings and suspicion kickstart the diagnostic process, imaging findings serve as the cornerstone of diagnosis.

The significance of echocardiography in diagnosis lies not only in identifying findings but also in its simplicity, accessibility, and essential role. Despite the introduction of new echocardiographic parameters, it is crucial not to lose sight of the primary focus, which necessitates a comprehensive evaluation of left ventricular structure and wall thickness, valvular structures, and diastolic function. Tissue Doppler assessment, strain analysis as necessary, and evaluating right ventricular wall thickness and function greatly aid in the diagnosis of cardiac amyloidosis.

The utilization of CMR, particularly for assessing LGE, T1, and ECV values, is indispensable. Non-invasive imaging serves as the foundation of diagnosis; however, it should not supersede hematologic tests, and it is imperative to prioritize the preliminary diagnosis of AL cardiac amyloidosis in cardiac emergencies.

While each imaging method offers unique advantages, they also come with their limitations. Therefore, to ensure the most accurate and comprehensive assessment, a multimodal imaging approach integrating echocardiography, MRI, bone scintigraphy, and even electrocardiography should be embraced. This holistic approach maximizes diagnostic accuracy and facilitates informed clinical decision-making in the management of cardiac amyloidosis.

Fabry Cardiomyopathy

Anderson-Fabry Disease (AFD) is an X-linked lysosomal storage condition resulting from insufficient activity of the enzyme α -galactosidase. AFD manifests as a progressive multisystem disorder, with infiltrative cardiomyopathy being the most significant and frequent cardiac complication, leading to a range of cardiovascular symptoms. Owing to the disease's rarity, its multi-organ impact, and low awareness, diagnosis is often delayed, with an average duration of 15 years after the initial onset of symptoms.

Cardiac manifestations of AFD may vary and include hypertrophy, conduction defects, arrhythmias, and heart failure. Advanced diagnostic techniques such as cardiac magnetic resonance (CMR) and T1 mapping have become crucial in the clinical evaluation of affected patients. Monitoring biomarkers like hs-Troponin and BNP is vital for tracking the disease's progression.

Enzyme replacement therapy (ERT) stand as the primary treatment for modifying the progression of the disease, and currently there are two authorized formulations accesible. Additionally, novel treatments, including oral chaperone therapy and substrate reduction therapies, have been developed. Research into gene-specific therapy is also progressing. The introduction of these therapies has markedly enhanced the survival rates of individuals with AFD.

Early diagnosis is imperative for an effective treatment response. This review aims to encapsulate strategies for the early detection of AFD, utilizing clinical evaluations, imaging, and laboratory biomarkers, alongside discussing contemporary treatments that manage cardiovascular risk factors and the complications of AFD.

Pathophysiology and Epidemiology

AFD is a rare X-linked glycogen storage disorder that often goes unrecognized and underdiagnosed, with little public awareness. The condition arises from a deficiency in the lysosomal enzyme α -galactosidase, which is due to mutations in the GLA gene. This enzymatic deficiency causes the gradual buildup of globotriaosylceramide (GL-3) and its deacylated form, globotriaosylsphingosine (lyso-GL-3), within cellular structures. The build-up of GL-3 contributes to oxidative stress and endothelial damage due to its pro-inflammatory properties. In the disease's advanced stages, this accumulation results in tissue ischemia and fibrosis. The deposition of GL-3 and lyso-GL-3 gives rise to clinical symptoms of Fabry disease across multiple organ systems, particularly in the heart, kidneys, and nervous system (Figure 72).³⁹⁷

The worldwide occurrence of AFD is documented to vary between 1 in 40,000 to 1 in 170,000 individuals.³⁹⁸ Despite the fact that mutations leading to Non-classical AFD are more prevalent than those responsible for Classical AFD, the latter is more commonly diagnosed in patient cohorts. This discrepancy indicates that Non-classical AFD is significantly under-recognized. Notably, the prevalence of AFD is quite high within certain clinical demographics, particularly among patients exhibiting symptoms. Recent cohort studies have identified AFD in 0.9% and 0.3% of patients with left ventricular hypertrophy (LVH).³⁹⁹

Genetics

AFD originates from mutations in the GLA gene, which is situated on the X chromosome at Xq22. In the past few years, more than 1,100 mutations of the GLA gene have been identified that are linked to AFH

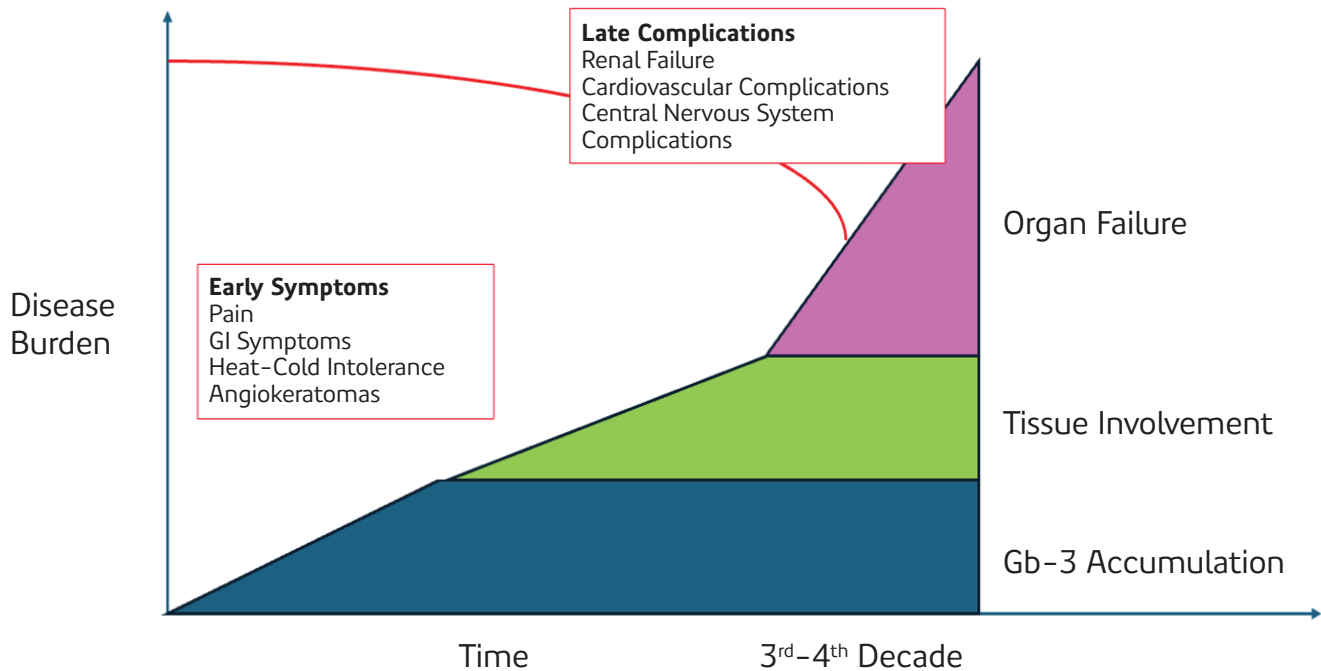


Figure 72. Clinical Findings of Fabry Disease by Age.

development.⁴⁰⁰ However, not all mutations result in the disease. The diversity of clinical presentations is due to the interaction of different mutations with epigenetic and environmental factors. Consequently, genetic analysis is recommended for all patients suspected of having AFD to confirm the genotype-phenotype correlation. Currently, there is no established match between specific mutations and organ-specific involvement in AFD.⁴⁰¹

The impact of X chromosome-related mutations on AFD differs between men and women due to X-linked inheritance. In females, random X chromosome inactivation may result in some cells expressing the healthy gene.⁴⁰² Consequently, while tissue manifestations of the disease may be present, enzyme levels in the plasma might appear normal.⁴⁰³ Typically, women experience a milder disease progression with symptoms appearing later in life, although there are exceptions.

Children diagnosed in early childhood, who show complete deficiency of the GLA enzyme (less than 1%), exhibit the classic presentation of Fabry disease. Certain mutations that allow for residual enzyme activity result in variations of the disease, such as Non-Classical, Late-Onset, Adult-Type, or Cardiac Variant Fabry disease. Key mutations linked to these forms include N215S and R112H. Patients with Non-classical Fabry disease are often diagnosed in adulthood, with cardiac involvement being the most common, affecting 68% of these patients.⁴⁰⁰

Clinical Presentations and Course of the Disease

AFD is characterized as a multisystem disorder with notable cardiac manifestations, including left ventricular hypertrophy (LVH), systolic and diastolic dysfunction, valvular disease, and microvascular ischemia. While symptoms and organ involvement may present similarly in both male and female patients, the frequency of involvement and the age of symptom onset can differ. According to the most extensive cohort study on AFD, the

average age of symptom onset was 9 years for males and 13 years for females. However, the average age at diagnosis was 23 years for males and 32 years for females. Moreover, Fabry disease has been shown to reduce life expectancy. Registry studies have reported that the average age at death was between 51.8 and 54.3 years for males, and 62.0 to 64.4 years for females, with cardiac disease accounting for 36% to 53% of the mortalities.⁴⁰⁴ These findings highlight that reduced life expectancy is reflective of diagnostic and treatment delays. The expected lifespan for contemporary patients who receive early ERT has not yet been fully established but is anticipated to be significantly longer.

In Classic AFD, neuropathic pain and episodic pain crises typically begin between the ages of 4 and 8. Early childhood is often marked by symptoms such as intolerance to temperature changes, reduced sweating (hypohidrosis), recurrent fevers, hearing loss, and distinctive asymptomatic corneal opacities. During adolescence, gastrointestinal disorders including diarrhea, abdominal pain, and bloating, as well as angiokeratomas, proteinuria, and intolerance to exertion may manifest. In adults, typically post-40 years of age, signs of cardiac and renal dysfunction, along with neurological symptoms, become apparent. For women, these symptoms of organ dysfunction tend to appear around a decade later, usually after the age of 50 (Table 25, Figure 72).^{405,406}

While many patients diagnosed in adulthood fall into the Non-classical Fabry group, there are also instances of Classical Fabry being identified during this stage. It has been reported that the typical timeframe from the initial symptom onset to diagnosis is approximately 15 years.⁴⁰⁷ Given that the heart is the most frequently affected organ in both disease forms in adults, a heightened awareness among cardiologists is crucial. It is essential to conduct a thorough investigation of the clinical manifestations of the disease and to compile an exhaustive family history. In

Table 25. Clinical Manifestations in Fabry Disease

Organ System	Clinical Manifestations	Related Pathology and Findings
Peripheral nervous system	Neuropathic pain (formerly “acroparesthesia”), pain crises, atypical (for pain characteristics and localization) chronic or episodic pain; heat and/or cold intolerance; inability to sweat (hypohidrosis)	Small fiber neuropathy, loss of small myelinated and unmyelinated fibers, GL-3 accumulation in dorsal root ganglia, ectopic discharges potentially resulting from upregulation of Na ⁺ channels (Nav1.8) and TRPV1 ⁴²⁷ , ischemia-induced axon degeneration secondary to massive microvascular endothelial GL-3 accumulation; hypohidrosis may also result from GL-3 accumulation in sweat glands
	Hearing loss, tinnitus, dizziness, vertigo	Potentially narrowing of cochlear and vestibular vessels, accumulation of GL-3 in spiral ganglia and vestibular structures; ischemic auditory neuropathy-induced
Dermatologic	Angiokeratoma	Capillary wall weakening and dermal ectasia caused by microvascular endothelial GL-3 accumulation
Gastrointestinal	Nausea, vomiting, intermittent diarrhea and constipation; abdominal pain and/or bloating; difficulty gaining weight in childhood	Mesenteric blood vessel constriction caused by microvascular endothelial GL-3 accumulation; mesenteric and submucosal plexus involvement; GL-3 accumulation in autonomic intestinal ganglia; autonomic neuropathy
Ophthalmologic	Corneal verticillata; conjunctival and retinal vasculopathy, cataract, central retinal artery occlusion (rare), low tear secretion	Scratches on corneal epithelium, vasculopathy
Renal	Pathologic albuminuria/proteinuria	GL-3 accumulation in podocytes and in multiple renal cell types; podocyte damage (pedicel effacement precedes pathologic albuminuria)
	Low glomerular filtration rate with progression to renal failure	Glomerular sclerosis, tubular atrophy, interstitial fibrosis, microvascular endothelial GL-3 accumulation and arteriolar damage secondary to podocyte loss
Cardiac	Cardiomyopathy (especially hypertrophic cardiomyopathy with concentric hypertrophy and minimal/no outflow obstruction); reduced exercise tolerance; syncope; cardiac fibrosis; heart failure (mostly with preserved ejection fraction). Bradycardia – chronotropy incompetence; atrial fibrillation, ventricular tachycardia; sudden cardiac death	ECG abnormalities (short PR interval, T-wave inversion only in early stages), LVH causing hypertrophic cardiomyopathy (echo and cardiac MRI) and myocardial fibrosis (late healing of the posterior inferobasilar wall on cardiac MRI)
Vascular	Aortic stiffness	Intima-media thickness
Cerebrovascular	TIA; ischemic stroke and (more rarely) hemorrhagic stroke; cerebral venous thrombosis; cervical carotid dissection	Strokes caused by small vessel occlusion, dolichoectasia (especially of the basilar artery), chronic white matter hyperdensities, TIAs and cardiac arrhythmias
Neuropsychologic	Common: Depression, anxiety, panic attacks, difficulties with social adaptive functioning. Uncommon: Decreased cognition and dementia	Potentially associated with living with chronic disease, also neuropathic pain and small vessel occlusions, as well as reduced hippocampus volume, multiple infarcts and small vessel occlusions; white matter lesions
Pulmonary	Dyspnea, wheezing, dry cough, sleep-disordered breathing	Obstructive flow limitation (with or without restrictive), decreased spirometric parameters; chest X-ray/CT scan abnormalities (pulmonary infiltrations, fibrosis, air trapping) if advanced; glycolipid accumulation in small-medium airway cells
Lymphatic	Lymphedema of all or part of the limb (also under the eyes), girdle-leaving edema	Glycolipid accumulation in lymph vessels; microlymphatic network disruption
Skeletal	Osteopenia, osteoporosis	Decreased bone mineral density in the lumbar spine and femoral neck
Other	Mild facial dysmorphism	Potentially due to the continuous accumulation of GL-3 in growing fascial bones and the development of fascial connective tissues

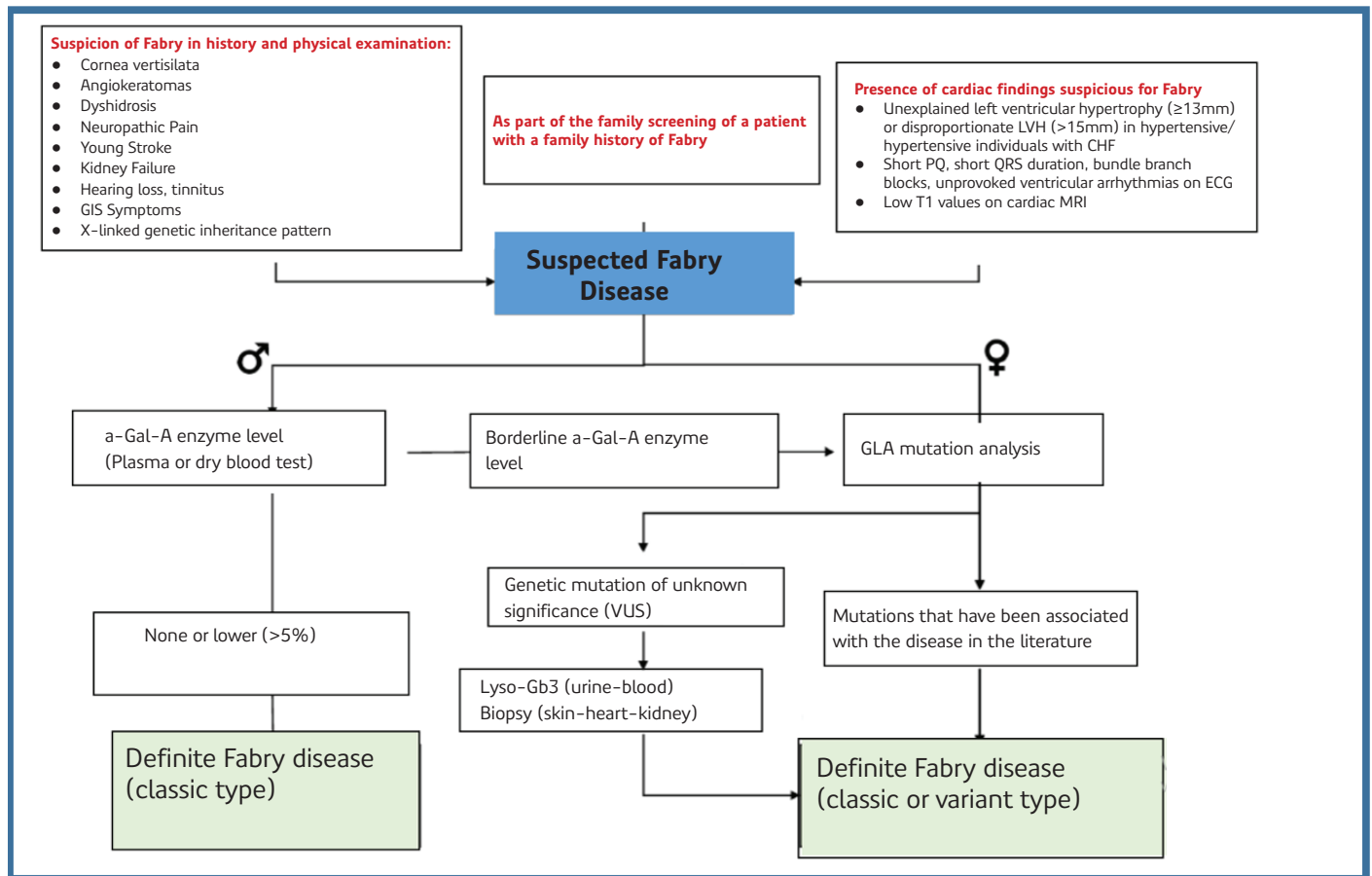


Figure 73. Fabry Diagnosis Algorithm.

patients suspected of having AFD, it is also important to screen for skin findings, including angiokeratomas, through careful examination, even though such findings may be rare.

Diagnosis

In instances where there is clinical suspicion of Fabry disease, the diagnosis is confirmed by measuring the α -galactosidase enzyme level and/or identifying the causative pathological mutation via genetic analysis. For male patients, the initial diagnostic step involves assessing α -galactosidase activity, which can be performed using leukocytes, plasma, or a dry blood spot. Genetic analysis of the GLA gene plays a crucial role for both male and female patients to determine the disease phenotype and to rule out benign polymorphisms that may lead to low enzyme levels.^{408,409} In female patients, GLA gene analysis is usually the initial diagnostic procedure because leukocyte enzyme activity may be low even when plasma enzyme levels are within the normal range, making the identification of the mutation crucial.

With the progress in biochemical and genetic diagnostic methods for AFD, endomyocardial biopsy (EMB) is generally not deemed necessary but can be considered in cases where there is diagnostic ambiguity. This is especially relevant for female patients with a variant of unknown significance (VUS) in the GLA gene or those presenting with a late-onset phenotype.⁴¹⁰ The histological evidence of lysosomal GL-3 deposition obtained from invasive

renal or cardiac biopsies might also be required in scenarios where there is uncertainty about initiating ERT or when the interpretation of the GLA mutation is challenging (Figure 73).⁴¹¹

Cardiac Involvement

Cardiac involvement is the most prevalent manifestation in AFD, affecting 68% of patients. This is followed closely by peripheral nerve involvement at 45% and kidney involvement, also at 45%. Cardiovascular complications stand as the primary cause of mortality, accounting for 75% of fatalities in AFD patients, with sudden cardiac death constituting the majority at 62%. Therefore, early diagnosis is crucial in order to prevent premature mortality (Figure 74).⁴¹²

Cardiac involvement in AFD results from the accumulation of GL-3 within myocytes, vascular endothelial cells, valvular fibroblasts, and the conduction system. In adulthood, 60% of patients experience cardiac symptoms. Reported symptoms include heart failure (HF) in 23% of patients, palpitations in 27%, angina in 23%, and syncope in 4%. The most commonly observed cardiac findings include LVH in 70% of patients, aortic root dilatation in 30%, a short PR interval in 14%, atrial fibrillation (AF) in 17%, non-sustained ventricular tachycardia (VT) ranging from 8 to 15%, and various degrees of bradycardia, chronotropic incompetence, and atrioventricular block (AVB) affecting 7 to 30% of patients. Predominantly, diastolic heart failure is seen in those who develop HF, with advanced HF being reported in 10% of patients.⁴¹³

Multiple Pathways of Cardiac Involvement in Fabry Disease

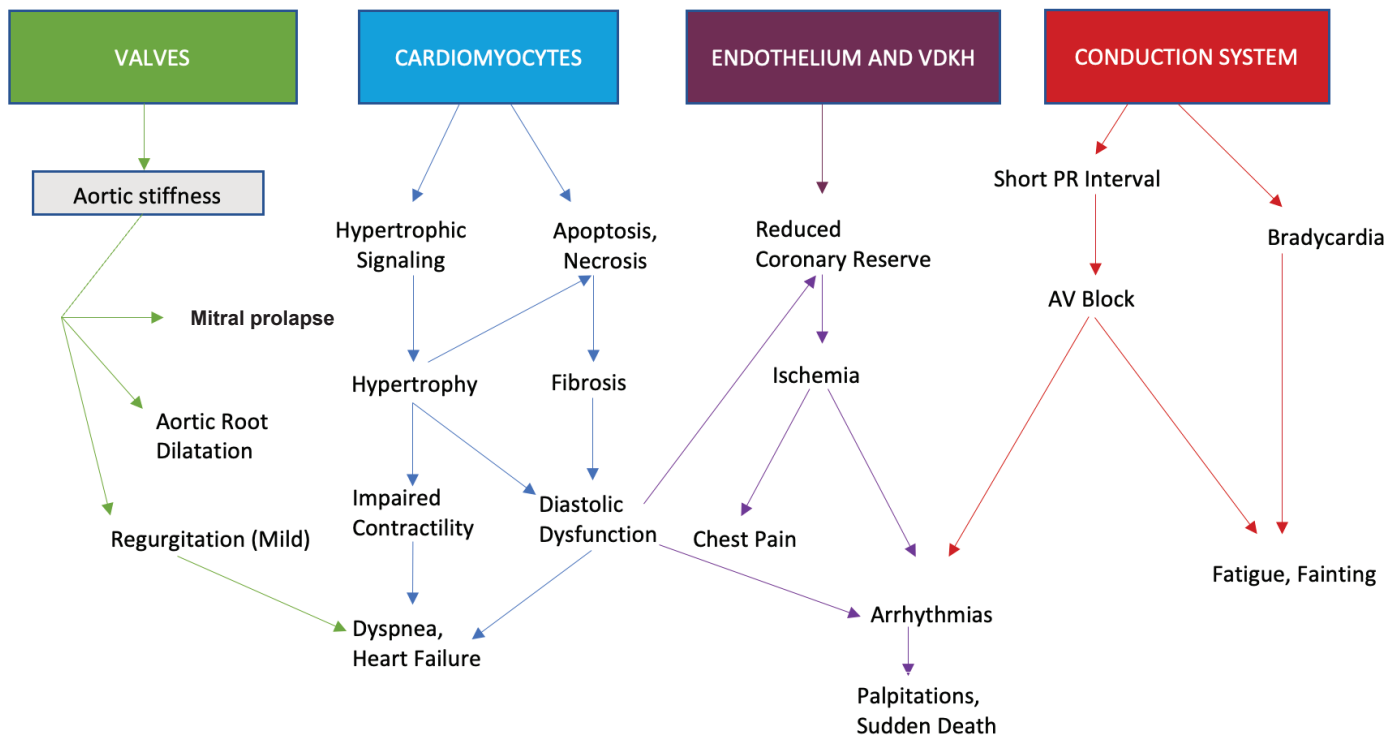


Figure 74. Fabry Cardiomyopathy - Cardiac Involvement.

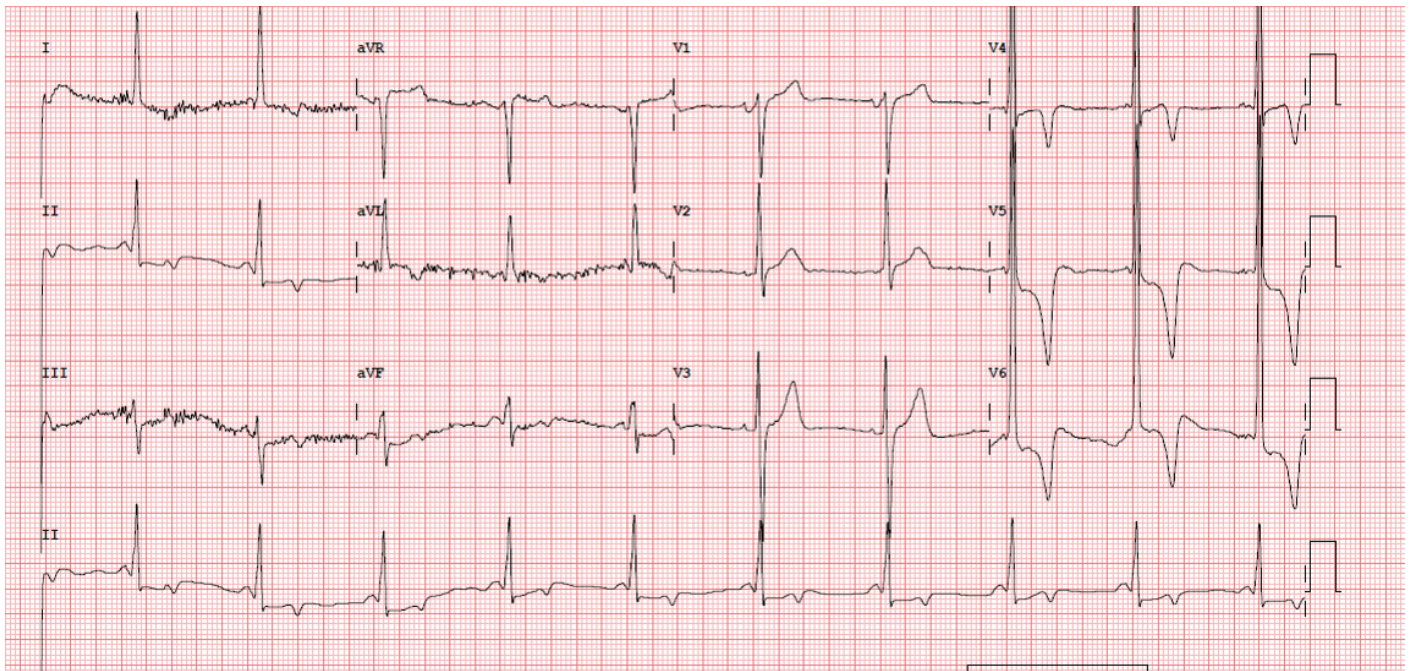


Figure 75. ECG findings in Fabry Disease: short PQ interval, narrow QRS complexes and left ventricular hypertrophy.

Electrocardiogram

In patients with Fabry Cardiomyopathy (FCMP), a normal ECG is an uncommon finding. Signs of LVH are frequently noted. The co-occurrence of a short PR interval and LVH should raise

suspicion of Fabry disease. In particular, left atrial dilatation can result in an extended p-wave duration, giving the impression of a longer PR interval than is actually present. The PQ interval, which spans from the end of the P wave to the start of the Q wave, is considered a more reliable parameter in Fabry patients because

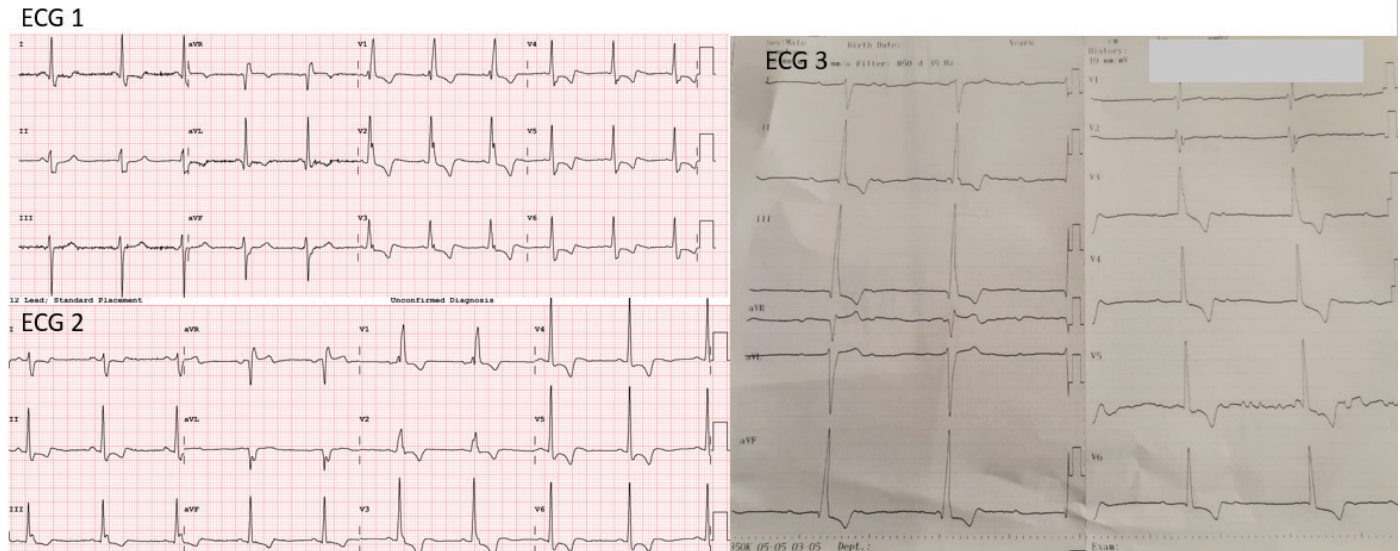


Figure 76. ECG Follow-up of a patient with Fabry Cardiomyopathy. ECG 1: RBBB, ECG 2: RBBB ve LPHB, ECG 3: Total AV Block

it more accurately reflects intra-atrial conduction. A shortened PendQ, which is defined as the duration of the PQ interval minus the P wave being less than 40 milliseconds, is more frequently observed in AFD (Figure 75).

The deposition of glycosphingolipids within the cardiac conduction fibers can result in diseases of the conduction system and various dysrhythmias in AFD. Electrophysiological investigations on conduction tissues from AFD patients have demonstrated shortened conduction times and prolonged refractory periods. Furthermore, the extent of infiltration in the conduction tissues has been correlated with the severity of conduction disease and the occurrence of arrhythmias. In the early stages of the disease, a narrow QRS complex may be observable, while bundle branch blocks, AVB, and atrial as well as ventricular arrhythmias may manifest in more advanced stages. AFD patients are particularly susceptible to AF, which can result from left atrial dilatation and dysfunction.^{414,415}

For all individuals with suspected or confirmed Fabry disease, a 24-hour Holter ECG is recommended to monitor for arrhythmias. Exercise ECG testing is also advised to evaluate chronotropic competence. Particularly for those being monitored for FCMP, comparing current ECGs with previous ones side by side can be beneficial during follow-ups. An increase in QRS duration over time may signal progressive deterioration of the conduction system. As a consequence, patients may require the implantation of a permanent pacemaker during their course of treatment if they develop complete AVB (Figure 76).

Risk factors for sudden cardiac death, which leads to premature mortality in patients with Fabry disease, are identified as male gender, advanced age, LVH, non-sustained VT, and increased late gadolinium enhancement on cardiac magnetic resonance imaging (CMR).⁴¹²

Echocardiography

Echocardiography in Fabry disease most frequently reveals LVH, which occurs in about 70% of cases. While LVH may present in

various patterns, it is predominantly concentric, with a thickness ranging from 13 to 22 mm. The principal mechanism behind cardiac hypertrophy is the inflammation and hypertrophy of vascular smooth muscle cells instigated by the accumulation of substances other than glycosphingolipids, such as GL-3.⁴¹⁶ This inflammatory process eventually leads to fibrosis as the disease progresses. Early diagnosis is crucial for patients, allowing for timely intervention before the development of fibrosis to maximize the treatment response.

In the analysis of the causes of LVH by age, FCMP is generally not anticipated in patients under the age of 20. However, there are rare cases where LVH may be associated with left ventricular outflow tract obstruction and apical aneurysms. In a minority of patients, hyperechogenicity of the basal inferolateral wall of the left ventricle may be observed directly on 2D echocardiography. Concurrent hypertrophy of the left and right ventricles also supports the diagnosis.

Papillary muscle hypertrophy is more commonly and significantly seen in Fabry disease than in other types of hypertrophic cardiomyopathy (HCM). An area greater than 3.6 cm² for the papillary muscles at the level of the papillary muscles, or a ratio exceeding 0.18 of the papillary muscle area to the left ventricular cavity area on the parasternal short-axis view, is a particularly notable finding for Fabry disease. Additionally, the 'binary sign,' described as a hyperechogenic line due to GL-3 deposition along the endocardial border, can be an indicative sign, although it should be noted that its specificity and sensitivity are not high.⁴¹⁷

Additional echocardiographic findings in patients with Fabry disease may include mild thickening of the cardiac valves, mild to moderate valvular insufficiency, dilation of the aortic root, diastolic dysfunction, and decreased longitudinal strain. When compared to sarcomeric hypertrophic cardiomyopathy (HCM), FCMP is more likely to exhibit mild left atrial dilation and diastolic dysfunction. In FCMP, global longitudinal strain (GLS) and right ventricular free wall strain are more significantly impaired than in sarcomeric HCM (SHCM) (Figure 77).⁴¹⁸

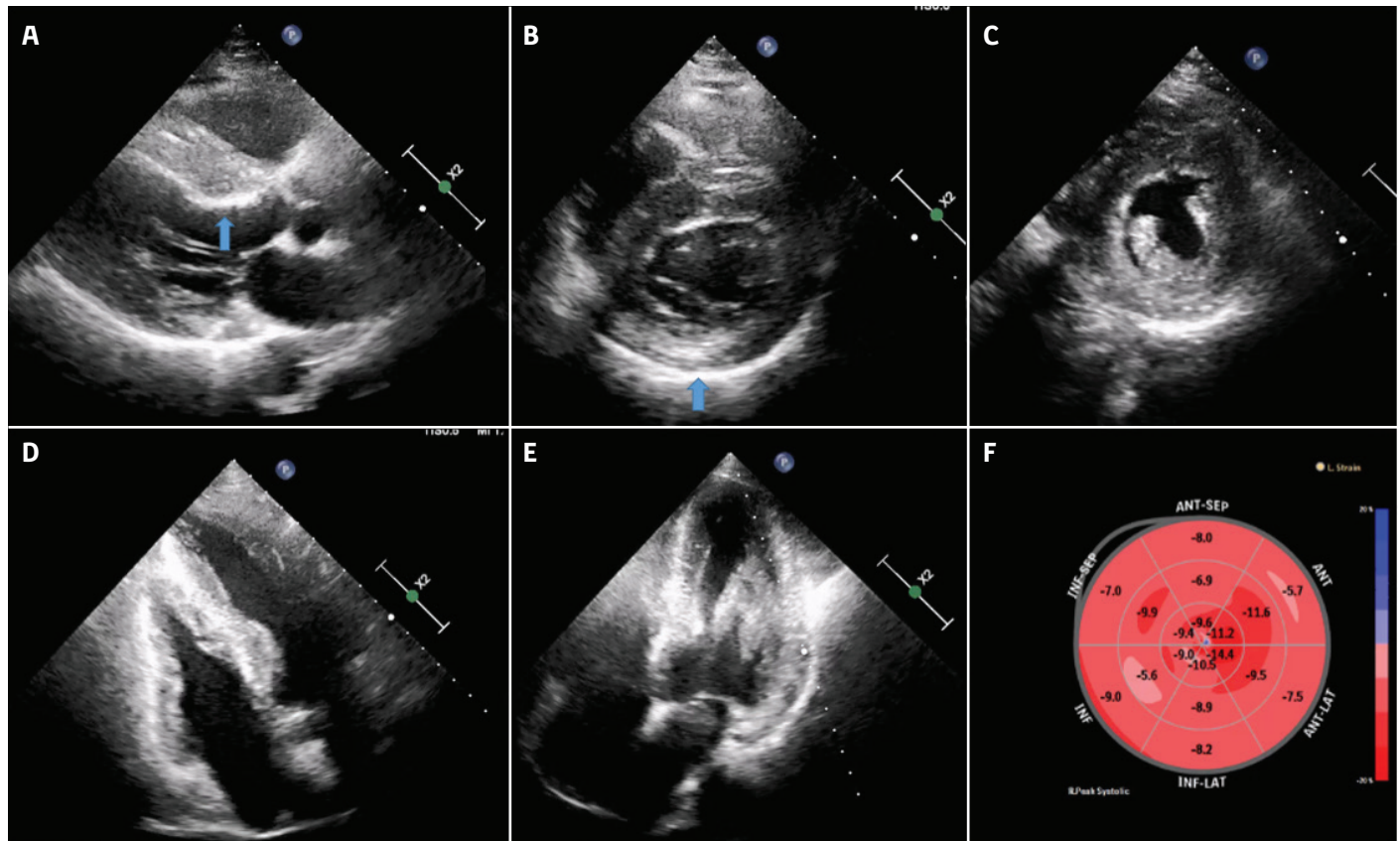


Figure 77. Typical Echocardiographic findings in a male patient with variant type Fabry Cardiomyopathy (A) Concentric symmetrical hypertrophy and Binary Sign (arrow) (C and E) prominent papillary muscles (D) Right ventricular hypertrophy (F) Decrease in global longitudinal strain of the left ventricle.

Overt systolic dysfunction, characterized by a reduced left ventricular ejection fraction (LVEF) below 55%, is rare in AFD, with a prevalence of only 6.8%.⁴¹⁹ Global longitudinal systolic strain (GLS), a more sensitive indicator of systolic function, is often abnormal and can be used for the early detection of the disease even before the manifestation of overt LVH. Diastolic dysfunction occurs more frequently, being present in 43.8% of AFD patients. It can arise with or without LVH and significantly contributes to the development of left atrial enlargement and atrial fibrillation. An elevated level of brain natriuretic peptide (BNP) is associated with diastolic dysfunction.^{420,421}

While valvular heart disease is relatively uncommon in FCMP, when it does occur, it is characterized by the development of valvular stenosis and regurgitation. These conditions are linked to the accumulation of glycosphingolipids in the valve leaflets and subvalvular apparatus.⁴²²

Aortic root dilatation in AFD is typically observed at the level of the sinuses of Valsalva or the ascending aorta. Currently, an optimal threshold for surgical intervention for aortic aneurysms in AFD patients has not been established.^{422,423}

Cardiac Magnetic Resonance

CMR plays a crucial role in diagnosing and staging AFD through tissue characterization. CMR is capable of distinguishing the three main stages of AFD: infiltration, inflammation, and fibrosis,

using T1 and T2 mapping techniques. As a preliminary screening tool, non-contrast T1 mapping can identify the disease in its early stages. In later stages, GL-3 accumulation leads to inflammation and myocardial edema, resulting in elevated T2 values. Subsequent fibrosis development increases T1 values and results in late phase contrast enhancement (LGE). Fibrosis tends to be patchy; therefore, decreased T1 values due to lipid accumulation in one segment might be offset by increased T1 values due to fibrosis in another, leading to an overall normal T1 value. To avoid this discrepancy, segment-specific T1 mapping is recommended.⁴¹⁵

The pattern of LGE in AFD tends to be nonspecific but is most frequently observed in the basal posterior wall. Patients exhibiting LGE greater than 15% are at the highest risk for cardiac events and have been associated with chronic troponin elevation (Figure 78).^{423,424}

CMR is particularly promising for detecting early cardiac involvement in AFD and identifying patients who are most likely to benefit from treatment.

Treatment

The specific treatment of Fabry Disease encompasses ERT and adjunct therapies aimed at preventing the progression of tissue damage. Current guidelines advocate for the initiation of ERT before the occurrence of irreversible organ damage. According

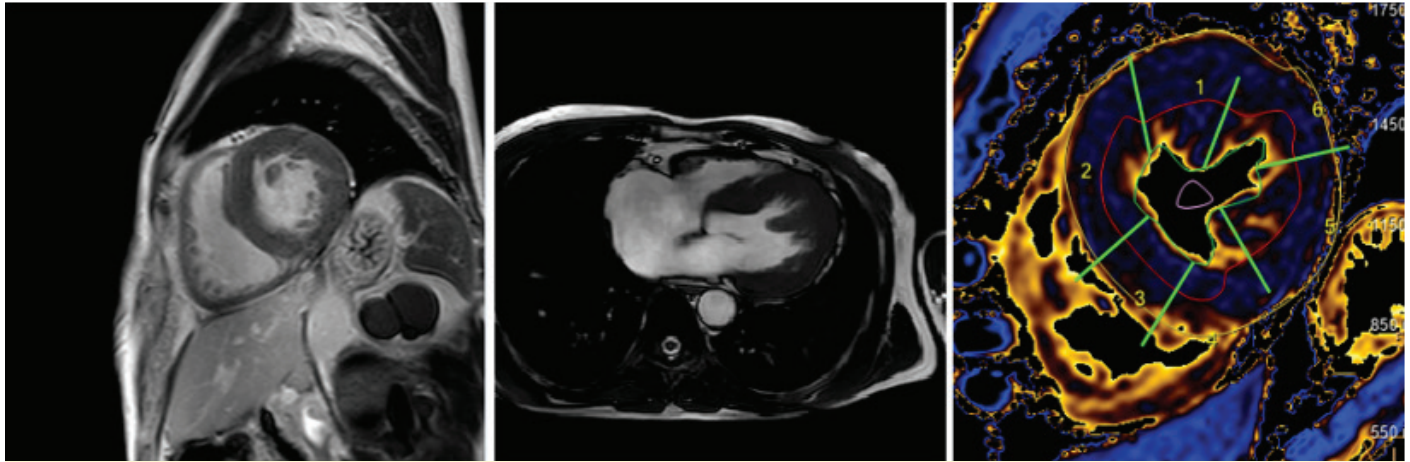


Figure 78. Fabry Cardiomyopathy: CMR Findings: Diffuse myocardial hypertrophy and low T1 mapping levels in a male patient with variant type Fabry cardiomyopathy.

to expert recommendations, treatment should be considered for all male patients, regardless of the presence of clinical symptoms, and for female patients, etiological treatment should commence upon the detection of organ involvement. However, treatment is not recommended for patients with end-stage renal disease, those with advanced heart failure, individuals exhibiting significant myocardial fibrosis, and patients with a life expectancy of less than one year, as they are unlikely to derive clinical benefits or experience improvements in quality of life from the treatment.⁴²⁵

Since the early 2000s, ERT has been a fundamental treatment for Fabry Disease. Currently, there are two available formulations: agalsidase alpha (Repagal, Shire HGT Inc., Cambridge, MA, USA) and agalsidase beta (Fabrazyme, Sanofi Genzyme, Cambridge, MA, USA). Agalsidase alpha is administered as a 0.2 mg/kg dose via weekly intravenous (IV) infusion, while agalsidase beta is given at a dosage of 1.0 mg/kg through IV infusion every two weeks. The efficacy of ERT tends to decrease as the disease progresses.^{426,427} Challenges associated with ERT include the requirement for bi-weekly IV administration, high costs, the risk of allergic reactions, and reduced bioavailability due to the development of antibodies. Second-generation ERTs, such as Pegunigalsidase- α and Moss-GaLA, are under study for their potential benefits in evading immunogenicity and having longer plasma half-lives.^{428,429}

From a cardiac perspective, ERT has been shown to slow the progression of LVH, enhance functional capacity, and decelerate the advancement to heart failure. If initiated before the development of fibrosis, ERT may also extend survival and decrease the incidence of arrhythmic events.⁴³⁰

Migalastat is an orally administered pharmacologic chaperone that has demonstrated efficacy as an alternative to intravenous ERT. It is designed to enhance residual enzyme activity. However, migalastat is not intended for concurrent use with ERT and is not suitable for patients with severe renal impairment (glomerular filtration rate (GFR) < 30 mL/min).⁴³¹

Research on substrate reduction therapy (SRT) aims to prevent the accumulation of metabolites that cannot be broken down

due to enzyme deficiency. Studies are ongoing with molecules such as eliglustat, venglustat, and lucerastat. Additionally, gene-specific treatment research is advancing, including therapies like recombinant α -galactosidase-encoding mRNA therapy, the infusion and vaccination of autologous hematopoietic stem cells, and gene editing using CRISPR/Cas systems. These innovative approaches are part of the efforts to find more effective treatments for Fabry Disease.^{432,433}

There is no specific treatment targeting the cardiovascular involvement in Fabry Disease. Patients exhibiting late gadolinium enhancement (LGE) on CMR are unlikely to see a regression in LVH with ERT. Given that a significant portion of cardiovascular fatalities in Fabry Disease result from sudden cardiac death, prevention is paramount. Although FCMP is often classified alongside hypertrophic cardiomyopathy (HCM), the sudden cardiac death risk scoring systems used for classical sarcomeric HCM do not apply to patients with FCMP. Implantable Cardioverter Defibrillators (ICDs) are used for secondary prophylaxis; however, these measures might not offer sufficient protection. Consequently, there is a need to develop a specialized risk score that considers a range of factors, including imaging results, family history, and genetic analyses, to assess the risk of sudden cardiac death in patients with Fabry Disease.

In older patients, AF is commonly associated with Fabry disease. It's important to recognize that the CHA2DS2-VASc score, typically used to evaluate the need for anticoagulation, is not applicable for assessing Fabry patients with AF. In the absence of contraindications, anticoagulation is advised for Fabry patients who have AF. The utilization of amiodarone for arrhythmia treatment in patients receiving ERT should be avoided, as it interferes with enzyme absorption and its corneal verticillata-like side effect may mimic disease manifestations. Caution is also advised in the use of beta-blockers for patients with heart failure (HF) due to the risk of bradycardia.

Furthermore, the accumulation of sphingolipids in the endothelial layer can cause anginal symptoms in patients without significant epicardial artery occlusion. These patients might benefit from

anti-anginal therapy. Additionally, the endothelial dysfunction seen in Fabry Disease increases susceptibility to atherosclerosis, making early preventative treatment critical.

Follow-Up

Patients diagnosed with AFD require periodic monitoring, although there is no universal consensus on the exact frequency of these follow-ups. It is recommended that basic evaluations, including echocardiography, high-sensitivity Troponin (hs-Troponin), B-type Natriuretic Peptide (BNP)/N-terminal pro b-type Natriuretic Peptide (NT-proBNP) measurements, and Electrocardiogram (ECG) examinations, be conducted every 3-6 months. These should be accompanied by clinical assessments to check for involvement of other organs. Additionally, for a more detailed evaluation, a 24-hour Holter ECG and strain echocardiography may be recommended every 6-12 months, and T1 mapping Magnetic Resonance Imaging (MRI) every 2-3 years.

In the diagnosis and prognostic monitoring of AFD, high-sensitivity Troponin (hs-Troponin) and B-type Natriuretic Peptide (BNP)/N-terminal pro b-type Natriuretic Peptide (NT-proBNP) measurements are pivotal. These biomarkers should be a routine part of patient follow-ups. Troponin levels may remain chronically elevated after the inflammatory phase, signaling ongoing disease progression and fibrosis. Elevated BNP levels can be indicative of patients who are developing renal failure or who are in advanced stages of the disease.^{421,434} Moreover, a correlation exists between elevated BNP levels and late gadolinium enhancement (LGE) on CMR, linking these biomarkers to the extent of myocardial fibrosis and damage.

Patients experiencing unexplained palpitations or who have been identified with left atrial enlargement should be evaluated with a 24-hour Holter ECG recording to monitor for arrhythmias. For cases of unexplained syncope where short-term monitoring does not provide a diagnosis, the use of an implantable loop recorder should be considered for longer-term heart rhythm

tracking. It's crucial to compare the ECGs of patients at each visit with their previous records. Observations such as changes in the PR interval, widening of the QRS duration, and the emergence of new bundle branch blocks can serve as indicators of progressive damage to the cardiac conduction system.

Conclusion

AFD is an X-linked genetic disorder caused by a deficiency in the enzyme α -galactosidase, due to mutations in the GLA gene. This deficiency leads to the accumulation of glycosphingolipids within various tissues. AFD does not have a singular, characteristic mutation; rather, a wide array of mutations have been discovered, each associated with different phenotypic expressions. Clinical manifestations may include the classic phenotype with premature-onset peripheral neuropathy, angiokeratomas, and proteinuric chronic kidney disease, or a later-onset form that predominantly involves cardiac complications.

The cardiovascular implications for patients with AFD are profound, encompassing heart failure, microvascular ischemia, bradyarrhythmias, tachyarrhythmias, valvular dysfunction, and aortic dilation. Diagnosing AFD demands a comprehensive, multidisciplinary strategy. Non-invasive diagnostic tools like echocardiography and CMR, alongside biomarkers such as high-sensitivity Troponin (hs-Troponin) and B-type Natriuretic Peptide (BNP), play crucial roles in evaluating the disease's impact and tracking the efficacy of treatments.

ERT is currently the mainstay of AFD treatment; however, chaperone therapy represents a viable alternative for individuals with specific GLA mutations. Additionally, cutting-edge treatments like substrate reduction therapy, mRNA therapy, and gene therapy are under investigation and show promise. Managing AFD necessitates long-term, multidisciplinary care to monitor and address the myriad organ complications and the overall activity of the disease.

Cardiac Sarcoidosis: Diagnosis and Disease Management with Multimodality Imaging

Sarcoidosis is a multisystem granulomatous inflammatory disorder with an uncertain etiology. Incidence varies between 5 and 40 cases per 100,000 people, depending on geographical region and ethnicity.⁴³⁵ Clinically evident sarcoidosis involving the heart has been observed in 2% to 7% of patients with systemic sarcoidosis, but occult involvement is much higher (>20%), and its prevalence also depends on the clinical practice of using advanced imaging methods.⁴³⁶ Diagnosing isolated cardiac sarcoidosis (CS) or cardiac involvement in systemic sarcoidosis is challenging and usually relies on multimodality advanced cardiac imaging since the diagnostic accuracy of both clinical criteria and endomyocardial biopsies is limited. Japanese Circulation Society guidelines have included late gadolinium enhancement (LGE) on Cardiovascular Magnetic Resonance (CMR) and abnormal Positron Emission Tomography (PET) findings as major criteria, offering the possibility of diagnosing isolated CS based on advanced imaging.⁴³⁷

According to the Heart Rhythm Society (HRS) consensus recommendations, CS is probable in the absence of histological confirmation if there is histological proof of extracardiac sarcoidosis and the presence of one or more of the following features: a) advanced CMR or fluorodeoxyglucose positron emission tomography (FDG-PET) imaging pattern consistent with CS; b) unexplained reduced left ventricular (LV) ejection fraction (EF) <40%; c) unexplained major arrhythmic events, including ventricular tachycardia (VT), second- or third-degree atrioventricular block, immunosuppressive-responsive cardiomyopathy/heart block; and other causes of cardiac manifestations have been excluded.^{438,439} Echocardiography has low sensitivity in detecting mild, localized abnormalities associated with CS but is a useful tool for diagnosing and following up on patients presenting with heart failure caused by LV dysfunction.⁴⁴⁰

Diagnosis

Pulmonary and systemic sarcoidosis are suspected based on symptoms, ECG, and multimodality imaging, and are confirmed through histopathological examination of biopsy specimens. Myocardial biopsy is an invasive procedure with associated risks, and the focal distribution of granulomas in the myocardium results in a low diagnostic accuracy of 20%–30% when performed blindly from the right side of the interventricular septum.⁴³⁹ Cardiac sarcoidosis should be viewed as part of a multiorgan disorder; therefore, a multidisciplinary team consisting of respiratory and cardiac physicians as well as cardiac imaging experts is recommended. In the absence of biopsy-proven disease, imaging can aid in making a diagnosis with varying levels of confidence by the team. LGE and FDG-PET were reported positive in 94% and 80% of patients with myocardial biopsy-proven sarcoidosis, respectively.⁴⁴¹

The diagnostic pathway recommended by the HRS follows an imaging-guided approach, but even typical findings on CMR or FDG-PET may not provide a definitive diagnosis without histologic confirmation. In the majority of cases, FDG-PET helps guide the selection of an extracardiac biopsy site, and if present, the most easily accessible lymph nodes with the highest inflammatory activity are sampled. Given its invasive nature, endomyocardial biopsy is not preferred in the initial diagnostic work-up unless imaging and clinical findings are inconclusive and there is another alternative diagnosis that may be identified through histology.

The role of CMR in diagnosing cardiac sarcoidosis is well established, particularly for T2-weighted myocardial edema imaging and LGE. Additionally, it provides information on myocardial wall

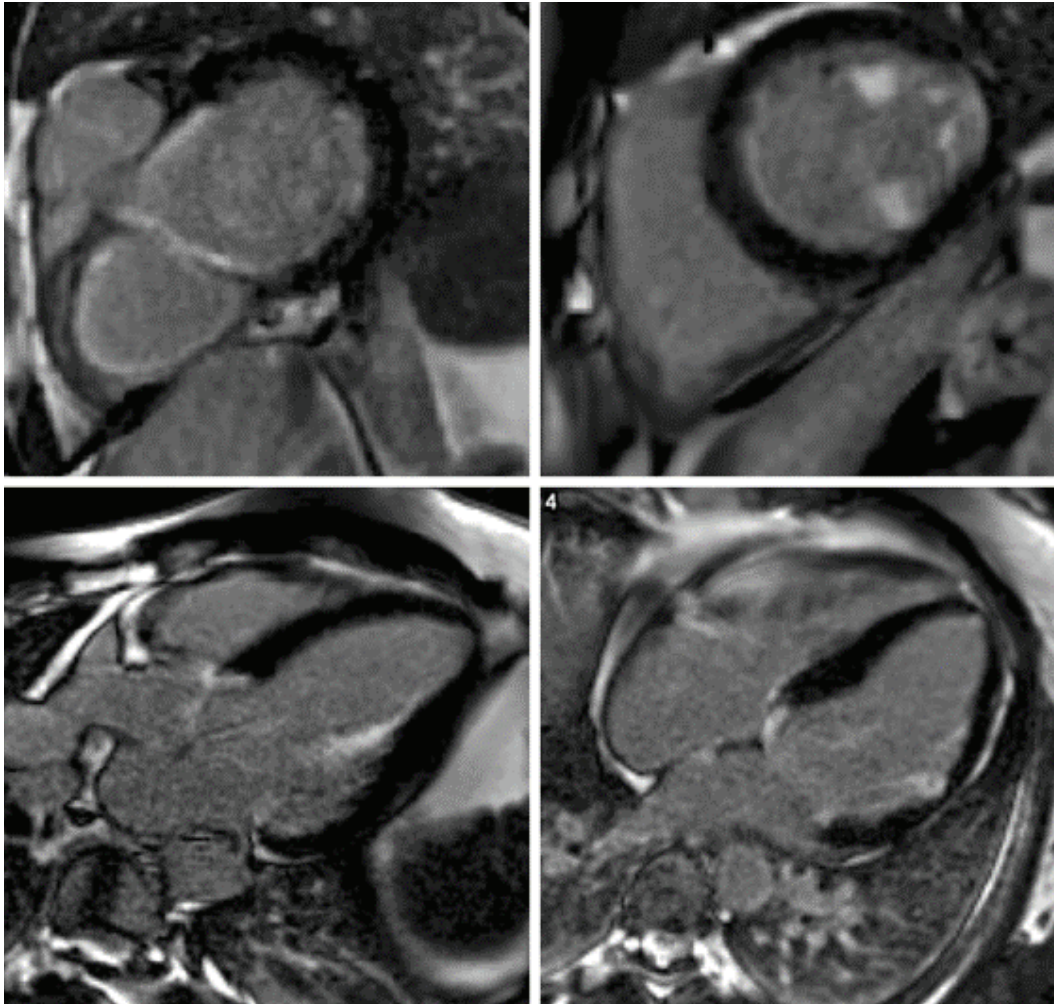


Figure 79. 55 years old female patient initially presenting with unstable VT and subsequently diagnosed with cardiac and pulmonary sarcoidosis.

thickness, biventricular volumes and function, regional wall motion abnormalities, and the presence of thoracic lymph nodes. Myocardial edema is detectable on T2-weighted imaging; however, LGE is the key CMR modality in cardiac sarcoidosis. LGE reflects extracellular expansion caused by necrosis or edema in the acute phase or chronic replacement fibrosis.

LGE most commonly involves the basal LV segments and the right ventricular (RV) side of the septum, but any part of the heart can be affected (Figure 79). LGE is most often distributed in a patchy, non-ischemic pattern, but subendocardial and even transmural involvement is possible. The "shepherd's hook sign," a septal LGE continuing into the RV free wall, has been defined as specific to sarcoidosis; however, a similar pattern can be present in giant cell myocarditis or arrhythmogenic cardiomyopathy (Figure 80).⁴⁴²

Alternative clinical diagnoses for high-degree atrioventricular (AV) block, ventricular tachycardia, or heart failure presentation with extensive LGE on CMR include coronary artery disease, arrhythmogenic right ventricular cardiomyopathy (ARVC), dilated cardiomyopathy, and myocarditis. Extensive and multipattern LGE, with basal/mid-septal (especially basal anterior septum)

and RV side septal involvement, should raise suspicion of CS in this patient group. Usually, a comprehensive assessment of available clinical data guides the diagnostic process.⁴⁴³

Differentiating sarcoidosis from ARVC can be especially challenging. Many patients who met task force criteria for ARVC were ultimately found to have biopsy-proven CS.⁴⁴⁴ While useful for diagnosing CS, CMR has shown limited sensitivity in edema imaging to detect myocardial inflammation. FDG-PET is a key technique for identifying active cardiac inflammation and extracardiac involvement in sarcoidosis.⁴⁴²

The role of FDG-PET in diagnosing cardiac sarcoidosis is based on the detection of myocardial inflammation, providing excellent negative and positive predictive values, as well as identifying extracardiac disease activity. Sensitivity of 89% and specificity of 78% have been reported for FDG-PET in detecting cardiac sarcoidosis; however, these data are limited by the lack of comparison with a gold standard.⁸⁵

Cardiac images can be displayed in the standard three views (short axis, horizontal long axis, and vertical long axis views) or polar maps similar to SPECT and MPI (Figure 81A). There are

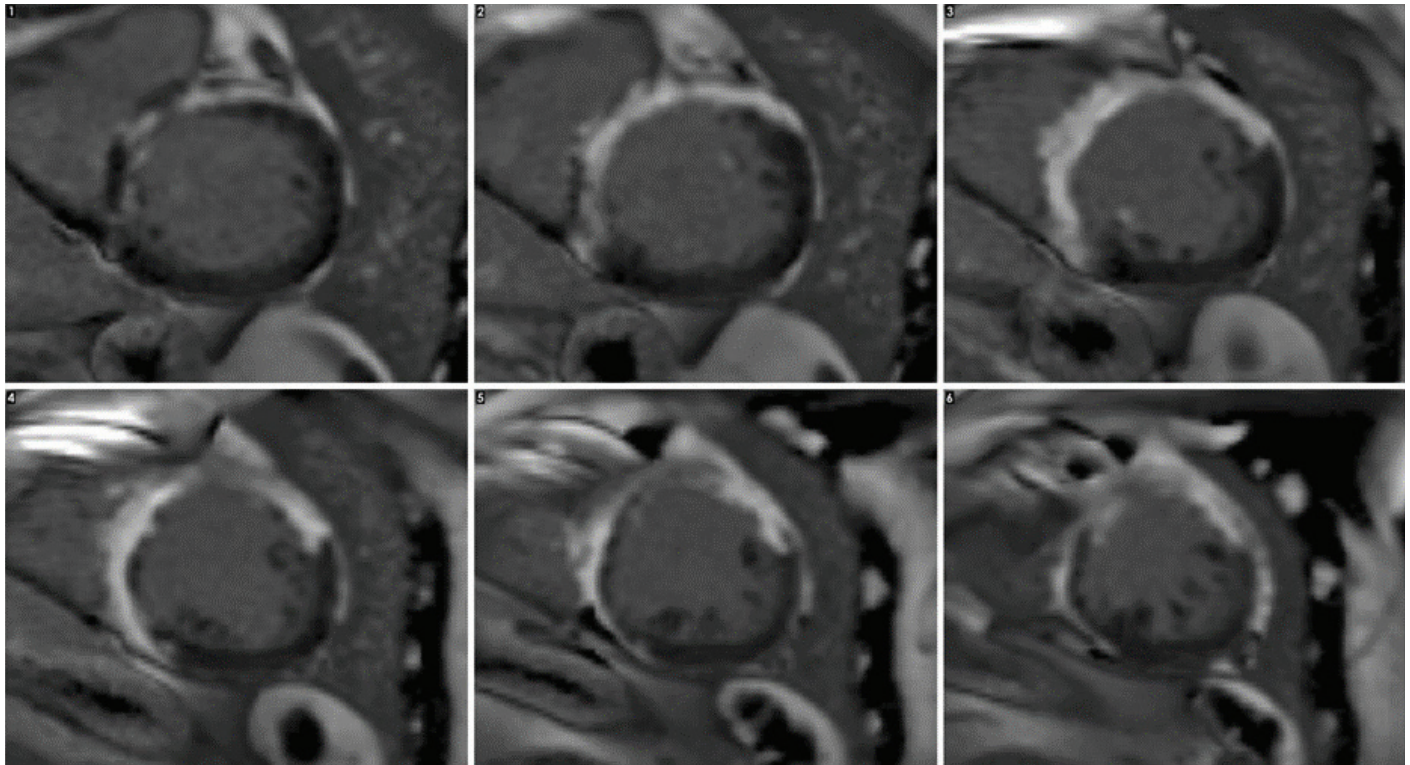


Figure 80. LGE images of a 46 years old male presenting with non-sustained VT. Note the Shepherd's hook sign. Patient also had patchy myocardial FDG uptake on FDG-PET suggesting active myocardial inflammation.

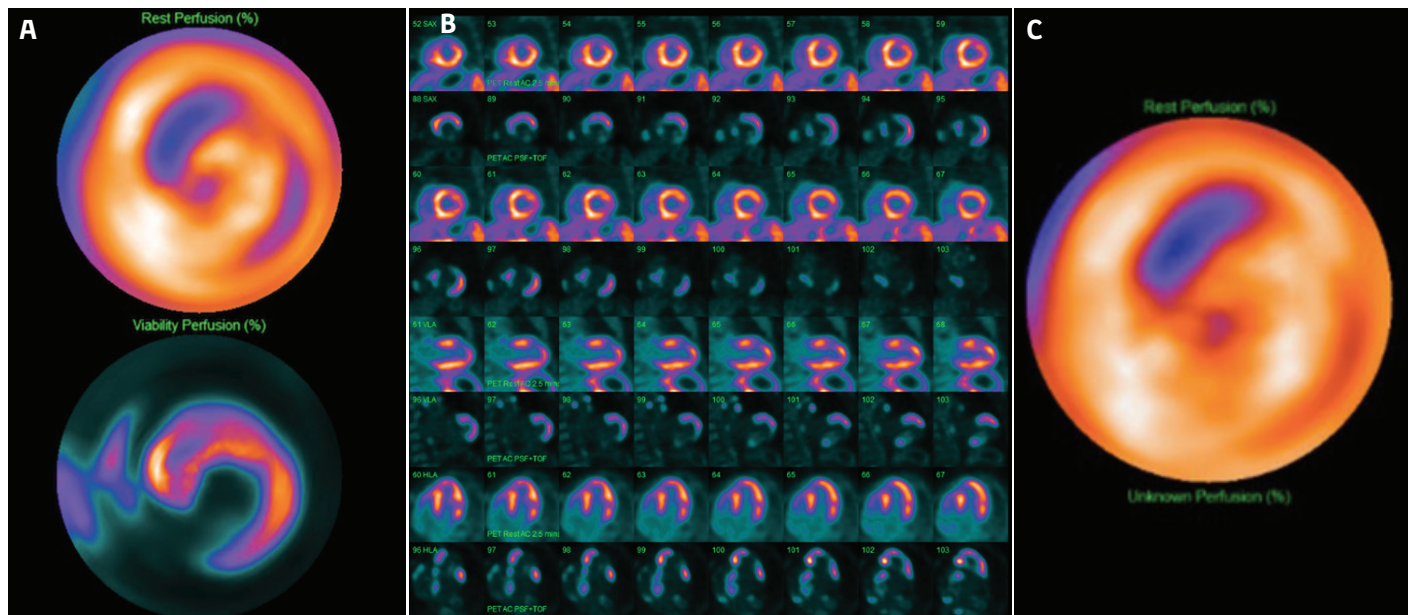


Figure 81. (A) Polar maps (A) and splash (B) representation of resting perfusion (upper panel) and cardiac FDG uptake (lower panel) in a 50 year-old female patient with new diagnosis of cardiac sarcoidosis, pattern is typical of metabolism and perfusion mismatch. Resting Rb perfusion images show moderate reduction of tracer uptake in the mid to apical anterior/anteroseptal region and in the basal to mid inferolateral myocardium. There was reduced thickening in the anterolateral and inferolateral walls but preserved ejection fraction of 69% on ECG gated images. In corresponding regions, intense patchy FDG uptake was seen and this was most prominent in the apical septum and in the lateral wall. (B) See figure legends above. (C) The resting perfusion polar map of the same patient after 8 months of immunosuppressive therapy. There is moderately reduced tracer activity in the mid to apical anterior/anteroseptal region and some minimal reduction of counts in the basal inferolateral wall. Overall, perfusion substantially improved compared to previous study especially in the inferolateral region.

several classification methods for cardiac FDG uptake. The expert consensus document recommends classifying uptake as follows:

1. No FDG uptake (none)
2. Diffuse FDG uptake (diffuse)
3. Focal FDG uptake (focal)
4. Focal on diffuse FDG uptake (focal on diffuse)

"Focal" and "focal on diffuse" uptake are considered consistent with patchy cardiac inflammation typical of sarcoid involvement. "Diffuse" uptake is difficult to interpret because it can also be caused by diffuse inflammation or inadequate suppression of glucose metabolism due to dietary failure. Ideally, a "normal" cardiac FDG image would show no myocardial uptake, with the blood pool brighter than the myocardium. Low-intensity, homogeneous FDG uptake in the lateral wall is considered a normal finding if the level of suspicion for cardiac sarcoidosis is low (based on clinical information) and no perfusion or myocardial wall thickening abnormalities are observed in this region.⁴⁴⁵

Other differentials of increased FDG uptake in the myocardium include ischemia (where myocytes cannot switch to fatty acid metabolism and will continue to use glucose despite fasting; this phenomenon is called ischemic memory and can be recognized by the coronary distribution of involvement), active myocarditis, eosinophilic granulomatosis with polyangiitis (EGPA), and other vasculitis or connective tissue diseases involving the heart. Although the mechanism is not fully understood, severe left ventricular hypertrophy (LVH) may also show FDG uptake.

Right ventricular uptake usually represents sarcoidosis activity, but care should be taken to avoid false positives from artifacts related to metal pacing or defibrillator leads. Visual analysis of non-attenuation-corrected images can be helpful in this case. Right ventricular uptake has also been demonstrated in ARVC. Atrial FDG uptake is usually associated with atrial fibrillation.

When interpreting half-body (eyes to thighs) images, in addition to assessing cardiac chamber uptake, careful evaluation of other disease sites should be conducted, such as lymph nodes, lungs, liver, spleen, and skeleton. The lymph nodes can be helpful for tissue diagnosis when accessible for biopsy via percutaneous or endobronchial routes.

There is evidence that semi-quantitative analysis of FDG images using SUVs improves diagnostic performance compared to visual analysis.^{446,447} SUVmax values are most commonly used and reported for both cardiac and extracardiac FDG uptake, helping assess patient response to treatment in serial studies.^{95,448} There are no established cutoff values for SUVs in sarcoidosis, and it has only been partly validated in inflammation and infection. In an FDG-PET study of infective endocarditis, an SUV cutoff >3.3 was suggested to avoid false-positive findings.⁴⁴⁹ However, extrapolating this cutoff value to other cardiovascular disease states is challenging, and cutoff values will also vary between different scanners, reconstruction methods, and hospitals due to slightly different patient preparation and injection/scanning practices.

The diagnostic performance of perfusion SPECT and perfusion PET in cardiac sarcoidosis is limited, but these methods potentially have additional value in conjunction with FDG-PET.^{445,448}

Standard resting PET or SPECT myocardial perfusion imaging (MPI) protocols are performed, and PET MPI has advantages over SPECT for identifying small perfusion defects.^{450,451} Perfusion abnormalities associated with cardiac sarcoidosis are not specific to inflammation or scarring from sarcoidosis, so alternative diagnoses, such as coronary artery disease (CAD), should ideally be ruled out before interpreting images.

While resting perfusion defects with no FDG uptake would indicate myocardial scarring, perfusion defects with corresponding increased FDG uptake may be caused by intense inflammation-related edema leading to microvascular compression and local ischemia. This pattern is called a metabolism-perfusion mismatch (no perfusion but inflammation in viable myocardium) and is considered to represent progressive myocardial impairment (Figure 81A–B). When this phenomenon is observed, some perfusion defects may improve after therapy (Figure 81C).

As a surrogate to perfusion, FDG-PET can be compared with CMR LGE images. Areas of increased uptake that correspond to LGE suggest active cardiac sarcoidosis. Areas of LGE enhancement with no uptake would be consistent with scarring, and regions of FDG uptake without LGE indicate either early sarcoidosis beyond the sensitivity of CMR or false-positive physiological activity. Myocardium with no FDG uptake and no LGE is considered normal.⁴⁵⁰ With newer software methods, it is possible to fuse CMR images with FDG images without necessarily using PET-CMR.

A recent report showed that in a patient cohort with suspected cardiac sarcoidosis, when FDG-PET information was added to CMR, approximately 45% of patients were reclassified to having a lower or higher likelihood of the diagnosis.⁴⁵²

Treatment and Follow-up

Cardiac involvement has a wide spectrum, ranging from silent myocardial inflammation to conduction disturbances, ventricular arrhythmias, progressive heart failure, and sudden death (13%–25% of disease-related deaths). In addition to immunosuppressive therapy, the treatment of cardiac sarcoidosis involves heart failure management when ventricular dysfunction develops and pacemaker or ICD therapy for heart blocks and rhythm disturbances.

ICDs are recommended for CS patients with a left ventricular ejection fraction (LVEF) $\leq 35\%$, sustained ventricular tachycardia (VT), or for survivors of cardiac arrest. Patients with an LVEF $>35\%$ and myocardial scar (as identified by CMR or PET) and/or syncope should also be considered for an ICD.⁴⁵⁴

Serial assessment of inflammatory status with FDG-PET is used clinically to monitor therapy effectiveness. The joint position statement on imaging in cardiac sarcoidosis by EANM, EACVI, and ASNC recommends the algorithm in Figure 82 for this purpose.⁴³⁹ Mortality rates of untreated CS are high, and corticosteroid treatment alone or in combination with additional immunosuppressive agents is the mainstay of treatment.⁴³⁸

Without histopathological verification, even typical abnormalities on CMR or PET-CT may not provide a definitive diagnosis. Therefore, decisions regarding long-term immunosuppression in patients with suspected, but not proven, cardiac sarcoidosis must be individualized.

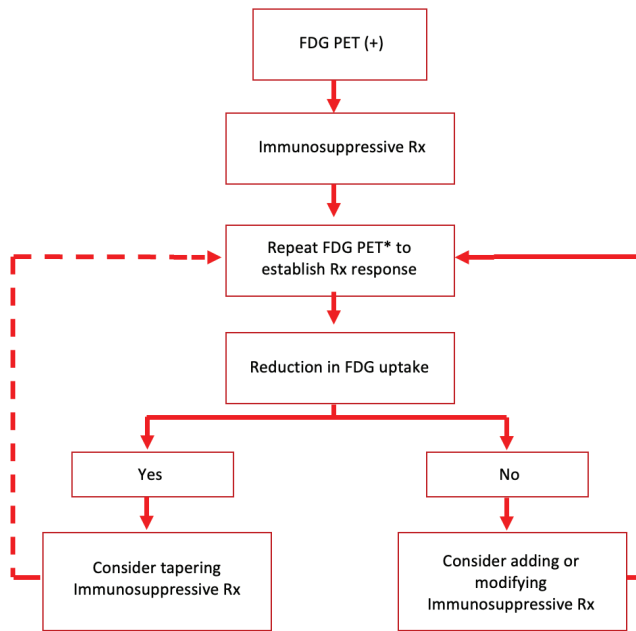


Figure 82. Algorithm for treatment response evaluation with serial FDG PET studies in cardiac sarcoidosis patients.⁴³⁸

In a clinical setting suggestive of cardiac sarcoidosis, FDG-avid mediastinal lymph nodes provide a biopsy target that may improve the success rate of identifying sarcoid histopathology.⁴⁴⁷ The role of image-guided endomyocardial biopsy in improving histopathologic sampling requires further evaluation, but it is recommended by HRS guidelines to improve the low sensitivity of the technique.

Sarcoidosis treatment is recommended for patients with LV dysfunction, ventricular arrhythmias, hypermetabolic activity on cardiac FDG-PET, conduction defects, LGE on CMR, or right ventricular dysfunction in the absence of pulmonary hypertension.⁴⁵³ However, due to the high side effect profile of immunosuppressive drugs, image-guided initiation and tailoring of therapy are preferred (Figure 83).

Although a clear response to therapy is seen in some cases, the use of visual analysis to assess serial changes in response to therapy may be limited. Therefore, SUV metrics and changes in myocardial perfusion are preferred quantitative serial assessment methods. Whole-body imaging detects extracardiac increased FDG uptake. Distribution and intensity (SUV metrics) should be compared to prior scans and reported as increased, similar, or decreased disease activity.

The duration of treatment is based on clinical response, and the optimal interval for repeat FDG-PET imaging is not known. A consensus document recommends repeating FDG-PET 4–6 months after initiation of therapy.⁴³⁹ In patients undergoing serial FDG-PET during treatment for cardiac sarcoidosis, a reduction in intensity (SUVmax) or extent was associated with improvement in LVEF.⁴³⁹

Echocardiography and CMR have limited value in assessing treatment response. LV systolic and diastolic function, as well as RV parameters, can be followed up with echocardiography but would not provide insight into disease activity. The use of CMR is limited because the majority of patients have intracardiac devices that may preclude CMR or produce artifacts.⁴⁵³ Edema imaging sequences are less sensitive and specific for inflammation compared to FDG-PET, and they are prone to artifacts caused by an irregular heart rate.⁴⁴²

Prognosis

The prognosis of CS is related to the extent and sites of involvement, and life-threatening arrhythmias might be induced by inflammation or fibrosis of the conduction system or ventricular walls.⁴⁵⁵ An association between LGE and poor prognosis has been shown in several studies. A meta-analysis comprising 7 studies and 694 subjects suggested that positive LGE in CS patients was associated with an increased risk of cardiovascular death or ventricular arrhythmia.⁴⁵⁶ Early initiation of immunosuppressive therapy has the potential to prevent cardiac dysfunction, and the extent of LV dysfunction and dilation are important predictors of survival.⁸⁵

Areas of focal FDG uptake in the right ventricle may also be associated with a worse prognosis.⁴⁵⁰ Patients with myocardial

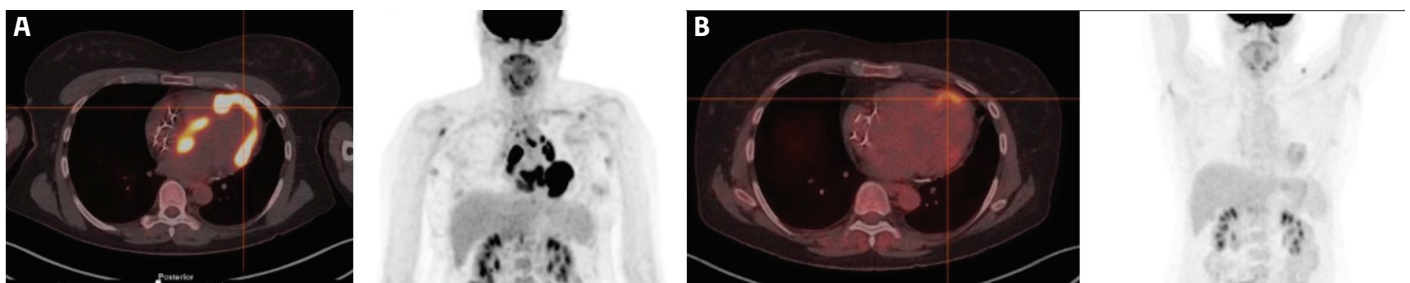


Figure 83. (A) Initial [18F] FDG PET images of 50 years-old female presenting with reduced ejection fraction and new diagnosis of cardiac sarcoidosis suggested by a CMR study. Patient had CRT-D implanted due to ventricular tachycardia and heart failure. Intense focal and patchy areas of FDG uptake in the myocardium mainly within the left ventricular apex apical septum and in the apical lateral wall with SUV max of 18.0. Further intense focal FDG uptake is in the basal inferolateral region with SUV max of the 12.6 and in the basal septum. (B) Follow up FDG-PET after 8 months of immunosuppressive treatment. Mild residual active inflammation in the left ventricular apical anterior/anteroseptal wall and basal inferolateral wall. When compared to the previous study, there was significant reduction of inflammation within the LV myocardium and the mediastinal lymph nodes were no longer FDG avid. Appearances are in keeping with good response to treatment.

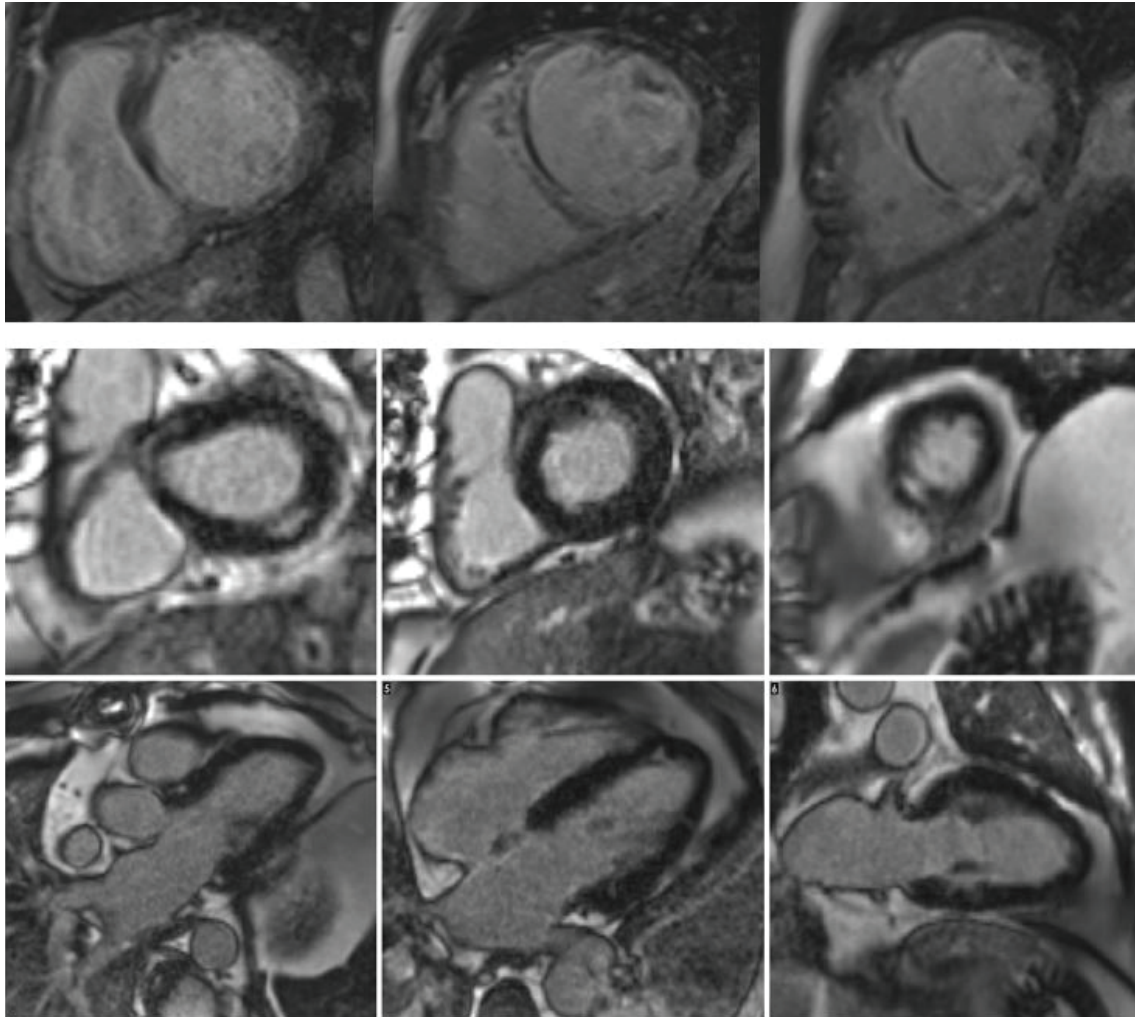


Figure 84. Pre-cardiac transplant (upper row) and post-transplant (lower 2 rows) LGE images of a male patient who experienced two VT arrests at their 40s. He was initially diagnosed with ischemic cardiomyopathy despite CMR reporting suspicion of CS. Histopathologic diagnosis of sarcoidosis was confirmed at explanted heart. FDG-PET study showed previously undiagnosed pulmonary sarcoidosis. Pre-transplant CMR (upper row) shows extensive multipattern LGE fibrosis and in the post-transplant follow up study (lower two rows, 3 years after transplant) recurrence of CS with focal mid-wall enhancement in the basal anteroseptal, basal inferolateral and apical septal walls.

perfusion defects have a higher risk of death or ventricular arrhythmias compared to cardiac sarcoidosis cases without perfusion defects.⁴⁵⁰ Patients with a combination of myocardial inflammation and resting perfusion defects corresponding to these regions (indicating metabolism and perfusion mismatch) are at high risk for death or VT (4-fold increased risk), independent of LVEF, clinical criteria, and the presence of active extracardiac disease.⁴⁵⁰

A multimodality imaging approach is advised to assess the need for pacemaker or ICD implantation. HRS guidelines recommend ICD implantation if LVEF remains <35% after immunosuppressive therapy (Class I) or if LGE is detected in patients with LVEF 35%-49% after immunosuppression (Class IIb). The presence of active extracardiac sarcoidosis was not associated with adverse cardiac events.⁸⁵

The event rate in patients referred for cardiac FDG-PET is higher

than in those referred for CMR. This difference can be explained by referral bias, as patients referred for FDG-PET are more likely to have an ICD or pacemaker.⁴⁵⁷ SUV values were also reported to have prognostic value, and a reduction in intensity during follow-up was associated with improved LVEF, which is one of the most important prognostic factors.⁴⁴⁷

For patients with end-stage involvement, lung, heart, or heart and lung transplantation is a viable option. Recurrent sarcoidosis has been described in cardiac allografts but is uncommon (<10%) and may respond to intensified corticosteroid treatment (Figure 84).⁴⁵⁸ Rejection rates, survival, freedom from cardiac allograft vasculopathy, and nonfatal cardiac events after heart transplantation were similar compared to control patients undergoing heart transplantation for other reasons. The first diagnosis of cardiac sarcoidosis at autopsy or after cardiac transplant is not unusual.⁴⁵⁹

Arrhythmogenic Cardiomyopathy

Arrhythmogenic cardiomyopathy (ACM) is a hereditary heart muscle disorder. It is marked by the substitution of the right ventricle (RV) myocardium—and occasionally the left ventricle (LV)—with fatty and fibrous tissue, extending from the epicardium to the endocardium. This condition is linked with ventricular arrhythmias (VA) and sudden cardiac death (SCD), predominantly affecting young individuals.⁴⁶⁰ The estimated prevalence of ACM exhibits geographical variability. Whereas the general population shows a prevalence of 1:5000, this rate can escalate to 1:1000 in certain European countries, including Italy and Germany.¹⁷¹ Given that SCD can be the initial manifestation, the prevalence of ACM is likely to be underestimated in many populations.⁴⁶¹ In areas of higher prevalence, ACM is the foremost cause of SCD among young athletes.^{460,461} The disease more commonly affects men, potentially due to hormonal differences, and it typically presents in the second to fourth decade of life. Moreover, the prognosis is notably poorer in male patients.¹

The disease was first described by Marcus et al.⁴⁶² in 1982, following the publication of electrophysiologic and clinical findings from a study of 24 patients with RV myocardial involvement and tachycardia originating from the RV. Initially, it was believed that the disease resulted from a congenital defect in the development of the RV myocardium, leading to the use of the term “dysplasia” (arrhythmogenic right ventricular dysplasia) to describe the condition.⁴⁶² In 1988, Thiene et al.²⁰ published a detailed case series describing young patients with arrhythmogenic RV cardiomyopathy who suffered SCD during exertion. Subsequent studies that demonstrated genetic defects in cardiac desmosomes led it to be classified as a cardiomyopathy, rather than a dysplasia, which is a congenital anomaly. Since 1994, the condition has been recognized as a cardiomyopathy in European-based publications and also by the American Heart Association.⁴⁶³

The clinical paradigm that originally led to the naming of the condition as “arrhythmogenic right ventricular cardiomyopathy,” focusing on RV involvement and malignant VAs, has since been recognized as not exclusively limited to the RV myocardium. The discovery of concealed or subclinical phenotypes, as well as types where biventricular or LV involvement is predominant, has expanded our understanding of the disease. Consequently, various terms such as “arrhythmogenic left ventricular cardiomyopathy (ALVC),” “left and/or right dominant cardiomyopathy,” “arrhythmogenic dilated cardiomyopathy,” and, most recently, “arrhythmogenic cardiomyopathy” have been adopted to describe this condition.^{1,463}

In initial diagnoses, the pathognomonic features of the disease were identified in the lower RV wall, apex, and RV infundibulum region, leading these three areas to be referred to as the “dysplasia triangle”.⁴⁶⁴ VAs originating from the RV, which exhibit a left bundle branch block morphology, are observed in patients with significant RV involvement. Therefore, during the echocardiographic (ECHO) evaluation of patients presenting with RV-originated premature beats (left bundle branch morphology) or other electrocardiography (ECG) indicators of ACM, increased vigilance is warranted.⁴⁶⁵

Characteristic ECG findings include T wave negativity in leads V1–V3 and an extended S wave (indicating terminal activation delay) in the right precordial leads.⁴⁶⁵ The epsilon wave, a more notable but less common ECG manifestation of ACM, represents electrical activity between the end of the QRS complex and the start of the T wave, reflecting the activity of myocardial islets persisting within fat and fibrous adipose tissue (Figure 85).⁴⁶⁶ In patients with prominent RV involvement,

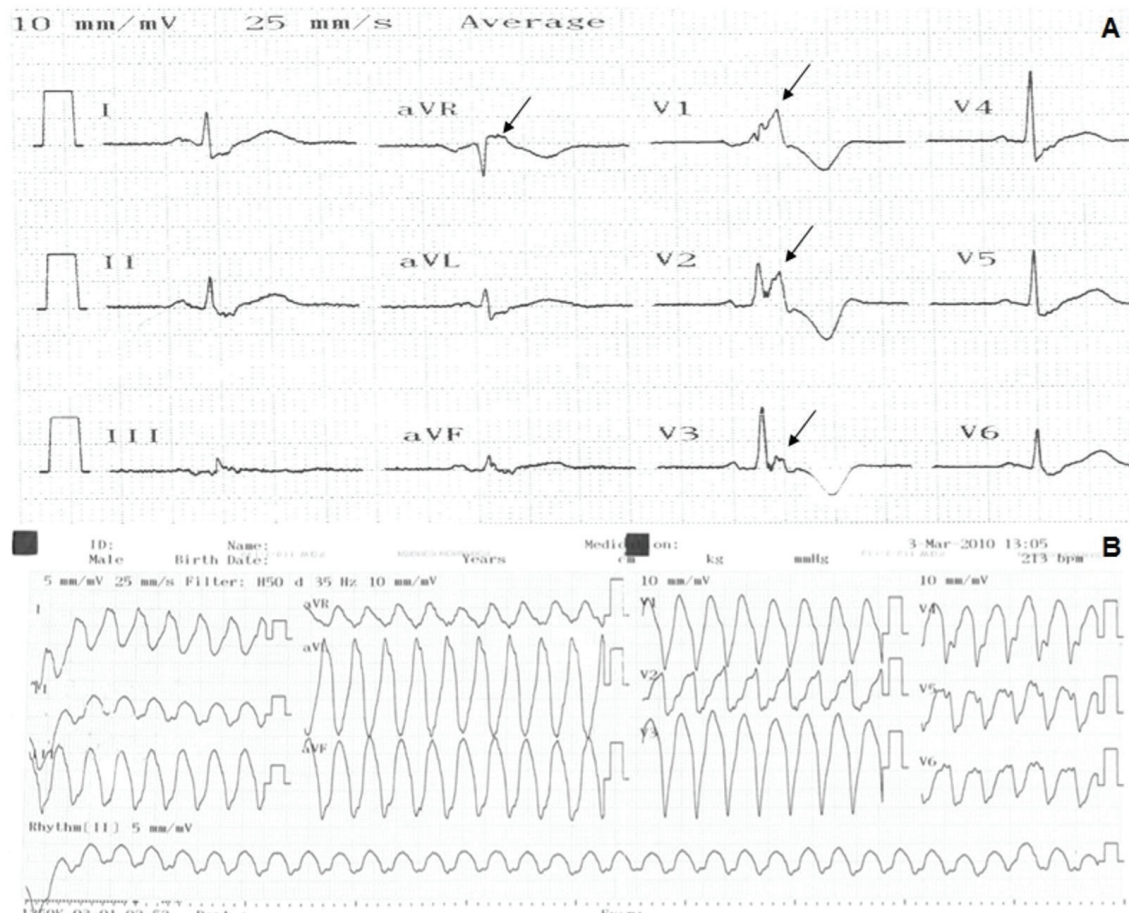


Figure 85. (A) Electrocardiogram of a patient with arrhythmogenic cardiomyopathy showing epsilon waves (arrows), V1-V3 T wave negativity and terminal S wave expansion. (B) ECG recording of the same patient when admitted with ventricular tachycardia.

the QRS complex is broader (by approximately >25ms) in the right precordial leads compared to the left precordial derivations. Conversely, in cases with dominant LV involvement, broadening is observed in the left and/or inferior derivations.⁴⁶⁶ ECG signs indicating LV involvement include low QRS voltage in limb leads, an important consideration during ECHO assessments.^{465,466} Accurately recognizing and documenting these ECG findings is crucial for the appropriate application and repetition of imaging modalities during follow-up.⁴⁶⁷

ACM may be considered to be one of the most challenging cardiomyopathies to diagnose among hereditary cardiomyopathies, owing to the absence of specific diagnostic criteria, variability in disease expression, and the highly variable penetrance observed among relatives.⁴⁶⁸ The primary challenge in diagnosing ACM lies in the fact that a definitive pathological diagnosis requires histologic sampling, which can only be obtained through biopsy, surgery, or autopsy. Indirect diagnostic criteria can be gathered using various cardiac imaging methods.^{467,468}

Pathophysiological Features

The distinctive histopathologic feature of ACM is the loss of RV myocardial cells, replaced by fat or a combination of fat and fibrous tissue. The presence of localized areas of inflammatory infiltration, predominantly composed of T lymphocytes,

alongside necrotic myocytes suggest an immune-mediated mechanism behind this pathological event. This fatty and fibrous scar tissue extends from the RV epicardium to the endocardium, leading to the thinning of the RV free wall and aneurysmatic dilatation.^{1,20,468} The involvement can be segmental, diffuse, or patchy. LV involvement, observed in more than half of the cases, typically affects the subepicardium or mid-myocardium and is often confined to the posterolateral region, although it may also exhibit a circumferential distribution.⁴⁶⁴ The septum is seldom involved; when it is, the right side of the septum is usually the affected area. The detection of fatty infiltration alone is insufficient for a definitive diagnosis, and its absence does not rule out ACM. The identification of displacement-type fibrosis and degenerative changes in myocytes is critical for diagnosis.⁴⁶⁹ Clusters of inflammatory cells with myocyte damage, frequently observed early in the disease and throughout its course, mimic myocarditis.⁴⁶⁴ The exact mechanisms by which mutant desmosomal proteins mechanically and/or functionally disrupt cellular junctions, leading to cardiomyocyte death and subsequent replacement by fibrous and adipose tissue, remain unclear.⁴⁶⁷ Moreover, abnormalities in cellular adhesion and intracellular signaling pathways, specifically Wnt and Hippo/YAP, have been linked to apoptosis, adipogenesis, and fibrogenesis. It is proposed that remodeling of cellular

Table 26. Recommended quantitative standard and advanced echocardiographic parameters (with relevant cut-off points) in patients with suspected or definite ACM

Parameter	Abnormal in the following cases:
PLAX RVOT (mm) ^a	≥ 29
Indexed PLAX RVOT (mm/m ²) ^a	≥ 16
PSAX RVOT (mm) ^a	≥ 32
Indexed PSAX RVOT (mm ²) ^a	≥ 18
RV basal diameter (mm)	> 41
RV fractional area change (%) ^a	≤ 40
TAPSE (mm)	< 17
Longitudinal strain of the RV free wall (%)	Lower than 23%
RV mechanical dispersion (standard deviation of time to peak spike) (ms)	> 25–30 ^b
3D ECHO RVEF (%)	≤ 40
LV global longitudinal strain (%)	Lower than 18%

^aMinor criteria of the 2010 task force, ^bThree-section model and six-section model.
3D, 3 dimensional; EF, Ejection fraction; LV, Left ventricular; RV, Right ventricular PLAX, Parasternal long axis; PSAX, Parasternal short axis; RVOT, Right ventricular outflow tract; TAPSE, Tricuspid annular plane systolic excursion.
Adapted from Haugaa KH, Basso C, Badano LP, et al.; EACVI Scientific Documents Committee, EACVI Board members and external reviewers; EACVI Scientific Documents Committee, EACVI Board members and external reviewers. Comprehensive multi-modality imaging approach in arrhythmogenic cardiomyopathy—an expert consensus document of the European Association of Cardiovascular Imaging. *Eur Heart J Cardiovasc Imaging*. 2017;18(3):237–253.

adhesion molecules and ion channels contributes to impaired mechanical and abnormal electrical coupling, increasing the susceptibility to arrhythmias.⁴⁷⁰

Features of Molecular Genetics

Desmosomes are symmetrical, complex, multiprotein structures that facilitate intercellular connections and communication. In patients with ACM, mutations in genes encoding desmosomes are most frequently observed. Pathogenic or potentially pathogenic variants are identified in up to 60% of patients diagnosed with ACM.⁴⁷¹ Desmoplakin gene mutations, for example, are associated with early LV involvement in patients with ACM, while some mutations in phospholamban (PLN) lead to alterations in intracellular calcium influx, thereby increasing the predisposition to arrhythmic events.^{471,472} Beyond genes encoding desmosomes, mutations in non-desmosomal genes have also been linked to ACM.

Clinical Presentation

In the initial stage of ACM, a patient may seek medical attention due to arrhythmia. ACM should be particularly suspected if VA are detected in the absence of significant ventricular dysfunction.⁴⁷³ The most common symptoms include palpitations, dizziness, and syncope. Patients may also report atypical chest pain that is not related to physical exertion and does not alleviate with rest. The exact cause of this chest pain remains uncertain; it may be due to inflammation in the arrhythmic or the 'hot stage' of the disease, although coronary artery disease may still need to be excluded in these patients.⁴⁶⁷ Symptoms such as dyspnea and pretibial edema are less common and, when present, are typically observed in the advanced stages of the disease or in cases with LV dominant or biventricular involvement.¹ One critical aspect of ACM is its progressive nature, meaning that symptoms can vary and intensify over time as the disease progresses.^{171,472}

Diagnosis

Diagnosing ACM involves synthesizing information from various diagnostic tests, as no single criterion is sufficiently definitive on its own. The primary components of the diagnostic work-up for ACM encompass ECG, Holter ECG monitoring, cardiac imaging, genetic testing, and, in certain situations, endomyocardial biopsy.

In 2010, a group of international researchers revised the criteria originally proposed by the 1994 Task Force.⁴⁷⁴ These revised criteria, known as the 2010 Task Force criteria, continue to be applied in diagnosing ACM with prominent RV involvement. The criteria were organized under histologic, electrocardiographic, arrhythmic, and genetic categories and further divided into major and minor subgroups. A diagnosis of "definite ACM" requires the presence of either two major criteria, one major and two minor criteria, or four minor criteria from different categories. "Borderline ACM" is diagnosed if one major and one minor criterion or three minor criteria are present. "Possible ACM" is considered if there is one major criterion or two minor criteria. Although the 2010 revisions increased diagnostic specificity, sensitivity remains low, particularly for detecting the early stages of the disease.¹ Additionally, because most of the diagnostic criteria were derived from studies comparing healthy individuals with those affected by the disease, specificity for differentiating ACM from other arrhythmogenic diseases affecting the right heart structures is also low.⁴⁶⁸

In 2017, the EACVI published a consensus document that established guidelines for the diagnostic application of various imaging techniques. This consensus set forth diagnostic parameters for tricuspid annular plane systolic excursion (TAPSE), RV basal diameter, and RV ejection fraction (EF), assessed through 'strain' imaging and three-dimensional (3D) ECHO. These parameters, utilized in everyday clinical practice, differ from the criteria outlined by the 2010 Task Force (Table 26). Video 5, Figure

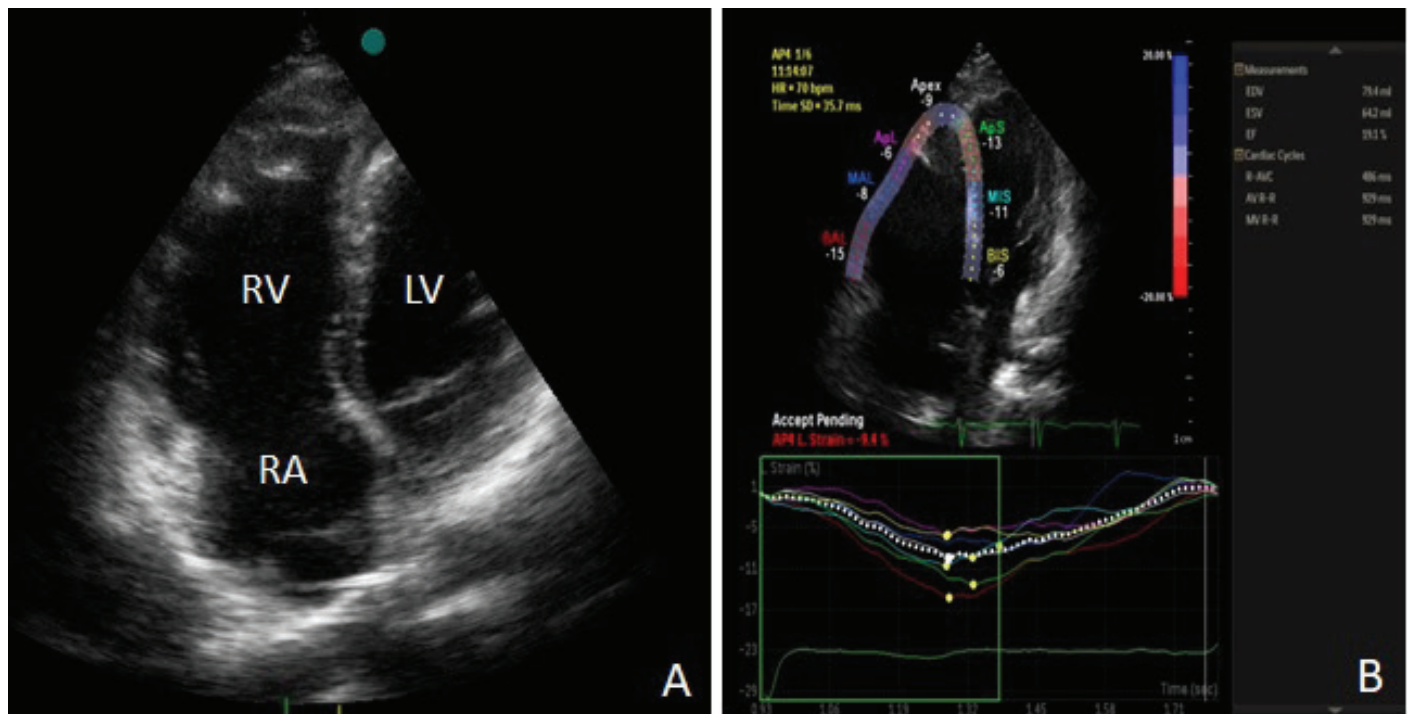


Figure 86. Figure 86 shows the echocardiography images of a patient with arrhythmogenic cardiomyopathy, both the 2-dimensional transthoracic (A) and strain (B) echocardiography images reveal an enlarged right ventricle, diminished systolic function and strain values, and increased mechanical dispersion between the different segments of the walls of the right ventricle.

LV, Left ventricle; RA, Right atrium; RV, Right ventricle

86A and 86B show RV systolic dysfunction, RV dilatation and reduced RV free wall strain value in a patient with ACM.

In 2020, the introduction of the "Padua criteria" marked a significant update to include LV involvement in the diagnosis of ACM, expanding the diagnostic framework beyond the primarily RV focus of previous criteria. Published as an international expert consensus, the Padua criteria have yet to be validated through studies conducted across large populations.¹ This consensus delineates the disease into three phenotypes: (1) the "dominant-right" variant, representing the classic ACM phenotype with predominant RV involvement and no LV involvement; (2) the "biventricular variant," where both the RV and LV are affected; and (3) the "dominant-left" variant, also known as ALVC, characterized by LV involvement without RV involvement.⁴⁷⁵ The Padua criteria not only define the different phenotypic variants of ACM but also establish diagnostic guidelines for ALVC.⁴⁷⁵

Furthermore, the consensus introduces six categories for diagnostic criteria: morpho-functional ventricular abnormalities, structural ventricular abnormalities, ECG depolarization changes, repolarization changes, VAs, and familial/genetic factors. A novel aspect of the 2020 Padua criteria is the inclusion of CMR findings for tissue characterization. The identification of both ventricles' myocardium replaced with fatty-fibrous tissue through gadolinium-enhanced MRI shows high agreement with endomyocardial biopsy (EMB) results. Moreover, the distribution pattern of gadolinium enhancement in the RV, LV, or both ventricles aids in identifying the different phenotypic variants of ACM.⁴⁷⁶

The Padua criteria emphasize that diagnostic tests should be evaluated based on their specific norms, taking body surface area (BSA) into consideration, to determine whether a finding is abnormal (Table 27). This approach is akin to the framework established by the 2010 Task Force criteria, wherein the Padua diagnostic criteria are categorized into "major" and "minor" classifications. The diagnosis of ACM is then classified as possible, borderline, or definite, depending on the number of criteria fulfilled. However, a distinctive aspect of the Padua criteria is the requirement that at least one morpho-functional or structural criterion, whether major or minor, must be met to diagnose ACM (Table 26). It is also crucial to note that only one major or minor criterion from each category can be considered in the diagnostic assessment. Video 6 and Figure 87 show a patient with an enlarged RVOT and RV hypokinesia that met the echocardiographic criteria recommended by the 2010 task force criteria.

Echocardiography in Diagnosis

Transthoracic echocardiography (TTE) stands as the preferred imaging method for the diagnosis and monitoring of ACM. However, its evaluation should be conducted by specialists proficient in this area. The echocardiographic examination for ACM demands a more comprehensive approach than the standard routine assessment.⁴⁶⁷ Diagnosing ACM can be challenging due to the anatomical position of the RVOT beneath the sternum, which restricts the acoustic window for imaging proximal structures. Additionally, the intricate shape of the RV complicates the segmental evaluation.⁴⁷⁷ While assessing RV function quantitatively is difficult owing to the RV's complex

Table 27. "Padua criteria"

RV Involvement Criteria	LV Involvement Criteria
I. Morpho-functional Ventricular Abnormalities	
By 2D ECHO, CMR or angiography:	By 2D ECHO, CMR or angiography:
Major - Regional RV akinesia, dyskinesia or bulging plus one of the following: - global RV dilatation (increase of RVEDV according to the imaging test specific nomograms for age, sex and BSA) - or - global RV systolic dysfunction (reduction of RVEF according to the imaging test specific nomograms for age and sex)	Minor Global LV systolic dysfunction (depression of LV EF or reduction of echocardiographic global longitudinal strain), with or without LV dilatation (increase in LVEDV according to the imaging test specific nomograms for age, sex, and BSA)
Minor Regional RV akinesia, dyskinesia or aneurysm of RV free wall	Minor Regional LV hypokinesia or akinesia of the LV free wall, septum or both
II. Structural Myocardial Abnormalities	
According to the CMR imaging:	According to the CMR:
Major Transmural LGE (stria pattern) of ≥ 1 RV region(s) (inlet, outlet, and apex in 2 orthogonal views)	Major LV LGE involvement of ≥ 1 bull's Eye segment (2 orthogonal views) of the free wall or septum or both (subepicardial or midmyocardial) (excluding septal junctional LGE)
According to EMB (limited indications):	
Major Myocardial replacement by fibrous tissue with or without fatty tissue in ≥ 1 sample	
III. ECG Repolarization Abnormalities	
Major Inverted T waves in right precordial leads (V1, V2 and V3) or beyond in individuals with complete pubertal development (in the absence of complete RBBB)	Minor Inverted T waves in left precordial leads (V_4-V_6) without complete LBBB
Minor - Inverted T waves in leads V1 and V2 in individuals with completed pubertal development (in the absence of complete RBBB) - Inverted T waves in V1, V2, V3 and V4 in individuals with completed pubertal development in the presence of complete RBBB.	
IV. ECG depolarization abnormalities	
Minor - Epsilon wave (reproducible low amplitude signals between end of QRS complex to onset of the T wave) in the right precordial leads (V1 to V3) - Terminal activation duration of QRS ≥ 55 ms measured from the nadir of the S wave to the end of the QRS, including R', in V1, V2 or V3 (in the absence of complete RBBB)	Minor Low QRS voltages (<0.5 mV peak to peak) in limb leads (in the absence of obesity, emphysema or pericardial effusion)
V. Ventricular arrhythmias	
Major Frequent ventricular extrasystoles (>500 per 24 h) or non-sustained or sustained ventricular tachycardia of LBBB morphology	Minor Frequent ventricular extrasystoles (>500 per 24 h) or non-sustained or sustained ventricular tachycardia with a RBBB morphology (excluding the "fascicular pattern")
Minor Frequent ventricular extrasystoles (>500 per 24 h) or non-sustained or sustained ventricular tachycardia of LBBB morphology with inferior axis ("RVOT pattern")	

Table 27. "Padua criteria" (continued)

RV Involvement Criteria	LV Involvement Criteria
VI. Family history/genetics	
Major	
• ACM confirmed in a first-degree relative who meets diagnostic criteria • ACM confirmed pathologically at autopsy or surgery in a first-degree relative • Identification of a pathogenic or likely pathogenetic ACM mutation in the patient under evaluation	
Minor	
• History of ACM in a first-degree relative in whom it is not possible or practical to determine whether the family member meets diagnostic criteria • Premature sudden death (<35 years of age) due to suspected ACM in a first-degree relative • ACM confirmed pathologically or by diagnostic criteria in second-degree relative	

ACM, Arrhythmogenic cardiomyopathy; ALVC, Arrhythmogenic left ventricular cardiomyopathy; BSA, Body surface area; CMR, Cardiac magnetic resonance; EDV, End diastolic volume; EF, Ejection fraction; EMB, Endomyocardial biopsy; LBBB, Left bundle-branch block; LGE, Late gadolinium enhancement; LV, Left ventricular; RBBB, Right bundle-branch block; RVOT, Right ventricular outflow tract.

Adapted from Corrado D, Perazzolo Marra M, et al. Diagnosis of arrhythmogenic cardiomyopathy: The Padua criteria. *Int J Cardiol.* 2020;319:106–114. and Mattesi G, Cipriani A, Bauce B, Rigato I, Zorzi A, Corrado D. Arrhythmogenic Left Ventricular Cardiomyopathy: Genotype-Phenotype Correlations and New Diagnostic Criteria. *J Clin Med.* 2021;10(10):2212.

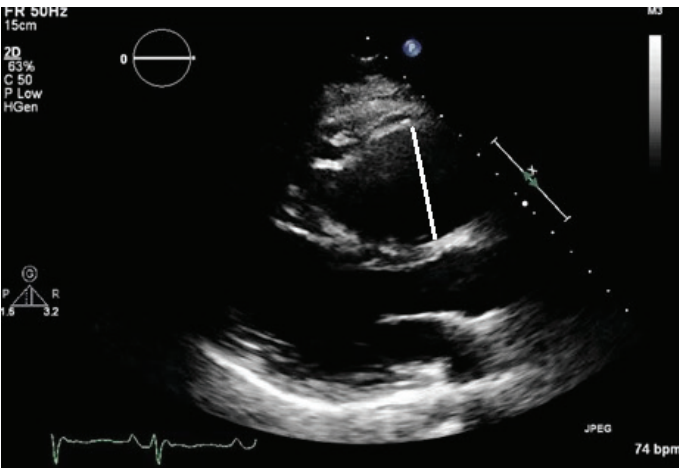


Figure 87. Both hypokinesia and enlargement of the right ventricular outflow tract in a patient with arrhythmogenic cardiomyopathy.

anatomy and its heightened sensitivity to increased load, the hallmark morphological characteristics of ACM include regional wall motion abnormalities of the RV, global RV dysfunction, or RV dilatation.⁴⁶⁷

The 2010 Task Force guideline identified specific criteria for the diagnosis of ACM through cardiac imaging using two-dimensional (2D) ECHO. Major criteria include the presence of RV regional akinesia, dyskinesia, or aneurysm, along with a RVOT diameter of ≥ 32 mm (≥ 19 mm/m²) in the parasternal long axis, a RVOT diameter of ≥ 36 mm (≥ 21 mm/m²) in the parasternal short axis, or an RV fractional area change of $\leq 33\%$. These parameters regarding RVOT diameters or RV fractional area

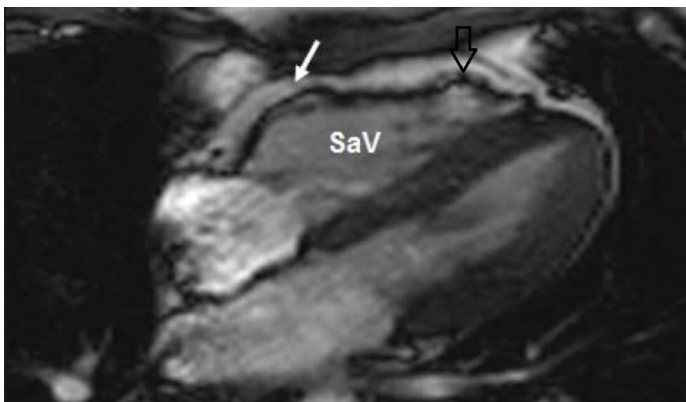


Figure 88. The right ventricular basal dyskinesia (white arrow) and apical aneurysm (black arrow) on a 4-chamber cardiac magnetic resonance image of a patient with a definite diagnosis of ACM.

change are diagnostic only when accompanied by RV akinesia, dyskinesia, or aneurysm. A RVOT diameter of ≥ 29 mm but < 32 mm (between ≥ 16 mm/m² and < 19 mm/m²) in the parasternal long axis, and ≥ 32 mm but < 36 mm (between ≥ 18 mm/m² and < 21 mm/m²) in the parasternal short axis, or an RV fractional area change of $> 33\%$ but $\leq 40\%$ are considered as minor criteria if accompanied by a regional RV motion abnormality. The inclusion of RVOT width as a criterion is based on its frequent and initial involvement in ACM, although a criterion for the basal diameter of the RV itself was not included in the consensus.⁴⁶³

Genotype/phenotype studies highlighting the frequent observation of LV involvement in ACM—initially characterized as an isolated or dominant RV disease—and the dominance of

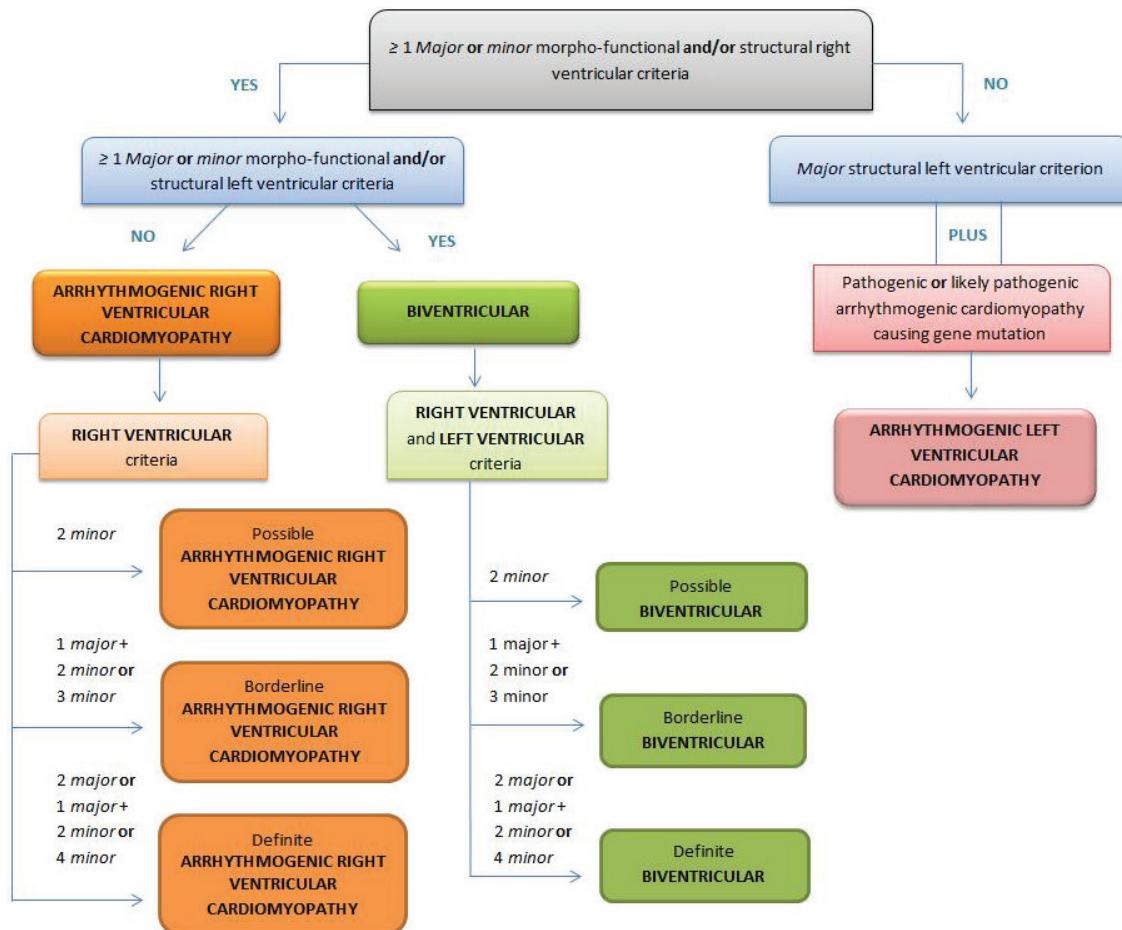


Figure 89. Diagnostic flowchart for arrhythmogenic cardiomyopathy phenotypic variants.

According to the 2020 International criteria (Padua criteria), at least one major or minor criterion from category I (i.e. morpho-functional abnormalities) or II (i.e. structural abnormalities) must be met for the diagnosis of arrhythmogenic cardiomyopathy. For the diagnosis of possible, borderline, or definite biventricular arrhythmogenic cardiomyopathy, in addition to ≥1 morpho-functional and/or structural criterion of both the right and left ventricles, the remaining criteria may be for either right or left ventricular involvement.

LV involvement in some mutation carriers at early stages were pointed out as deficiencies in the 2010 Task Force criteria.⁴⁶⁸ These criteria, which still remain in use, has also faced criticism for their focus on RV systolic dysfunction, leading to low sensitivity in detecting the early stage of the disease.

The 2020 Padua criteria introduced several notable updates differing significantly from the 2010 Task Force criteria, especially in the evaluation of morpho-functional alterations and LV involvement in ACM. A key addition to the Padua criteria is the inclusion of isolated regional wall motion abnormality without global dilatation or dysfunction in the RV as a minor criterion within the morpho-functional alterations section. This update was proposed after observing a significant number of patients exhibiting regional RV fibro-fatty tissue changes without an increase in RV volume or a decrease in systolic function. The diagnostic specificity of regional RV dyskinesia or akinesia is considered high.⁴⁷⁸

Distinct from the 2010 Task Force, the Padua criteria also meticulously define findings related to LV involvement. The

presence of global LV systolic dysfunction, with or without LV dilatation, has been added as a minor criterion. The indicators for LV systolic dysfunction include a decrease in left ventricular ejection fraction (LVEF) or a reduction in global longitudinal strain, as determined by strain ECHO. In various studies, LV systolic dysfunction has been characterized as LVEF <55% by ECHO, <57% by MRI in non-athletes, and <58% in athletes.⁴⁷⁹⁻⁴⁸¹ Regarding LV dilatation, the use of limits specific to the imaging method being utilized is recommended, rather than applying a uniform approach across different modalities. Additionally, regional LV hypokinesia or akinesia of the LV free wall, septum, or both was incorporated as a separate minor criterion (Table 27 and Figure 88) by the Padua criteria, further refining the diagnostic process for ACM.

Cardiac Magnetic Resonance Imaging in Diagnosis

Cardiac magnetic resonance imaging is recognized as more diagnostically effective than ECHO due to its superior accuracy in identifying myocardial tissue. MRI surpasses ECHO in visualizing the RV and in differentiating between fibrosis and fibro-fatty

infiltration. The 2010 Task Force highlighted major MRI criteria for the diagnosis of ACM, including findings of regional RV akinesia, dyskinesia, or dyssynchrony in RV contraction, along with an RV end-diastolic volume/BSA ratio of ≥ 110 mL/m² in men and ≥ 100 mL/m² in women, or a right ventricular ejection fraction (RVEF) of $\leq 40\%$.⁴⁷⁴ Additionally, RV regional wall motion abnormalities accompanied by an RV end-diastolic volume/BSA ratio of ≥ 100 mL/m² but <110 mL/m² in men and ≥ 90 mL/m² but <100 mL/m² in women, or an RVEF of $>40\%$ but $\leq 45\%$, were classified as minor criteria in CMR.⁴⁷⁴

One of the criticized issues of 2010 Task Force criteria was the specificity of the normal reference values for RV end-diastolic volume–100 mL/m² for men and 90 mL/m² for women. These values overlap with the physiological adaptations seen in athletes' hearts, where both RV and LV dilatation is common, particularly where physiological adaptive changes are pronounced, aligning with the pathologically determined numbers in the 2010 Task Force criteria.⁴⁷⁹ Therefore, an ACM diagnosis should be considered with caution in athletes, especially when there is an increase in RV volume beyond the appropriate reference values established in prior studies.^{480,481} This consideration is particularly crucial in sports like rowing, where an increase in RV volume is more significant, to avoid misdiagnosis of ACM in professional athletes.

In 2010, the Task Force defined the criterion for EMB to identify fat and fibrous replacement in the myocardium but did not incorporate non-invasive fat and fibrous tissue characterization by MRI into the diagnostic criteria. This omission was due to limited experience with this method at the time and concerns about its reliability as a diagnostic tool.⁴⁷⁹ However, the 2020 Padua criteria introduced significant updates, including the identification of regional dyskinesia, akinesia, or aneurysms in the RV by MRI or ECHO as a minor morpho-functional criterion. The classification of this criterion as minor rather than major for MRI aims to prevent potential misinterpretations that could lead to an exaggerated diagnosis of the disease.

Furthermore, the 2020 Padua criteria specified the detection of transmural gadolinium involvement/fibrosis affecting ≥ 1 RV region on two orthogonal images (with or without replacement by fatty tissue) as a major structural criterion for myocardial tissue characterization by MRI. Despite potential challenges in sensitivity due to the thin RV wall's low spectral resolution and suboptimal contrast-to-noise ratio, this finding is highly specific.⁴⁸²

Figure 88 shows basal dyskinesia and apical aneurysm on cardiac MR of a patient with a definite diagnosis of ACM. Videos 7, 8 and 5 exhibit four-chamber (Video 7) and short axis CMR images (Videos 8 and 9) of a patient with ACM presenting dyskinesia, marked dilatation, systolic dysfunction of RV and aneurysmatic pouches in the RV myocardium..

Nuclear Medicine in Diagnosis

The measurement of 18F-fluorodeoxyglucose (FDG) uptake using positron emission tomography (PET) can be instrumental in diagnosing cardiac conditions, particularly with focal or diffuse-on-focal FDG uptake patterns, which are indicative of cardiac sarcoidosis.⁴⁸³ However, it has been observed that patients with ACM may also exhibit 18F-FDG-PET myocardial

involvement.⁴⁸⁴ Consequently, the utility of radionuclide imaging in ACM is generally considered limited unless accompanied by abnormal 18F-FDG-PET uptake in extracardiac tissues or the presence of other clinical indicators suggestive of cardiac sarcoidosis.¹

The Role of Imaging in the Early Phase of Arrhythmogenic Cardiomyopathy

ACM can undergo a silent period characterized by minimal or no disease signs before the condition becomes evident. However, life-threatening VA tend to emerge only following myocardial structural changes, with the presence of such abnormalities significantly increasing the risk of VA. Detecting ACM during its early stages via echocardiography proves challenging, as this phase is typically marked by only mild RV hypokinesia and dilatation. In these instances, cardiac MRI, strain echocardiography, and possibly three-dimensional (3D) ECHO can provide additional insights, though data from the latter two techniques remain limited or incomplete. Early echocardiographic indicators of ACM may include reduced RV strain, an increased RV basal diameter, and significant RV mechanical dispersion (Table 26).^{485,486}

CMR stands as the preferred imaging modality for the early diagnosis of ACM, thanks to its ability to evaluate both the function and tissue characterization of the ventricles. Late gadolinium enhancement (LGE) plays a key role in assessing myocardial fibrous-fatty tissue displacement, aiding in the diagnosis of ACM. However, it's important to note that gadolinium enhancement is not specific to ACM and may also be observed in other cardiomyopathies (Table 28).⁴⁸⁷

Differential Diagnosis

A correct diagnosis of ACM is more likely when considering a patient's family history, occurrences of syncope or arrhythmias, and sports history. However, pronounced RV dilatation and motion abnormalities identified through visual evaluation, accompanied by a normal ECG, are uncommon in ACM. Consequently, genetic testing for ACM is rarely indicated in these instances.^{1,467} It is advisable to prioritize other differential diagnoses for such patients initially. Nonetheless, genetic testing is recommended if there are ECG abnormalities or other indicators that might suggest ACM, particularly in patients where RV dysfunction is incidentally identified through imaging.⁴⁶⁷

Although ECG findings may suggest RV involvement, diagnosing ACM can be challenging due to the similarity of these findings with those of myocarditis, sarcoidosis, or Uhl's disease.^{30,488,489} A systematic approach is essential for investigating phenocopies in patients suspected of having ACM. The differential diagnosis for such patients should include myocarditis, sarcoidosis, RV infarction, dilated cardiomyopathy, Chagas disease, pericardial agenesis, pulmonary hypertension, and congenital heart diseases associated with volume overload (e.g., Ebstein anomaly, atrial septal defect, and pulmonary venous return anomaly).^{1,467,490} Idiopathic RV outflow tract ventricular arrhythmias (RVOT VA) should also be considered. The idiopathic nature of VA, absence of family history, normal baseline 12-lead ECG, and normal ventricular structure as confirmed by cardiac imaging and electroanatomic mapping,

Table 28. Advantages and limitations of imaging techniques for diagnosing ACM			
	ECHO	CMR	CT
Advantages	Easily applicable	Evaluation of structure and function	Advantageous if there are inadequate echocardiographic images and contraindications for CMR
	New techniques (strain)	Evaluation of myocardial fibrous–fatty tissue displacement	
Limitations	Need for special expertise	Need for special expertise	Radiation
	The complex anatomy of the RV	Frequent ectopic beats impede acquisition	Limited
	Load dependency of the RV	The complex anatomy of the RV	Documentation
	Difficult quantitative evaluation	Load dependence of the RV	RV’s complex anatomy
	Limited value in the early stage	Limited availability	Load dependency of the RV
	Risk of underdiagnosis	Difficult in early stages	
		Risk of overdiagnosis	

CMR, Cardiac magnetic resonance; CT, Computed tomography; ECHO, Echocardiography; RV, Right ventricle.
Adapted from Haugaa KH, Basso C, Badano LP, et al.; EACVI Scientific Documents Committee, EACVI Board members and external reviewers; EACVI Scientific Documents Committee, EACVI Board members and external reviewers. Comprehensive multi-modality imaging approach in arrhythmogenic cardiomyopathy—an expert consensus document of the European Association of Cardiovascular Imaging. *Eur Heart J Cardiovasc Imaging*. 2017;18(3):237–253.

alongside a single VA morphology, are critical factors for differentiation from ACM.¹

In highly trained athletes, the physiological adaptations resulting from intensive training should be considered in the differential diagnosis.⁴⁸¹ RV enlargement, ECG abnormalities, and arrhythmias in athletes often reflect the increased hemodynamic load associated with rigorous exercise routines. However, global RV systolic dysfunction and/or dyskinesia, along with the presence of an aneurysm, are findings that are more indicative of ACM rather than mere athletic adaptations.¹

C-reactive protein, liver function tests, N-terminal pro b-type natriuretic peptide (NT-proBNP) or BNP, renal function tests, and serum troponin levels are recommended laboratory tests for each patient with a preliminary diagnosis of ACM.¹ Additionally, chest pain, dynamic ST-T wave changes on baseline 12-lead ECG, and troponin elevation, despite normal coronary arteries, are frequently observed and necessitate a differential diagnosis with myocarditis or acute myocardial infarction.¹ In 2020, Bariani et al.⁴⁶⁷ introduced the concept of the “hot phase” of ACM.⁴⁹¹ This phase is predominantly observed in children and young adults. The pathogenic mechanism underlying this acute phase, characterized by chest pain, the release of myocardial necrosis enzymes, and the presence of ECG changes in patients with ACM, remains unclear. However, it is speculated that an inflammatory process may trigger tissue necrosis and subsequent replacement with fibrous–fatty tissue. In such clinical scenarios, which resemble myocarditis, a family history of ACM should be investigated, and genetic testing should be considered for differential diagnosis.^{467,491}

The 2023 European Society of Cardiology Cardiomyopathy Guideline indicates that EMB can be utilized as needed to exclude myocarditis and sarcoidosis, particularly in cases involving patients with sporadic forms of ACM.¹ EMB is deemed beneficial for selected patients where non-invasive assessments prove insufficient.¹ Furthermore, in cases where MRI findings are ambiguous, electroanatomic voltage mapping-guided EMB may be considered for more precise diagnostic clarification.¹

Regional wall motion defects are commonly observed in congenital right/left ventricular aneurysms, but enlargement of the RV or LV is typically not present. While subepi/mid-myocardial gadolinium enhancement in other regions of the myocardium is detected with CMR in ACM, such an enhancement is not expected in congenital aneurysms of the ventricles. While apical thinning or wall motion abnormality is observed in the apical part of the RV/LV in congenital aneurysms, presence of myocardial hypokinesia or dyskinesia is not expected in other regions. Although myocardial involvement can manifest at multiple locations in cardiac sarcoidosis, the RV free wall is more commonly affected. Although the RV free wall may also be involved in ACM, the subtricuspid region and RVOT are more frequently affected in ACM than in sarcoidosis. While the inferolateral, inferior wall, or septal junction point may be involved as a part of LV involvement in ACM, the basal segments of the LV, particularly the free wall of the septum, are more frequently involved in in sarcoidosis.

Left Ventricular or Biventricular Involvement in Arrhythmogenic Cardiomyopathy

The biventricular or left dominant variants of ACM present with findings that diverge from the classical RV dominant ACM. The pathological changes in these variants extend beyond the RV, affecting the LV either simultaneously or, in some instances, predominantly.⁴⁹² An autopsy study highlighted that LV involvement was prevalent among patients who suffered SCD related to ACM, with it being the sole pathological finding in nearly one-fifth of the cases examined. This underscores the critical importance of identifying LV involvement in ACM, given its significant implications for diagnosis, management, and prognosis.⁴⁹³

The phenotypic features of ALVC are characterized by several distinctive signs and imaging findings. These include:

- (I) T wave negativity in the inferolateral leads on an ECG, specifically leads II, III, aVF, and/or V4-V6.
- (II) Low QRS voltages, less than 0.5 mV, in the extremity leads.
- (III) VAs exhibiting right bundle branch block (RBBB) morphology, which indicates an origin in the LV.

- (IV) Morpho-functional imaging features that demonstrate a "hypokinetic, non-dilated, and fibrotic LV." This is characterized by mild systolic dysfunction, no or mild dilatation, and a significant presence of subepicardial/mid-myocardial LGE, indicative of non-ischemic fibrosis.^{170,465,492,494,495}

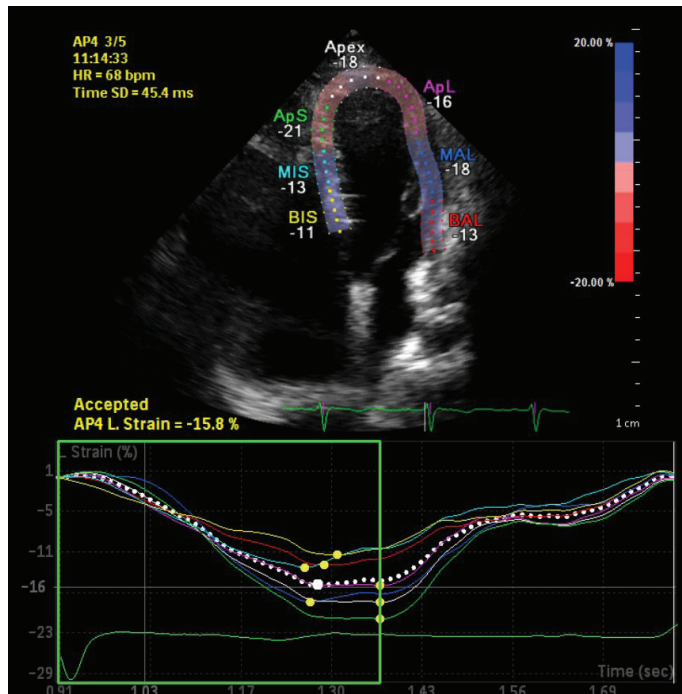


Figure 90. The apical-four chamber strain echocardiographic image of a patient indicating a left ventricular involvement in a patient with ACM.

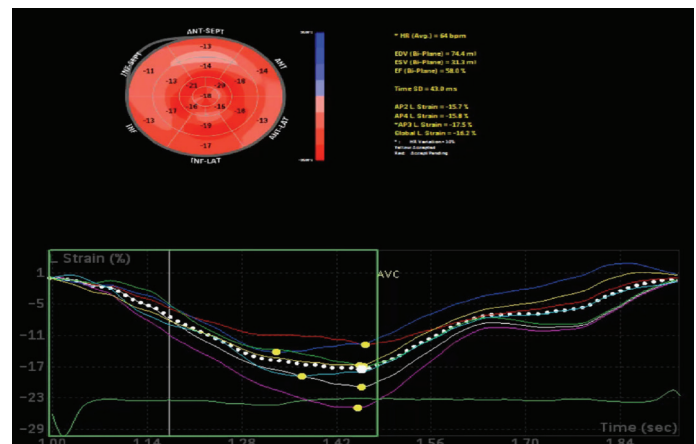


Figure 91. The 'bull-eye' view of the left ventricle of the same patient obtained by strain echocardiography.

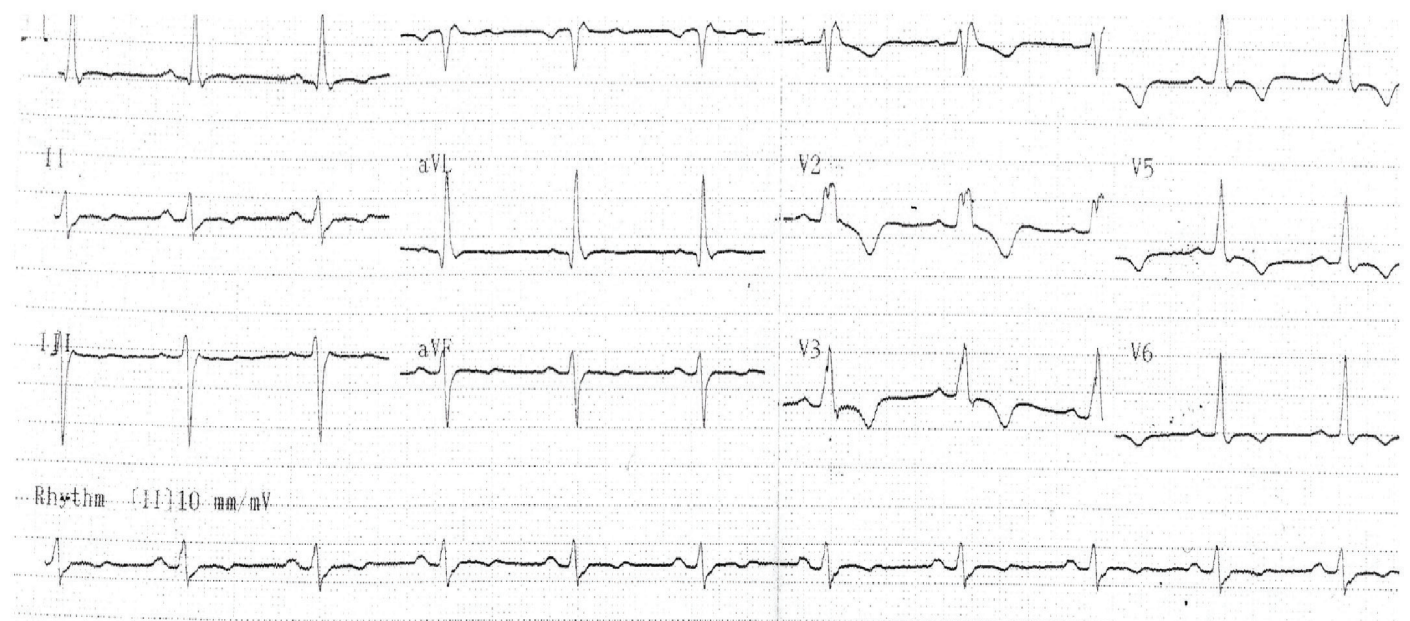


Figure 92. ECG recording of the same patient shows T wave negativity including inferior and lateral leads indicating a left ventricular involvement.

Table 29. Recommended imaging methods and follow-up intervals in patients with a definitive diagnosis of ACM and the family members (first-degree relatives of mutation-positive or mutation-free families) of the patient

ECHO		CMR
ACM patients with ICD	When indicated	Not indicated but also not contraindicated ^a
ACM patients without ICD	Annually or when clinically indicated ^b	First visit. Repeated every 3–5 years or when there is a change in clinical condition and/or ECG In patients where ECHO examination is difficult
Family members aged about 10 years with borderline symptoms	Annually for subjects under 40 years of age or when indicated ^b	First visit Repeated every 1–2 years for subjects <40 years of age or when clinically indicated ^b
	Repeated every 2 years in subjects > 40 years of age or when clinically indicated ^b	Repeated every 3–5 years in subjects > 40 years of age or when clinically indicated ^b
Approximately 10-year-old family members with no morphologic findings	Then repeated every 1–2 years in subjects <40 years of age or when clinically indicated ^b	First visit Then repeated every 1–2 years in subjects <40 years of age or when clinically indicated ^b
	Every 3–5 years in subjects > 40 years of age or when clinically indicated ^b	Repeated every 3–5 years in subjects >40 years of age or when clinically indicated ^b

^aIn patients with CMR compatible devices, ^bClinical or ECG changes suggestive of the disease progression
ACM, Arrhythmogenic cardiomyopathy; CMR, Cardiac magnetic resonance; ICD, Implantable cardioverter defibrillator.
Adapted from Haugaa KH, Basso C, Badano LP, et al.; EACVI Scientific Documents Committee, EACVI Board members and external reviewers; EACVI Scientific Documents Committee, EACVI Board members and external reviewers. Comprehensive multi-modality imaging approach in arrhythmogenic cardiomyopathy—an expert consensus document of the European Association of Cardiovascular Imaging. *Eur Heart J Cardiovasc Imaging*. 2017;18(3):237–253.

Signs such as LV fatty infiltration, LV wall motion abnormalities, and LV dilatation can also be observed.⁴⁸² While LV systolic function may not be drastically impaired, recognizing ACM with LV involvement is crucial due to its implications for patient management, including the potential need for implantable cardioverter defibrillator (ICD) implantation to mitigate the risk of arrhythmic events.^{1,482}

LGE-MRI has a high diagnostic sensitivity because it allows identification of non-transmural LV scars. These scars may not be detected by TTE because they separate the subendocardial layers and thicken the myocardial layer.^{465,495}

The Role of Imaging Methods in Risk Stratification

Imaging methods play a crucial role in the risk stratification of patients with ACM, particularly in identifying those at increased risk for VA. Significantly reduced RV function and the presence of LV involvement emerge as key indicators for the development of VA.⁴⁹⁷ The assessment of LV involvement is especially critical given its association with VA. Research has linked RV dilatation, decreased tricuspid annular plane systolic excursion (TAPSE), decreased fractional area change, right atrial dilatation, and tricuspid regurgitation with SCD.⁴⁶⁷

The 2023 European Society of Cardiology cardiomyopathy guideline advocates for the utilization of validated and reliable risk scores to assess the arrhythmic risk in patients with ACM.¹ It recommends using the risk assessment tool available at 'www.arvcrisk.com,' which has been externally validated.^{1,498} This risk calculator includes variables such as age, gender (with male gender posing a higher risk), occurrence of syncope in the last 6 months, the number of leads with negative T waves, the number of ventricular premature beats in 24 hours, history of non-

sustained VA, and RVEF as measured by CMR imaging. Notably, this calculator does not incorporate variables related to LV involvement,⁴⁹⁸ highlighting an area for potential enhancement in risk stratification methodologies.

The 2023 European Society of Cardiology guideline offers specific recommendations for the implantation of an ICD for primary prevention in patients at high risk for ACM, irrespective of the results from the ACM risk calculator. These recommendations include patients who experience arrhythmic syncope, non-sustained VA, have a RVEF less than 40%, a LVEF less than 45%, and those with sustained monomorphic VA triggered by programmed electrical stimulation.¹ This guideline underscores the importance of proactive measures in preventing sudden cardiac death in ACM patients, highlighting the need for individualized patient assessment beyond risk calculator outputs.

Moreover, a study has raised concerns about the performance of the ACM risk calculator, specifically its efficacy in patients who receive negative results from genetic testing.⁴⁹⁹ This suggests that while the risk calculator is a valuable tool in stratifying risk, reliance on a broader spectrum of clinical assessments, including genetic, imaging, and electrophysiological evaluations, is crucial for comprehensive risk management in ACM patients.

Usage of Imaging Methods for Patients' Monitoring

Given that ACM is a progressive disease, periodic repetition of cardiac imaging is crucial to monitor disease progression in ACM patients. Such follow-up is essential not only for tracking changes in cardiac structure and function but also for reassessing the risk of developing life-threatening VA (Table 29)⁴⁶⁷. This proactive approach enables timely adjustments in management

and therapeutic strategies, aiming to mitigate the risk of adverse outcomes associated with ACM.

It is advisable to repeat echocardiographic study when symptoms of heart failure manifest in patients who have undergone ICD implantation. While the evaluation of these patients with CMR is not obligatory, it is also not contraindicated, provided that an MR-compatible device was implanted. This approach ensures that the assessment of cardiac function and structure can be accurately updated, allowing for appropriate management adjustments in response to the evolving clinical scenario.

In patients with ACM who have not received an ICD, echocardiographic evaluation should be repeated if there are symptoms or ECG changes that suggest disease progression. For asymptomatic patients with no new ECG findings, an annual ECHO evaluation is deemed sufficient. MRI is recommended at the initial diagnosis or when ACM is suspected, and similar to ECHO, it should be repeated upon the development of symptoms or ECG changes indicative of disease progression. In cases where the patient remains asymptomatic with no ECG changes, CMR should be conducted every 3–5 years to monitor the disease status. Cardiac computed tomography may be considered for patients who have poor echogenicity and are not suitable candidates for CMR.⁴⁶⁷ This stratified approach ensures comprehensive monitoring and timely intervention, tailored to the patient's clinical status and risk profile.

Follow-up of Family Members with Imaging Methods

For family members over the age of 10 years displaying 'borderline' findings of ACM, an annual CMR evaluation is recommended until they reach 40 years of age, after which the frequency should be adjusted to every 2 years. An initial

CMR is also advised during their first evaluation. Should there be any changes in ECG or the development of symptoms, CMR should be promptly repeated. If asymptomatic, CMR should be conducted every 1–2 years until the age of 40. Beyond the age of 40, in the absence of symptoms or ECG changes, it is sufficient to repeat CMR every 3–5 years.⁴⁶⁷

Relatives without evidence of structural disease should commence follow-up from the age of 10, undergoing CMR every 1–2 years until the age of 40, with the frequency adjusting to every 3–5 years post-40 years of age. Provided there are no developments of symptoms or ECG findings, MRI should be carried out initially and then repeated every 1–2 years until the age of <40 years, transitioning to every 3–5 years after >40 years of age⁴⁶⁷ (Table 30). This structured approach aims to ensure early detection and management of ACM in individuals at risk, adjusting surveillance intensity based on age and clinical findings.

Video 5. Reduced right ventricular systolic function and dilatation of the right ventricle detected by 2D transthoracic echocardiography in a patient with arrhythmogenic cardiomyopathy.

Video 6. Parasternal long axis imaging in 2D transthoracic echocardiographic imaging of a patient with arrhythmogenic cardiomyopathy shows hypokinesia and marked dilatation of the right ventricular outflow tract.

Video 7. Cardiac MR 4-chamber image of a patient with arrhythmogenic cardiomyopathy showing dyskinesia and aneurysmatic pouches in the right ventricle, marked dilatation of the right ventricle and systolic dysfunction.

Video 8-9. Short axis cardiac MR images of the same patient show aneurysms and dilatation of the right ventricle.

Diagnosis and Management of Tachycardia / Arrhythmia-Induced Cardiomyopathies

Tachycardia/arrhythmia-induced cardiomyopathy constitutes a subset of rare cardiomyopathies and heart failure.⁵⁰⁰ With the escalating prevalence of heart failure, it becomes imperative for clinicians to acquaint themselves with treatable causal factors and address them clinically. Tachycardia-induced cardiomyopathy emerges as a frequently reversible cause of heart failure, stemming from both atrial and ventricular tachyarrhythmias, typically leading to left ventricular systolic dysfunction. The onset of cardiomyopathy may be swift following arrhythmia or may manifest with a delayed onset spanning months to years. Subsequent treatment of the accountable arrhythmia can partially or completely ameliorate left ventricular dysfunction.^{501,502} The extent of improvement is significantly contingent upon the type and duration of the arrhythmia.⁵⁰³ Therefore, accurate identification and management of tachycardia-induced cardiomyopathy are paramount.⁵⁰⁴ Additionally, it is important to note that arrhythmia could exacerbate heart failure in patients with tachycardia and left ventricular systolic dysfunction, irrespective of other underlying causes of heart failure.^{505,506}

Definition

Tachycardia-induced cardiomyopathy denotes a form of heart failure characterized by the enlargement and impaired systolic function of the left ventricle, stemming from supraventricular or ventricular tachyarrhythmias.⁵⁰⁰ The earliest documented instance of tachycardia-induced cardiomyopathy related heart failure dates back to 1913, observed in a young male patient presenting with atrial fibrillation accompanied by rapid ventricular response and subsequent heart failure.⁵⁰⁷ Subsequent case reports and research studies have clarified that sustained ventricular or supraventricular tachycardia can lead to biventricular enlargement and systolic dysfunction, which can be reversible with appropriate arrhythmia treatment.⁵⁰⁸ The term “arrhythmia-induced cardiomyopathy” refers to a clinical entity whose diagnosis is confirmed by therapeutic response, constituting an inclusive definition regardless of the origin of the arrhythmia. In other words, the diagnosis of arrhythmia-associated cardiomyopathy is confirmed by the observed improvement in ventricular systolic function following treatment aimed at the underlying arrhythmia. Due to its rarity, most of the literature on this subject is based on animal studies rather than human trials.⁵⁰⁰

The literature delineates two distinct types of arrhythmia-induced cardiomyopathies.⁵⁰⁴ In the first type, designated as arrhythmia-induced cardiomyopathy (type 1), the arrhythmia serves as the sole precipitating factor for the development of cardiomyopathy. Treatment of the arrhythmia leads to significant or complete improvement in left ventricular systolic dysfunction⁵⁰⁹ (Video 10,11). Conversely, in the second type, termed arrhythmia-mediated cardiomyopathy (type 2), an alternative underlying cause of heart failure coexists alongside the associated arrhythmia, whereby the arrhythmia significantly exacerbates impairment of ventricular contractility. Consequently, treatment aimed at addressing the arrhythmia results in only partial correction of systolic dysfunction, primarily impacting the left ventricle.⁵⁰³

Epidemiology

Traditionally, arrhythmias have been viewed as symptomatic manifestations of heart failure and various cardiomyopathies. However, recent evidence has indicated that arrhythmias may contribute to the etiology of non-ischemic cardiomyopathy.⁵¹⁰ Nevertheless, epidemiological data on arrhythmia-induced cardiomyopathy remain unclear, largely stemming from limited awareness and underestimation of its prevalence. Given its potential reversibility as a cause of dilated cardiomyopathy, clinicians should maintain suspicion for arrhythmia-induced cardiomyopathy when encountering cases of dilated cardiomyopathy with unclear origins. While heart failure commonly affects the elderly, arrhythmia-

associated cardiomyopathy exhibits a distinct pattern, affecting individuals across all age groups. It is characterized by ventricular enlargement and reduced left ventricular systolic function, irrespective of the underlying arrhythmogenic source. However, the specific type of arrhythmia responsible for cardiomyopathy varies among different age groups. In adults, atrial fibrillation stands out as the predominant cause of arrhythmia-induced cardiomyopathy.^{511,512} Conversely, within the pediatric population, focal atrial tachycardia emerges as the most frequently identified culprit arrhythmia.⁵⁰⁴

Pathophysiology

Animal studies, particularly in canine models, have unveiled that rapid atrial or ventricular stimulation triggers significant neurohumoral and hemodynamic responses, culminating in a clinical presentation akin to left ventricular systolic heart failure in humans.⁵¹³ These effects encompass increased pressures in both ventricles induced by tachycardia, notable systolic impairment, reduced cardiac output, and elevated systemic vascular resistance.⁵⁰⁶ Concurrently, an intensified neurohumoral response ensues, characterized by elevated levels of natriuretic peptides, concentrations of epinephrine and norepinephrine, and aldosterone levels subsequent to renin activation.⁵¹⁴ At the cellular level, there is a decrease in the utilization of calcium ions by myocytes. Morphologically, the cardiac chambers exhibit enlargement and thinning of the walls with a decline in ventricular systolic function.^{500,515}

The development of cardiomyopathy due to arrhythmia involves three primary mechanisms: tachyarrhythmia, dissynchrony, and irregular rhythm.⁵¹⁶ While the main contributor among these mechanisms remains unclear, it is widely accepted that all three can contribute to the onset of cardiomyopathy in most cases. Therefore, it's crucial to acknowledge that frequent premature beats or dissynchrony can lead to arrhythmia-associated cardiomyopathy even when the heart rate is adequately controlled. This comprehensive understanding highlights the inclusive definition of arrhythmia-induced cardiomyopathy, which encompasses all cardiomyopathies resulting from tachyarrhythmia, dissynchrony, and premature ventricular beats.

The principal event underlying the pathogenesis of arrhythmia-induced cardiomyopathy involves aberrations in calcium ion (Ca⁺⁺) utilization by myocardial cells secondary to arrhythmia.⁵¹⁷ Experimental animal models have outlined a progression of heart failure occurring in three distinct phases in response to the stimulus: the compensatory phase, the left ventricular dysfunction phase, and the left ventricular failure phase.⁵¹⁸

The compensatory phase, spanning approximately 7 days (3-7 days) from the onset of stimulation, is characterized by the activation of the sympathetic system, while left ventricular systolic function remains preserved. Simultaneously, changes in the extracellular space and neurohumoral responses remain relatively limited. The subsequent phase, the left ventricular dysfunction phase, ensues 1-3 weeks following the initiation of rapid atrial or ventricular stimulation. During this phase, there is escalating activation of neurohumoral and renin-angiotensin-aldosterone systems. Remodeling occurs both at the cellular level and within the intercellular extracellular matrix. Deficiencies in Ca⁺⁺ utilization manifest alongside reductions in myocardial energy storage and increased oxidative stress. Consequently, myocardial contractility is impaired, leading to the onset of left ventricular systolic dysfunction and dilatation.⁵¹⁹

Lastly, around 3-4 weeks after rapid stimulation, the left ventricular failure phase appears, marked by hemodynamic disturbances

showing systemic and pulmonary congestion due to worsening and significant left ventricular systolic dysfunction and enlargement.^{520,521}

Arrhythmia Type

Arrhythmia-induced cardiomyopathy encompasses a broad spectrum of arrhythmias, including various supraventricular and ventricular tachyarrhythmias. While supraventricular or ventricular tachyarrhythmias are commonly implicated, the pathogenesis of cardiomyopathy can also be attributed to rapid atrial or ventricular excitation, as well as early ectopic atrial or ventricular contractions.⁵⁰³ It's essential to acknowledge that in patients with arrhythmias, the continued presence of these arrhythmias, even if they are well tolerated, can increase the risk of developing cardiomyopathy. Therefore, maintaining vigilance in managing arrhythmias is crucial to reduce the risk of cardiomyopathy onset or progression.

Arrhythmia-induced cardiomyopathy can manifest at any stage of life, with documented cases even occurring during intrauterine development, leading to hydrops fetalis. There have been reports of cardiomyopathy arising from fetal supraventricular tachycardia, with documented improvement following cardioversion.⁵²² In pediatric populations, focal atrial tachycardia emerges as the most prevalent arrhythmia, followed by persistent junctional reciprocating tachycardia.⁵⁰⁴ Conversely, in adults, atrial fibrillation stands as the leading cause of arrhythmia-induced cardiomyopathy. Following atrial fibrillation, ventricular premature beats and non-sustained ventricular tachycardias constitute the most common arrhythmia types.⁵¹² While supraventricular arrhythmias have a higher incidence of inducing cardiomyopathy, ventricular tachycardias pose a greater risk of developing cardiomyopathy and have a more significant impact on left ventricular function in humans.

Arrhythmias with normal ventricular rates can induce cardiomyopathy. A frequently encountered culprit in clinical practice, especially among adults, is atrial fibrillation with rapid ventricular response. An essential consideration in such cases is determining the optimal target heart rate range.⁵²³ While the notion of ideal rate control may vary based on age and individual patient tolerance, as a general guideline, the target resting heart rate should fall within the range of 60-80 beats per minute. However, aberrant heart rate responses during exercise are frequently observed, especially in individuals with atrial fibrillation. Consequently, it is imperative to take into consideration patients' heart rates during physical activity, with the target heart rate during exercise typically set between 90-115 beats per minute.⁵²⁴ Patients surpassing these thresholds, particularly those with compromised left ventricular systolic function, should be considered tachycardic and require attention. Additionally, another mechanism emphasized in the pathophysiology of arrhythmia-induced cardiomyopathy is the occurrence of early atrial or ventricular ectopic beats. Importantly, most patients showing frequent ventricular ectopic beats alongside associated left ventricular systolic dysfunction experience near-complete recovery of left ventricular systolic function after successful ablation procedures.⁵⁰⁴

Clinical Presentation and Diagnosis

Reversible etiologies of cardiomyopathy encompass a range of conditions, including arrhythmia-induced cardiomyopathy, subacute valvular heart disease, myocardial dysfunction secondary to transient ischemia, uncontrolled hypertension, substance-induced cardiomyopathy (such as from drugs or alcohol), inflammatory cardiomyopathy, and postpartum cardiomyopathy.⁵²⁵

The primary symptoms associated with arrhythmia-induced cardiomyopathy typically include palpitations and reduced functional capacity. Syncope or presyncope may occur less frequently. Although sudden cardiac death is rare, occurring in 8–12% of cases, it remains a potential complication. However, it's important to recognize that tachycardia-induced cardiomyopathy, similar to other types of heart failure, can also present asymptotically.⁵²⁶

Clinicians should maintain a high level of suspicion for the diagnosis of arrhythmia-associated cardiomyopathy in patients who present with persistent or frequent paroxysmal arrhythmias and unclear etiology of cardiomyopathy. Even if an established arrhythmia diagnosis is lacking, patients with cardiomyopathy of unknown origin should undergo ambulatory rhythm monitoring for at least two weeks to facilitate the detection of underlying arrhythmias. Another significant mechanism implicated in the pathophysiology of arrhythmia-induced cardiomyopathy is the occurrence of premature atrial or ventricular ectopic beats. It's noteworthy that a considerable proportion of patients displaying frequent ventricular ectopic beats alongside associated left ventricular systolic dysfunction experience near-complete recovery of left ventricular systolic function following successful ablation procedures. Investigating arrhythmias in patients with cardiomyopathy of unknown origin is crucial as well as it's equally important to remain vigilant in heart failure patients with identifiable toxic, drug-related, infiltrative, or ischemic causes, especially when there's a decline in left ventricular systolic function. It's acknowledged that arrhythmias may be a consequence of underlying pathology. However, whether the arrhythmia or clinical deterioration originates from the underlying pathology, optimal rhythm or rate control tailored to the individual patient's needs is essential. In summary, arrhythmia-induced cardiomyopathy may present in three different clinical scenarios:

- (i) Evidence of systolic dysfunction and heart failure, alongside tachyarrhythmia or frequent ectopy, in a symptomatic patient without a history of cardiac disease.
- (ii) Detection of cardiomyopathy concurrent with tachyarrhythmia or frequent ectopy in an asymptomatic patient.
- (iii) Development of left ventricular systolic dysfunction and new arrhythmia in a patient with known structural cardiac pathology.^{509,527}

The primary factor that increases clinical suspicion is the relation between the onset or escalation of arrhythmia and the development of cardiomyopathy or heart failure. Similar to other cardiomyopathies, the use of appropriate imaging modalities is pivotal for diagnosis following a thorough medical history and comprehensive physical examination. Furthermore, similar to other cardiomyopathies, the diagnosis of arrhythmia-induced cardiomyopathy relies primarily on clinical evaluation and cannot be confirmed by a single finding alone.

In addition to employing various imaging modalities, monitoring natriuretic peptide levels can also be valuable in diagnosing arrhythmia-induced cardiomyopathy. Studies have shown that natriuretic peptide levels decrease significantly within one week after initiating treatment for arrhythmia. Thus, monitoring these levels can provide crucial insights and help differentiate between arrhythmia associated with cardiomyopathy and arrhythmia-induced cardiomyopathy.^{509,528}

It is notable that endomyocardial biopsy specimens obtained from patients with arrhythmia-induced cardiomyopathy typically do not exhibit myocardial fibrosis, indicating a reversible etiology. Additionally, histopathologic examination reveals

distinctive features such as infiltration of CD68+ macrophages and heightened expression of class 2 major histocompatibility complex molecules. However, the exact role of endomyocardial biopsy in the diagnosis remains uncertain and requires further extensive investigation.⁵²⁹ Similar to other forms of cardiomyopathy, specific findings identified through imaging modalities play a crucial role in aiding clinicians toward the diagnosis of arrhythmia-induced cardiomyopathy.

Differential diagnosis between arrhythmia-induced cardiomyopathy and cardiomyopathy associated with another etiology can be challenging. However, in such cases, the diagnosis can often be clarified through follow-up assessments after treating the underlying arrhythmia. Importantly, a near-total improvement in left ventricular systolic function following appropriate control of the arrhythmia strongly supports the diagnosis of arrhythmia-induced cardiomyopathy.⁵⁰⁹ In essence, a clear diagnosis of arrhythmia-induced cardiomyopathy can often be confidently established post-treatment, further underscoring the critical role of longitudinal monitoring and therapeutic intervention in achieving diagnostic clarity.

The timeline for the development of cardiomyopathy following the onset of the responsible arrhythmia, as well as the expected duration for systolic function improvement after treatment of the arrhythmia, remains a subject of considerable variability and ongoing investigation. Numerous studies have explored this topic, revealing heterogeneous findings. Cardiomyopathies have been reported to emerge between 3 days and 120 days following the initiation of the responsible arrhythmia.⁵³⁰ It is worth noting that the development of cardiomyopathy is more commonly associated with insidious and persistent arrhythmias. Consequently, determining the precise onset of the responsible arrhythmia can be challenging in many cases, further complicating the establishment of a clear timeline for cardiomyopathy development.

Similarly, the duration for left ventricular systolic function improvement following treatment of the responsible arrhythmia also varies widely among individuals and may be influenced by various factors such as the type and duration of the arrhythmia, the presence of underlying cardiac pathology, and the efficacy of treatment interventions. Therefore, while existing literature offers valuable insights into these temporal relationships, clinicians should approach each case with careful consideration of individual patient factors and clinical context.

Studies have indeed provided a relatively clear understanding of the time interval in which systolic function tends to recover following treatment of arrhythmia. On average, this period spans approximately four weeks.⁵⁰⁷ However, it is important to acknowledge that individual variations exist, and the duration of recovery may range from a few weeks to several months, depending on various factors including the specific characteristics of the arrhythmia, the underlying cardiac condition, and the effectiveness of the treatment.⁵⁰⁹

Multimodal Imaging in Arrhythmia-associated Cardiomyopathy

Conventional 2D Transthoracic Echocardiography

The initial evaluation of cardiomyopathies typically starts with conventional transthoracic echocardiography. Left ventricular ejection fraction measurement stands as the most commonly used method for assessing left ventricular systolic function, although it's essential to note that this parameter can be influenced by loading conditions. Research

indicates that left ventricular systolic dysfunction tends to be more severe in arrhythmia-associated cardiomyopathy compared to inflammatory dilated cardiomyopathy, which represents a relatively more prevalent reversible form of cardiomyopathy.⁵³¹⁻⁵³³

However, in the presence of arrhythmias such as atrial fibrillation, ejection fraction assessment may be compromised due to beat-to-beat variability and exhibits low reproducibility. Hence, ventricular remodeling can alternatively be evaluated by assessing cavity dimensions. Patients with arrhythmia-induced cardiomyopathy typically present with smaller left ventricular end-diastolic diameters and lower left ventricular mass indices compared to patients with dilated cardiomyopathy attributed to other etiologies. Notably, left ventricular wall thickness tends to remain within normal limits.⁵⁰⁹

Furthermore, given the potential impact of arrhythmias on biventricular systolic function in arrhythmia-associated cardiomyopathy, deterioration of right ventricular systolic function may manifest at an earlier stage compared to other forms of cardiomyopathy.⁵⁰⁹ Additionally, mitral valve regurgitation may arise secondary to mitral annular dilatation, similar to other types of cardiomyopathies (Video 12,13).⁵⁰³

Transthoracic Speckle Tracking Echocardiography

While ejection fraction remains the predominant parameter for assessing left ventricular systolic function in clinical practice due to its widespread availability, it's crucial to acknowledge its limitations. Primarily, ejection fraction indirectly measures myocardial contractility by estimating pump function. It can be influenced by loading conditions and heart rate, making it less sensitive to subtle changes in contractile function.⁵³⁴ However, many of these limitations can be mitigated through speckle tracking echocardiographic evaluation conducted by experienced imaging specialists. This technique allows for the assessment of myocardial contractility that is relatively independent of load and heart rate. One of the most notable findings that may aid in the diagnosis of arrhythmia-associated cardiomyopathy is the pronounced reduction in longitudinal strain values observed in the apical segments of the left ventricle compared to the middle and basal segments. This discrepancy highlights the potential of speckle tracking echocardiography to detect subtle alterations in myocardial function, thereby providing valuable insights for clinicians in diagnosing arrhythmia-induced cardiomyopathy.^{509,535}

3D Transthoracic Echocardiography

Indeed, a critical limitation shared by both speckle tracking echocardiographic evaluation and conventional echocardiography lies in their reliance on geometric assumptions for two-dimensional assessments. This inherent constraint poses a significant challenge for accurate evaluation. However, three-dimensional echocardiographic methods have revolutionized cardiac imaging by enabling realistic measurements without the need for geometric assumptions. By capturing volumetric data from a single apical window, three-dimensional echocardiography offers a more comprehensive and precise assessment of cardiac structure and function. Numerous studies have demonstrated that three-dimensional echocardiographic evaluations, which are notably more cost-effective than cardiac magnetic resonance imaging, provide volumetric and functional assessments that closely approximate those obtained via cardiac magnetic resonance imaging.⁵³⁶ Consequently, three-dimensional echocardiography holds promise as a valuable tool for clinicians in diagnosing arrhythmia-induced cardiomyopathy. Three-dimensional echocardiographic data on patients with arrhythmia-

induced cardiomyopathy remain relatively scarce in the literature, highlighting the need for further research in this area.

Cardiac Magnetic Resonance Imaging

Cardiac magnetic resonance imaging, renowned as the gold standard non-invasive imaging modality for diagnosing various cardiomyopathies, plays a pivotal role in elucidating the diagnosis of arrhythmia-induced cardiomyopathy. Recent advancements in cardiac magnetic resonance imaging technology have offered novel insights into ventricular remodeling associated with arrhythmia-induced cardiomyopathy. Specifically, the utilization of late gadolinium enhancement facilitates the detection of focal myocardial scarring and fibrosis. Unlike other inflammatory etiologies, the absence of myocardial late gadolinium enhancement in patients with arrhythmia-associated cardiomyopathy holds significant diagnostic value.⁵³³

Furthermore, evaluating the early deterioration of right ventricular function in arrhythmia-induced cardiomyopathy is challenging with echocardiography due to the complex anatomy and sub-sternal localization of the right ventricle. In contrast, cardiac magnetic resonance imaging demonstrates notable superiority in assessing right ventricular dysfunction. Despite its diagnostic benefits, cardiac magnetic resonance imaging has several limitations including high cost, inability to be conducted at the bedside, and limited accessibility. However, CMR remains an indispensable tool for providing crucial insights into the diagnosis and management of arrhythmia-induced cardiomyopathy.⁵⁰⁹

Treatment

Effective management of the responsible arrhythmia is substantial in the treatment of arrhythmia-induced cardiomyopathy, alongside the conventional therapies recommended for cardiomyopathy and heart failure.⁵³⁷ The choice between rate or rhythm control strategies depends on various factors including the type of arrhythmia and the clinical characteristics of the patient. Studies have demonstrated that restoration of sinus rhythm can contribute significantly to the improvement of systolic function in arrhythmia-induced cardiomyopathy.

Atrial Fibrillation and Atrial Flutter

Atrial fibrillation stands as the most prevalent cause of arrhythmia-induced cardiomyopathy in adults, often coinciding with heart failure. The challenge of distinguishing between arrhythmia-induced cardiomyopathy and arrhythmia-mediated cardiomyopathy, particularly in individuals of advanced age (>60 years), underscores the importance of prioritizing rate and rhythm control as the primary therapeutic objectives. For effective rate control, pharmacological interventions or pacemaker implantation following AV node ablation may be performed.⁵²³ Pharmacotherapy options include beta-blockers or cardiac glycosides, while calcium channel blockers are generally avoided in patients with impaired left ventricular systolic function due to their negative inotropic effects. The target heart rate in atrial fibrillation typically falls below 110/min. Rhythm control, on the other hand, can be attained through pharmacological antiarrhythmics, electrical cardioversion, or ablation procedures.⁵³⁸ While several studies have investigated the comparative efficacy of rhythm versus rate control methods on mortality, no clear superiority has been consistently demonstrated, likely due to the adverse effects associated with antiarrhythmic drugs.⁵³⁹ Nonetheless, rhythm control remains the preferred approach, particularly in cases where arrhythmia-induced cardiomyopathy is suspected or confirmed.⁵⁴⁰ Among the available methods, catheter ablation has emerged as the most favorable option, resulting in lower rates of arrhythmia recurrence, enhanced quality of life, and reduced hospitalizations.⁵⁴¹

In atrial flutter, due to the greater difficulty in achieving rate control compared to atrial fibrillation, prioritizing rhythm control as the primary therapeutic goal is recommended.

Before initiating rhythm control strategies in patients with atrial fibrillation or flutter, it's crucial to assess the left atrial appendage to evaluate the risk of thromboembolism. This evaluation is particularly important unless the atrial fibrillation or flutter has recently onset (<48 hours) or if the clinician is confident that the patient has been effectively anticoagulated for at least 3 weeks.⁵³⁸ Before considering rhythm control strategies like electrical cardioversion or ablation, it's crucial to confirm that the patient's risk of thromboembolism has been thoroughly evaluated by transesophageal echocardiography for possible occurrence of thrombi.

Other Supraventricular Tachycardias

While atrioventricular nodal reentrant tachycardia and atrioventricular reciprocating tachycardia are common types of supraventricular tachycardias, they are less frequently associated with arrhythmia-induced cardiomyopathies. In contrast, focal atrial tachycardia and persistent junctional reciprocating tachycardia are identified as the predominant causes of arrhythmia-induced cardiomyopathy in the pediatric population.⁵⁰⁴ In cases of arrhythmia-associated cardiomyopathy linked with any type of supraventricular tachycardia, current guidelines advocate for catheter ablation as the primary treatment modality. Catheter ablation has demonstrated efficacy in restoring normal rhythm and improving cardiac function, making it the preferred therapeutic approach in such scenarios. By targeting the underlying arrhythmogenic substrate, catheter ablation offers the potential for long-term resolution of arrhythmia-induced cardiomyopathy and its associated symptoms.^{503,509}

Ventricular Ectopic Beats

Idiopathic ventricular arrhythmias occurring in the absence of organic heart disease typically exhibit a favorable prognosis; however, they can potentially lead to arrhythmia-induced cardiomyopathy.⁵⁴² Studies utilizing speckle tracking echocardiography have revealed that ventricular ectopic beats, when present at rates of approximately 10%, can impair myocardial contractility.⁵⁴³ Furthermore, ventricular ectopic beats ranging from 10% to 26% or exceeding 10,000 beats per day have been linked to the development of arrhythmia-induced cardiomyopathy.⁵⁴⁴ Several factors contribute to the propensity for arrhythmia-induced cardiomyopathy, including the site of ventricular ectopic beat origin (e.g., right ventricle, epicardium), widened QRS complexes (>150 msec), male gender, advanced age, and elevated body mass index.^{503,509} The primary therapeutic goal for managing ventricular ectopic beats is pharmacological treatment. However, if medication fails to produce the desired response or is poorly tolerated by the patient, catheter ablation becomes an alternative treatment option. Catheter ablation can target and eliminate the ectopic focus, potentially relieving symptoms and halting the progression of arrhythmia-induced cardiomyopathy.⁵⁴⁵

Pacemaker-associated Cardiomyopathy

In a subset of patients undergoing chronic right ventricular stimulation, the manifestation of left ventricular systolic dysfunction has been documented, predominantly ascribed to myocardial

dissynchrony.⁵⁴⁶ The onset of arrhythmia-induced cardiomyopathy in these instances depends on multiple variables, including pre- and post-stimulation QRS duration, the stimulation ratio, and male gender. Additionally, a reduced left ventricular ejection fraction at baseline is a significant determinant predisposing to the progression of cardiomyopathy. Considering these factors, cardiac resynchronization therapy is recommended over right ventricular stimulation for individuals with a reduced left ventricular ejection fraction and complete atrioventricular block, following prevailing clinical guidelines.⁵⁴⁷ Cardiac resynchronization therapy aims to synchronize ventricular contraction by pacing both the left and right ventricles simultaneously. This approach enhances cardiac performance and reduces the risk of developing arrhythmia-induced cardiomyopathy. By optimizing ventricular synchrony, cardiac resynchronization therapy is a targeted therapeutic intervention designed to improve myocardial function and alleviate the adverse effects associated with prolonged right ventricular stimulation.⁵⁰⁹

Follow-up

Arrhythmia-induced cardiomyopathy demonstrates potential for reversibility, characterized by complete or significant recovery of left ventricular systolic function following treatment of the responsible arrhythmia. However, prolonged exposure to untreated arrhythmia can result in irreversible adverse ventricular remodeling. Therefore, early intervention targeting the responsible arrhythmia and diligent clinical monitoring are essential in managing these patients. Research indicates that effective treatment of arrhythmia typically yields improvements in left ventricular systolic function around the four-week mark, with no noticeable improvement observed at one-week post-treatment. However, it's crucial to note that this improvement hinges on the absence of arrhythmia recurrence.⁵⁰⁹

Many arrhythmias, including atrial fibrillation and atrial flutter, have a propensity to recur, potentially impairing left ventricular function if left untreated. Because of the risk of arrhythmia recurrence, continuous ambulatory rhythm monitoring and regular echocardiographic follow-up are crucial for promptly detecting and managing recurrent arrhythmias. By closely monitoring cardiac rhythm and function, clinicians can promptly intervene to mitigate the risk of recurrent arrhythmia-induced cardiomyopathy and optimize long-term patient outcomes.

Video 10. Transthoracic echocardiography images of a patient with cardiomyopathy induced by rapid ventricular response atrial fibrillation before and after pulmonary vein isolation. (A) Parasternal short axis image (pre-pulmonary vein isolation), (B) Apical three-chamber image (pre-pulmonary vein isolation), (C) Apical two-chamber image (post-pulmonary vein isolation, no improvement), (D) Apical four-chamber image (post-pulmonary vein isolation, no improvement).

Video 11. Transthoracic echocardiography images of the same patient in Video 1, 5 weeks after pulmonary vein isolation. (A) Apical two-chamber image, (B) Apical four-chamber image (C) Parasternal short axis image.

Video 12. Transthoracic apical four-chamber view of a patient with atrial fibrillation and severe mitral regurgitation.

Video 13. Transthoracic echocardiography images of the same patient in Video 3 after pulmonary vein isolation. (A) Apical three-chamber image, (B) Apical four-chamber image.

Non-Dilated Left Ventricular Cardiomyopathy

The term "non-dilated left ventricular cardiomyopathy" was formally introduced by the European Society of Cardiology (ESC) in the 2023 ESC guidelines for the management of cardiomyopathies. This phenotype is characterized by the presence of non-ischemic left ventricular (LV) scarring or fat replacement without LV dilatation, and may include global or regional wall motion abnormalities.¹

Additionally, abnormal loading conditions such as hypertension, valvular disease, or isolated left ventricular hypokinesia without scarring in the late gadolinium phase, which cannot be attributed to coronary artery disease, is included in this phenotype. Global left ventricular systolic dysfunction is defined by an abnormal left ventricular ejection fraction (LVEF) of less than 50%.¹

This concept was previously proposed by the ESC Working Group on Myocardial and Pericardial Diseases in 2016 under the term "hypokinetic non-dilated cardiomyopathy".⁸ It was defined as the early clinical stage of dilated cardiomyopathy. However, in the 2023 ESC guideline, the definition was expanded by adding the phrase "with or without systolic dysfunction" and redefined as "non-dilated left ventricular cardiomyopathy".¹

Imaging Methods

Imaging modalities are our most critical tools in the diagnosis, treatment, and follow-up of cardiomyopathies. Echocardiography and cardiac magnetic resonance imaging (MRI) are the primary methods used. Computed tomography (CT) and nuclear imaging techniques are also viable options. It is essential to utilize these modalities while considering the capabilities of the clinic, patient-specific conditions such as the presence of implants, devices, previous radiation exposure, and contrast media, and costs.^{1,548}

Telecardiography

Non-dilated left ventricular hypertrophy (NDLVH) is often missed on chest radiography due to the absence of cardiomegaly. Therefore, other radiologic findings should be meticulously examined.⁵⁴⁹ Radiologic signs of pulmonary arterial hypertension include dilatation of the main pulmonary artery, peripheral pruning of the distal pulmonary vessels, and right ventricular dilatation.⁵⁵⁰ Kerley lines, perihilar peribronchial cuffing, and bat wing edema are indicative of pulmonary venous hypertension.⁵⁵¹

Echocardiography

Echocardiography is widely available, inexpensive, and reproducible. A comprehensive transthoracic echocardiogram (TTE) examination is recommended for all patients with non-dilated left ventricular cardiomyopathy (NDLVC) as it provides comprehensive information on global and regional LV anatomy, function, and hemodynamics; valvular heart disease; right heart function; pulmonary pressure; and atrial geometry.^{1,2,182}

Global hypokinesia with a normal end-diastolic LV size is a typical echocardiographic feature of NDLVC. Regional wall motion abnormalities, such as akinesia or dyskinesia of the LV septum or apex, with better contractility of the posterior and lateral walls, may also be observed.⁵⁵² The mean LVEF has been found to be higher in groups related to LVNDC than in those with dilated cardiomyopathy.

(DCM).⁵⁵³⁻⁵⁵⁵ LVEF is an important predictor of mortality and hospitalization, independent of LV end-diastolic diameter.⁵⁴⁹

Speckle tracking echocardiography is an advanced echocardiographic technique that offers higher sensitivity than ejection fraction (EF) for assessing systolic function and is effective in detecting small changes in systolic function.^{182,556} It enables the early recognition of impairments in systolic function, crucial for early diagnosis and disease follow-up.⁵⁵⁷ Two-dimensional speckle tracking echocardiography has shown less impaired echocardiographic features in patients with NDLCV compared to those with dilated cardiomyopathy. Patients with NDLCV tend to exhibit lower positive global circumferential strain (GCS) and less mechanical dispersion compared to patients with dilated cardiomyopathy, regardless of LVEF. GCS measured by 2D speckle tracking echocardiography is superior to global longitudinal strain (GLS) or twist for discriminating between these two different phenotypes.⁵⁵⁸ GLS and mechanical dispersion have been associated with arrhythmia risk in dilated cardiomyopathy patient cohorts and may be considered in patient follow-up and implantable cardioverter-defibrillator (ICD) planning in the NDLCV patient group.^{558,559}

Exercise stress echocardiography has a significant role in the follow-up of hypertrophic cardiomyopathy, but its use in non-dilated left ventricular cardiomyopathy is limited. It can be used to evaluate coronary ischemia in selected patient groups.¹ Pharmacological stress echocardiography evaluates wall motion under dobutamine or dipyridamole. Pharmacological stress echocardiography may be preferred for the diagnosis of ischaemic heart disease when exercise stress echocardiography test cannot be performed. It can be used in cases where the patient has orthopedic problems, left bundle branch block, pacemaker rhythm, or stress electrocardiography is not diagnostic.⁵⁶⁰ The diagnostic power of both stress exercise or pharmacological stress echocardiography is related to the pre-test probability, the sensitivity is high in a well-selected group of high-risk patients, but the possibility of false positivity and false negativity should be considered. It should be preferred to evaluate CAD only when other imaging modalities cannot be used.^{560,561}

Magnetic Resonance Imaging

Cardiac magnetic resonance with late gadolinium enhancement (LGE) is the leading imaging modality in NDLCV as it provides confirmation of the presence of non-ischemic myocardial

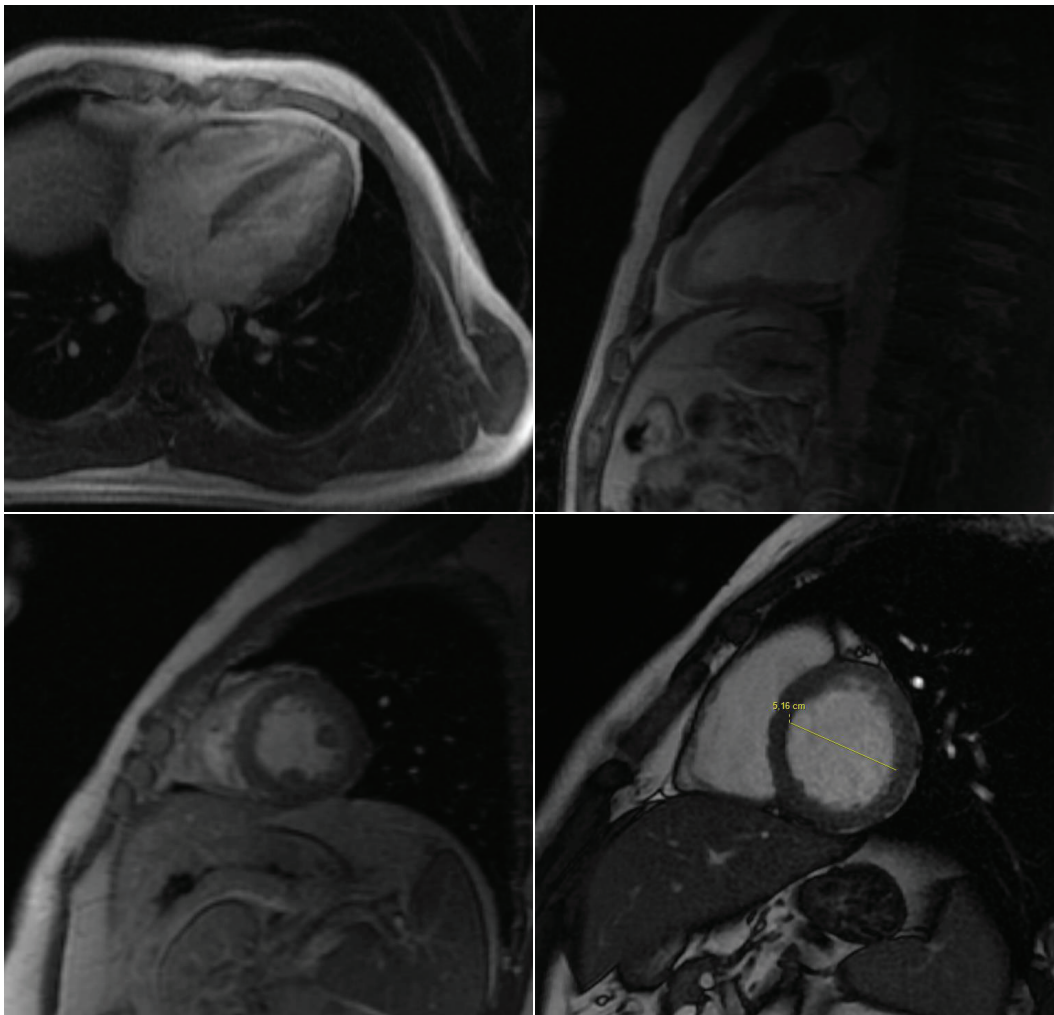


Figure 93. Although left ventricular functions are reduced, LV volumes are within normal limits and there is no LGE involvement.

fibrosis, which is essential for diagnosis. It is also useful for defining the extent and distribution pattern of fibrosis.⁵⁶² LGE is an important predictor of mortality, hospitalization, and sudden cardiac death.⁵⁶³

In NDLVC, the ejection fraction decreases, whereas the cardiac volume remains within the normal range (Figure 93). The presence of LGE is crucial for determining the risk of sudden death, and genetic testing is recommended. It is also advised that first-degree relatives of diagnosed patients undergo clinical evaluation, including electrocardiography, echocardiography, and possibly cardiac MRI. Cardiac magnetic resonance can also detect the presence of myocardial edema, which may indicate an inflammatory or myocarditis etiology. Distinct LGE patterns provide clues for the evaluation of different etiologies. Patchy

midwall LGE may occur in dystrophin mutations. The presence of focal LGE involving the subepicardium and midwall myocardium may represent myocarditis. LGE involving the basal LV segments of the heart or the submitral region may help to exclude other etiologies such as sarcoidosis.⁵⁶²

Nuclear Medicine

In patients with NDLVC who have a DSP gene mutation, isolated 18F-Fluorodeoxyglucose uptake has been demonstrated by positron emission tomography.⁴⁸⁴ In NDLVC patients with amyloidosis, focal or diffuse uptake is observed, and this uptake is also noted in non-cardiac tissues.⁵⁶⁴

Video 14-16. Although left ventricular functions are reduced, LV volumes are within normal limits.

Echocardiography for Patients with Left Ventricular Assist Devices

In patients suffering from end-stage heart failure (HF), heart transplantation stands out as the gold standard therapy. However, despite its efficacy, a scarcity of donors contributes to prolonged waiting periods, resulting in a heightened mortality rate among these patients. As an alternative, a left ventricular assist device (LVAD) presents itself as a viable option, serving various purposes such as providing mechanical support as a bridge to heart transplantation, candidacy, recovery, or destination therapy. LVADs offer crucial support for patients unresponsive to intensive HF therapy, sustaining cardiovascular circulation for periods ranging from weeks to years. Furthermore, they play a significant role in enhancing both quality of life and end-organ function.⁵⁶⁵⁻⁵⁶⁸

In modern times, three generations of LVADs are available. The first generation consisted of devices like Heartmate I, Novacor, and Thoratec, which were pulsatile pumps requiring extensive surgical

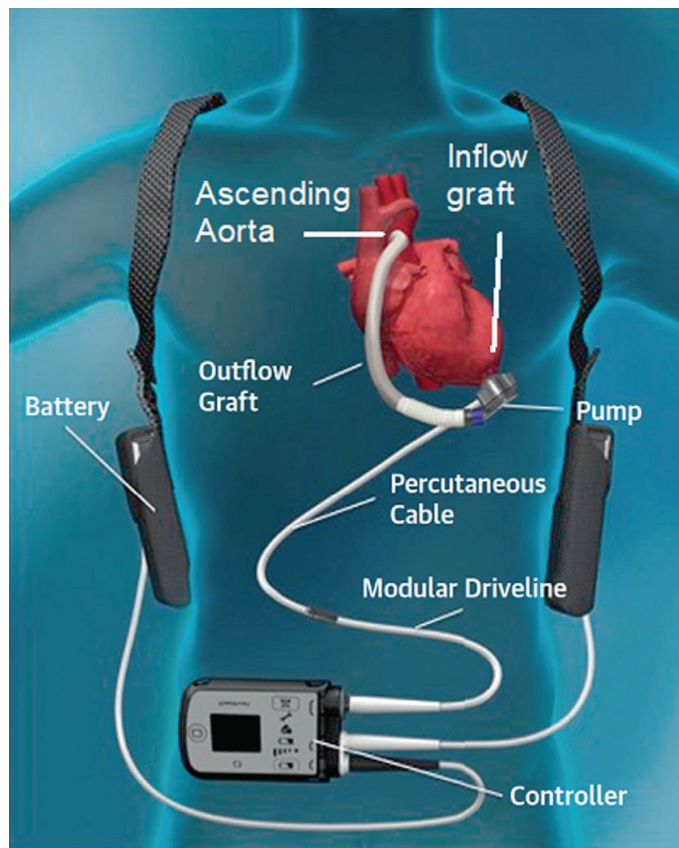


Figure 94. Components of a LVAD system
LVAD: Left ventricular assist device Permission to publish was received from Abbott.

Table 30. Preoperative Echocardiographic Evaluation of the LVAD Candidates
● Left ventricle and right ventricle dimensions ● Left ventricle and right ventricle systolic function ● Left atrium volume, dimension of mitral annulus, geometry of the leaflets and papillary muscles, and degree of mitral regurgitation ● Diastolic function ● Degree of tricuspid regurgitation, dimension of tricuspid valve function, and pulmonary artery systolic pressure ● Aortic valve morphology, degree of aortic regurgitation, and size of ascending aorta clots ● Shunts
Table 31. Preimplantation Transthoracic echocardiography/Transesophageal echocardiography High Risk "red-flag" Findings
Left Ventricle and Interventricular Septum
● Small left ventricle size, particularly with increased left ventricle trabeculation ● Left ventricle thrombus ● Left ventricle apical aneurysm ● Ventricular septal defect
Right Ventricle
● Right ventricle dilatation ● Right ventricle systolic dysfunction
Atria and Interatrial Septum
● Left atrial appendage thrombus ● Patent foramen ovale or atrial septal defect
Valvular Abnormalities
● Any prosthetic valve (especially mechanical aortic valve) ● > mild aortic regurgitation ● ≥ moderate mitral stenosis ● ≥ moderate tricuspid regurgitation or > mild tricuspid stenosis ● > mild PS; ≥ moderate pulmonary regurgitation
Other
● Any congenital heart disease ● Aortic pathology: aneurysm, dissection, atheroma, coarctation ● Other shunts: patent ductus arteriosus, intrapulmonary shunts ● Mobile mass lesion

dissection. They were associated with a high infection rate and were most suitable for individuals with large body habitus.^{566,569} Moving to the second generation, devices such as Heartmate II and Jarvik emerged as continuous devices utilizing axial flow pumps. These devices are proved to be more durable, smaller, easier to implant, quieter, and associated with a lower rate of drive-line infection compared to their first-generation counterparts.^{569,570} The latest, third-generation devices include HeartWare and Heartmate III, which are continuous flow centrifugal pumps. These devices boast a low risk of hemolysis or thrombosis, with Heartmate III showing lesser risk compared to HeartWare. They offer easy surgical insertion and have a long durability, ranging from 5 to 10 years.^{569,571}

Since their creation, the basic structure of LVADs has not changed (Figure 94). Current continuous flow-LVADs have intracorporeal (inflow cannula, outflow cannula, and rotor/mechanical impeller) and extracorporeal components (controller monitors). An inflow cannula is inserted into the apex of the left ventricle (LV) and transports the blood from the LV to mechanical impeller. An outflow cannula is anastomosed to the right anterior aspect of the ascending aorta (the most common) or descending aorta. A mechanical impeller pulls blood from the inflow cannula through

diastole and systole into the ascending aorta via the outflow cannula. A controller monitor receives process data from the pump and offers information about its functioning. The controllers have several LVAD related parameters and may trigger device alarms.⁵⁶⁹

Transthoracic echocardiography (TTE) stands as the foremost and most vital imaging tool for LVAD assessment. It serves multiple purposes including preoperative evaluation for candidacy, providing guidance during LVAD insertion, detecting complications, and facilitating long-term monitoring. In situations where TTE is not technically feasible, transesophageal echocardiography (TEE) steps in. TEE is particularly useful for evaluating patients with poor echogenicity, conducting detailed assessments of valve functions, detecting inter-atrial shunting, or performing perioperative evaluations.^{572,573}

Pre-Left Ventricular Assist Device Echocardiography

The pre-LVAD echocardiographic evaluation of cardiac structure and function serves two primary objectives: firstly, to determine the suitability of LVAD therapy for a patient with HF, and secondly, to identify any cardiac abnormalities that may predict postsurgical complications. Such an examination should encompass the assessment of both left and right cardiac structure and function,

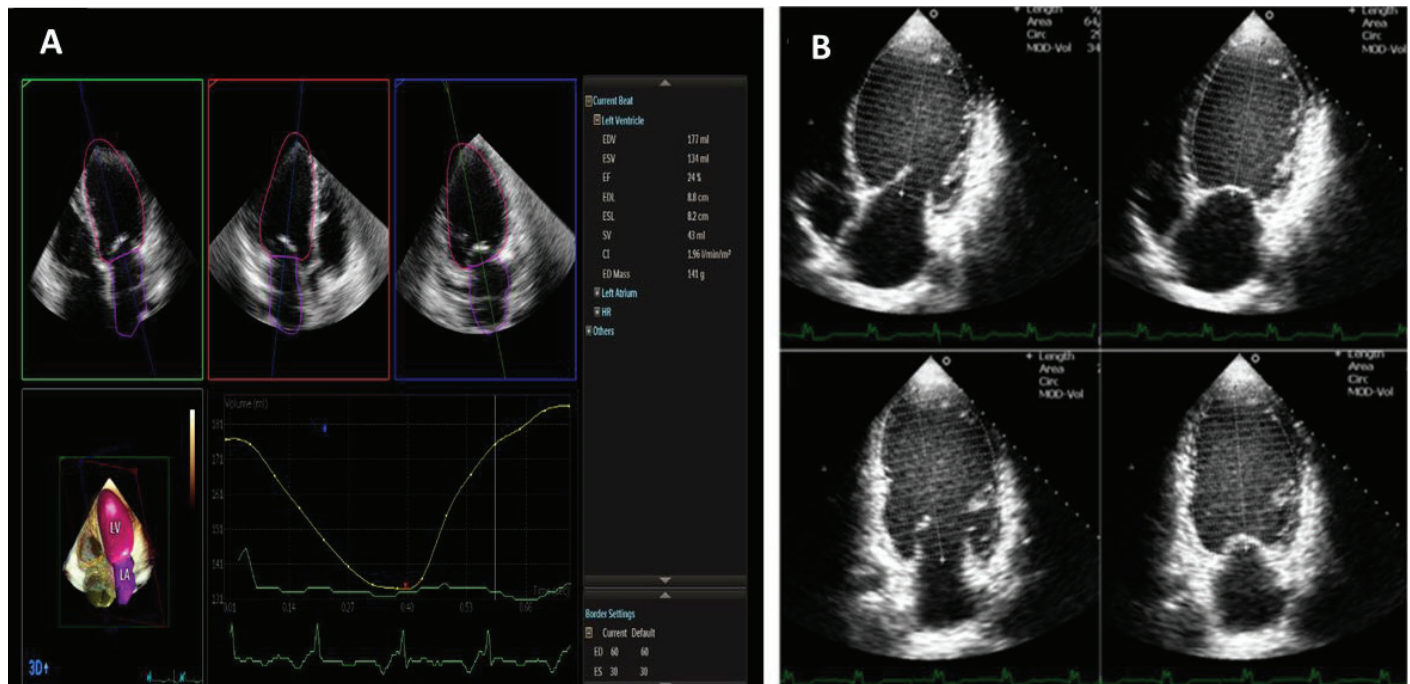


Figure 95. LV volumes and LVEF measurement; (A): 3D-TTE; (B): Modified Biplane Simpson's method. 3D-TTE, three dimensional transthoracic echocardiography; LV, left ventricle; LVEF; left ventricular ejection fraction.

valvular function, as well as the presence of intracardiac thrombus and shunts. Moreover, particular attention should be given to echocardiographic findings carrying high-risk implications for LVAD therapy (Table 30 and Table 31).^{572,574}

Left Ventricular Function

The decision to refer a patient for LVAD placement is not solely determined by reduced left ventricular ejection fraction (LVEF); various clinical parameters are also taken into account. Guidelines for durable LVAD recommendation primarily rely on the patient's clinical status (including symptoms, dependency on inotropes, and the need for temporary circulatory support) rather than LVEF.⁵⁶⁸ Nonetheless, despite these considerations, LVEF remains a significant factor when determining whether to refer a patient to an advanced HF facility and is incorporated as a parameter in major HF risk assessment scores. While there are no strict cutoff values, typical LVAD candidates exhibit LVEFs around 25–30%. According to guidelines, a patient with an LVEF of <35% should be considered for referral to an advanced HF center if clinically warranted.⁵⁶⁸

Measurement of LVEF and left chamber dimensions should adhere to previous guidelines.² When imaging conditions allow, three-dimensional (3D) assessment is preferred for determining LV volumes and LVEF. Alternatively, if 3D assessment is not feasible, the biplane method (modified Simpson's) using two-dimensional (2D) images should be utilized.^{4,575} (Figure 95, Video 17).

In cases where LV endocardial borders are not clearly defined, the application of microbubble contrast material is recommended.⁵⁷⁶ LV end-diastolic dimension (LVEDd) obtained from 2D parasternal long-axis windows serves as a crucial measurement in LVAD candidates, alongside LVEF. Comparing preoperative and postoperative LVEDd is pivotal as it serves as the primary

clinical indicator of the degree of LV unloading achieved by the LVAD. While measuring LV unloading by comparing pre- and postoperative LV end-diastolic volumes (LVEDVs) would be preferable, obtaining these measurements in the early postoperative phase can be challenging.

It's noteworthy that smaller LV dimensions and higher LVEF prior to LVAD implantation have been linked to poorer outcomes following implantation. While a small LV cavity doesn't necessarily rule out LVAD implantation, an LVEDd <63 mm is associated with higher 30-day rates of mortality and morbidity following implantation.⁵⁷⁷ Patients with infiltrative cardiomyopathies and elderly women with smaller body habitus often have smaller LV cavities, making them more susceptible to interventricular septal (IVS) shifts and suction. IVS shifts occur when the septum obstructs the device's inflow cannula during LVAD decompression.^{572,573,578,579}

Right Heart Function

Right ventricle (RV) failure emerges as one of the most prevalent and challenging complications following LVAD implantation, as it leads to a reduction in LVAD flow.⁵⁷⁸ It is believed that RV dysfunction stems from septal shift induced by increased LV flow and preload on the right heart.

Understanding which patients are prone to RV failure in the postoperative period is crucial for enhancing patient selection and outcomes. Despite numerous studies conducted on this matter, the findings remain inconsistent. This inconsistency may arise due to variations in patient characteristics selected for LVAD implantation across HF centers, the absence of a universal definition for RV failure post-LVAD, or the limitation of small sample sizes in these studies.^{578,579}

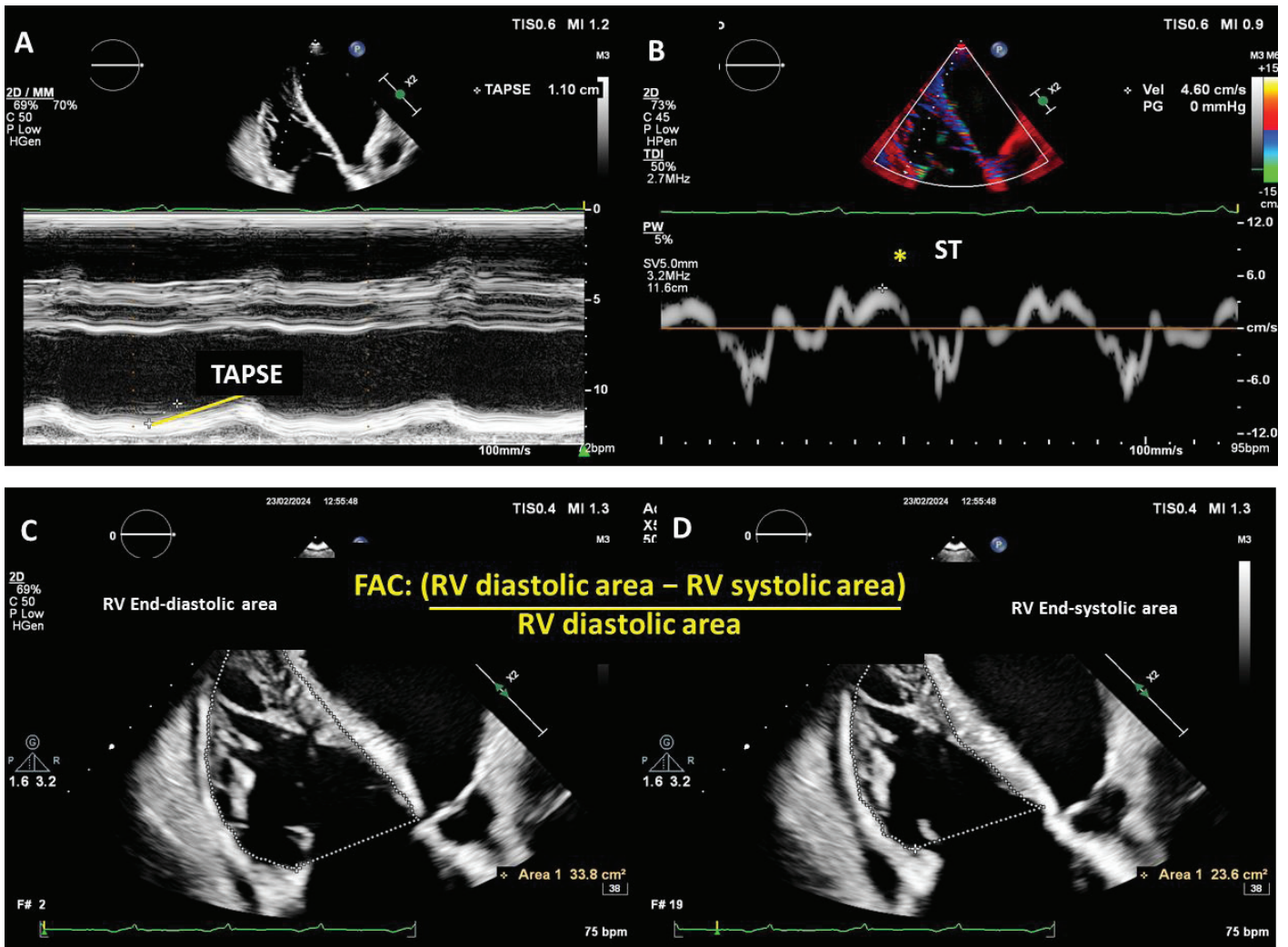


Figure 96. RV systolic function methods; (A): TAPSE; (B): tissue Doppler-derived lateral annular systolic velocity (ST); (C) RV end-diastolic area; (D): RV end-systolic area. FAC, fractional area change; RV, right ventricle; TAPSE, tricuspid annular peak systolic excursion.

Several echocardiographic parameters are associated with RV failure. However, it's important to note that echocardiographic findings alone are often insufficient to conclusively demonstrate RV dysfunction. To effectively diagnose possible right-sided HF syndrome, it's crucial to combine echocardiographic findings with the patient's clinical signs and symptoms, along with the results of right heart catheterization (RHC).

Utilizing multiple acoustic windows allows for a comprehensive view of the right heart from various angles, aligning with current guidelines for cardiac chamber quantification. Additionally, given the absence of a single contractility index that perfectly characterizes RV performance, it's essential to measure a variety of parameters.^{572,573,579}

Right Heart Anatomic Parameters

Long-term reverse remodeling, observed in the LV following LVAD implantation, does not extend to the RV. Anatomical changes in the RV before surgery indicate chronic RV dysfunction unlikely to improve by device implantation. Specifically, the RV short-axis dimension, the ratio of the RV short-axis to its long axis, and the

RV end-diastolic dimension (RVEDd) / LVEDd ratio have been correlated with post-LVAD RV failure.⁵⁷⁹ Among these, the RVEDd / LVEDd ratio emerges as the most robust anatomical predictor of early postoperative RV failure and mortality. A ratio exceeding 0.72 is indicative of RV dysfunction following LVAD implantation.¹⁶² However, since postoperative RV failure is not observed in over 66% of patients meeting this criterion, it's not recommended to rely solely on this parameter. Instead, incorporating it as an additional component to the risk score would be beneficial.¹⁶² Additionally, tricuspid annular dilation has been linked to early postoperative RV failure, though it should be interpreted in conjunction with other signs of RV failure and mortality.

In theory, a large right atrium (RA) might suggest elevated filling pressures on the right side over time and could potentially be linked to unfavorable outcomes. However, the size of the RA on 2-D echocardiography alone cannot reliably predict results following LVAD implantation.⁵⁸⁰ Moreover, although RV failure is connected with increased RA pressure measured by RHC, estimates of RA pressure derived from inferior vena cava (IVC)

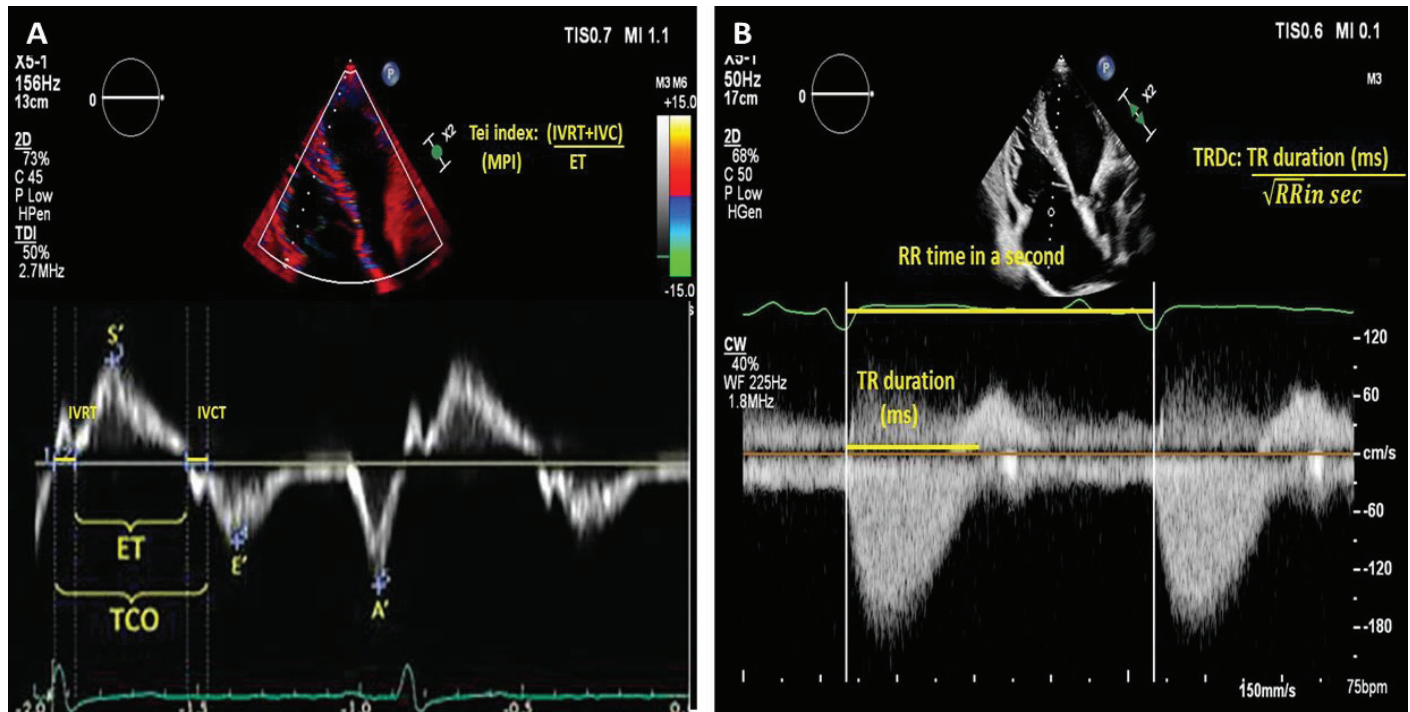


Figure 97. RV systolic function methods; (A): Tei index (myocardial performance index); (B): Tricuspid regurgitation duration corrected by heart rate (TRDc).

diameter and collapsibility do not exhibit a strong correlation with outcomes after LVAD implantation.⁵⁸⁰

Right Ventricular Systolic Function

Tricuspid annular plane systolic excursion (TAPSE), measured by M-mode from the apical four-chamber window, assesses the longitudinal function of the RV (Figure 96). TAPSE operates under the assumption that the movement of one segment reflects the overall complex 3D structure of the RV. However, in certain conditions, such as regional RV hypokinesia, TAPSE may not provide valid results. A TAPSE cutoff value of 17 mm exhibits high specificity in distinguishing abnormal from normal systolic function.⁵⁸¹ It was among the first quantitative measures of RV function to be associated with post-LVAD RV failure. Retrospective analysis of LVAD recipients indicated that TAPSE was significantly lower in patients experiencing RV failure compared to those who recovered well postoperatively.⁵⁸² Unfortunately, other larger analyses have not consistently replicated TAPSE's predictive value in these patients.^{162,580,582}

Fractional area change (FAC) serves as a commonly utilized quantitative measure, serving as a surrogate for RV ejection fraction (Figure 96). An RV FAC of $\geq 40\%$ is deemed normal. Typically, an LVAD candidate exhibits an RV FAC ranging from 20% to 30%. One study suggests that patients with an RV FAC $< 20\%$ are susceptible to RV failure following LVAD implantation.⁵⁷³ However, other larger analyses have not consistently replicated FAC's predictive value in these patients.^{582,583}

The RV index of myocardial performance (RIMP), also known as the Tei index, offers a comprehensive estimate of both systolic and diastolic function (Figure 97). It can be derived using continuous-wave Doppler or tissue Doppler of the tricuspid annulus. This

index provides a more quantitative evaluation of RV myocardial performance, with a value of ≤ 0.4 considered normal.⁵⁷³ However, it has been determined that there is no association between the Tei index and adverse outcomes in terms of RV failure among patients who have undergone LVAD implantation.⁵⁸²

Tricuspid regurgitation duration corrected for heart rate (TRDc) serves as an important parameter in assessing RV failure and cardiac mortality following LVAD implantation, as it is associated to the rapid equalization of RA and RV pressures (Figure 97). A low TRDc suggests elevated RA pressure and decreased RV systolic pressure. In a study involving patients with advanced HF, those with a TRDc < 461 ms were found to have a higher risk of mortality and New York Heart Association Functional Classification III or IV symptoms after surgery.^{577,579}

The RV contraction pressure index (RVCPI), derived from echocardiography, exhibits correlation with the RV stroke work index (RVSWI) derived from RHC, which is associated with early RV failure after LVAD implantation (Figure 98).⁵⁸⁴ While this correlation is promising, further studies are warranted to confirm and elucidate the strong association between RVCPI and RVSWI.

RV strain has been identified as a significant factor influencing outcomes following LVAD implantation (Figure 99).⁵⁷⁸ Although the sensitivity and specificity of strain are not exceptionally high, it remains one of the most powerful single-variable predictors of post-operative outcomes following LVAD.

In one study, RV failure post-LVAD was found to have a specificity of 76% and sensitivity of 68% when a peak strain cutoff of -9.6% was used. However, a notable limitation of this technique is the challenge of obtaining sufficient images for analysis. Nearly one

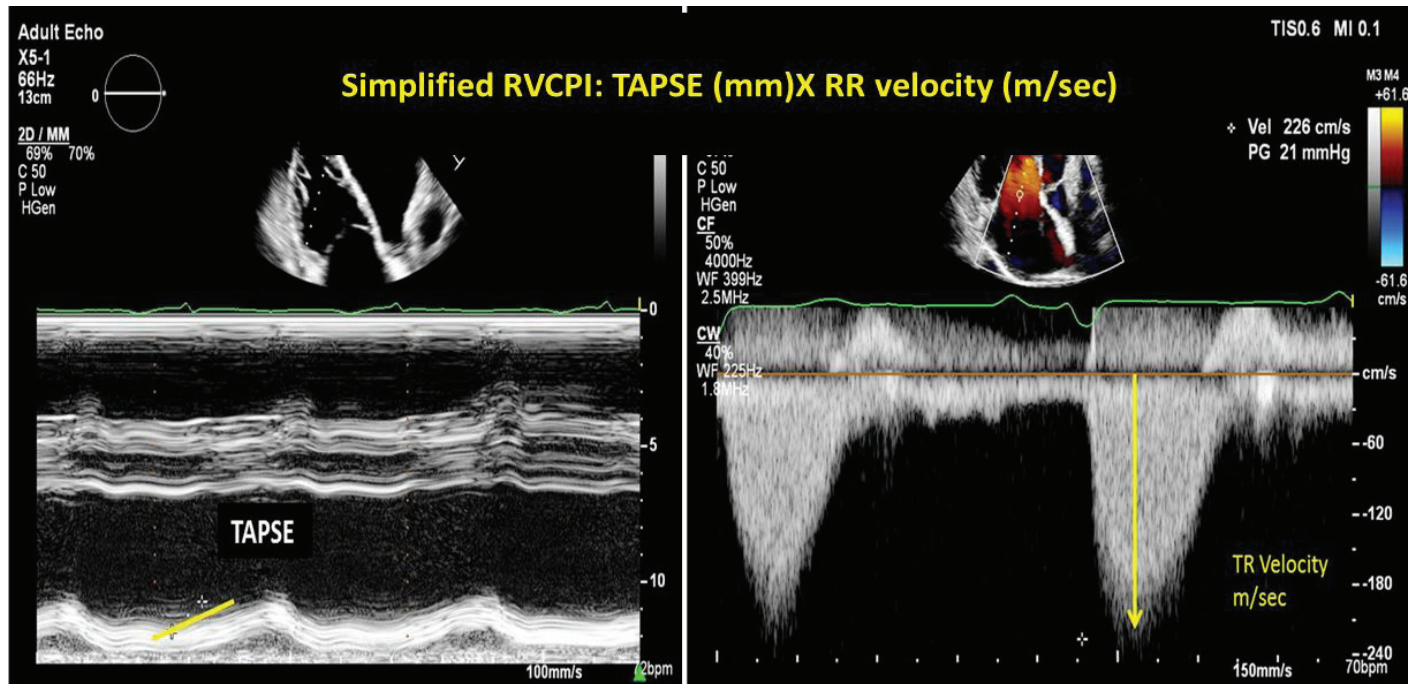


Figure 98. RV contraction pressure index. RVCPI, Right ventricular contraction pressure index; TAPSE, tricuspid annular peak systolic excursion.

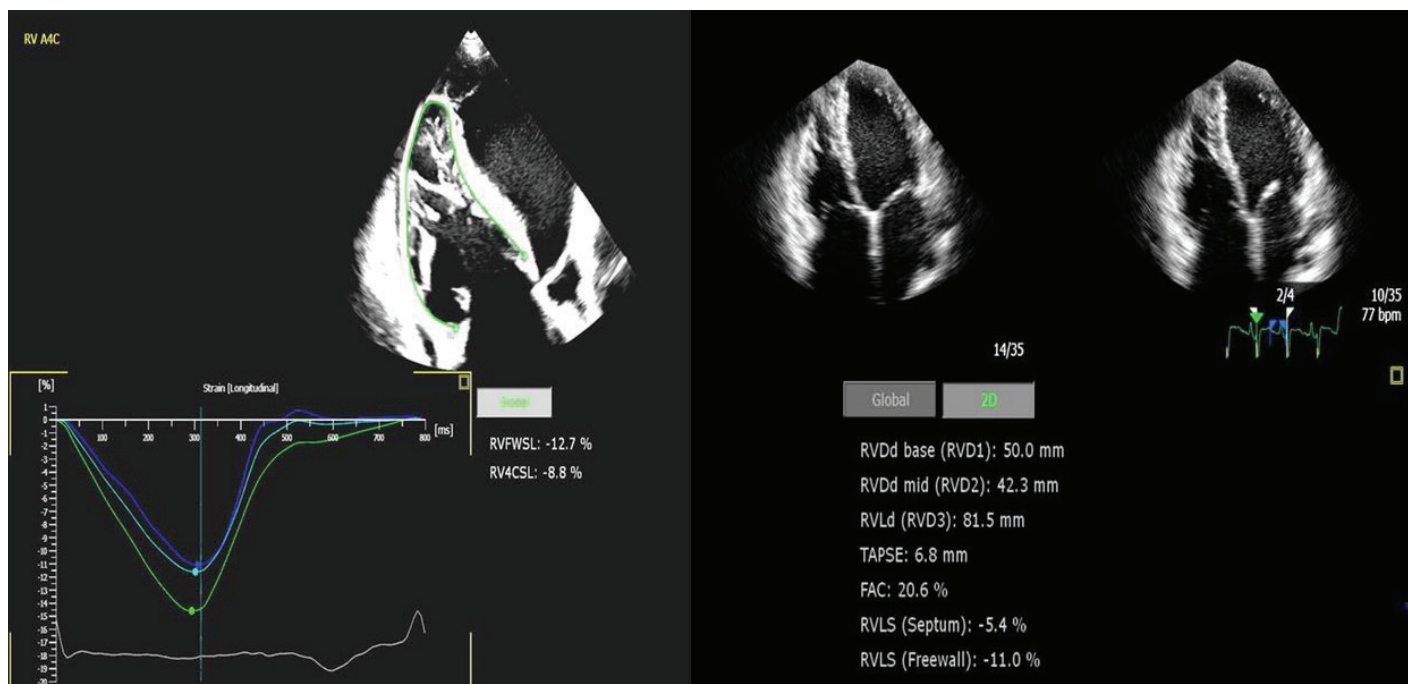


Figure 99. RV strain.

in five of the evaluated patients was excluded from the analysis due to inadequate acoustic windows.⁵⁸³

3D RV ejection fraction and RV volumes are considered the ideal method for determining RV systolic function (Figure 100, Video 18). However, this method is not widely available and poses technical challenges according to current guidelines. In one study, it was discovered that a RV end-systolic volume index of

47 ml/m² had a sensitivity of 83% and specificity of 93%, while a RV end-diastolic volume index of 61 ml/m² had a sensitivity of 92% and specificity of 79% in predicting postoperative RV failure.⁵⁸⁵

Tricuspid regurgitation (TR) severity is closely associated with RV failure following LVAD implantation. A study revealed that 75% of the patients with grade 3 or 4 TR developed RV failure, whereas

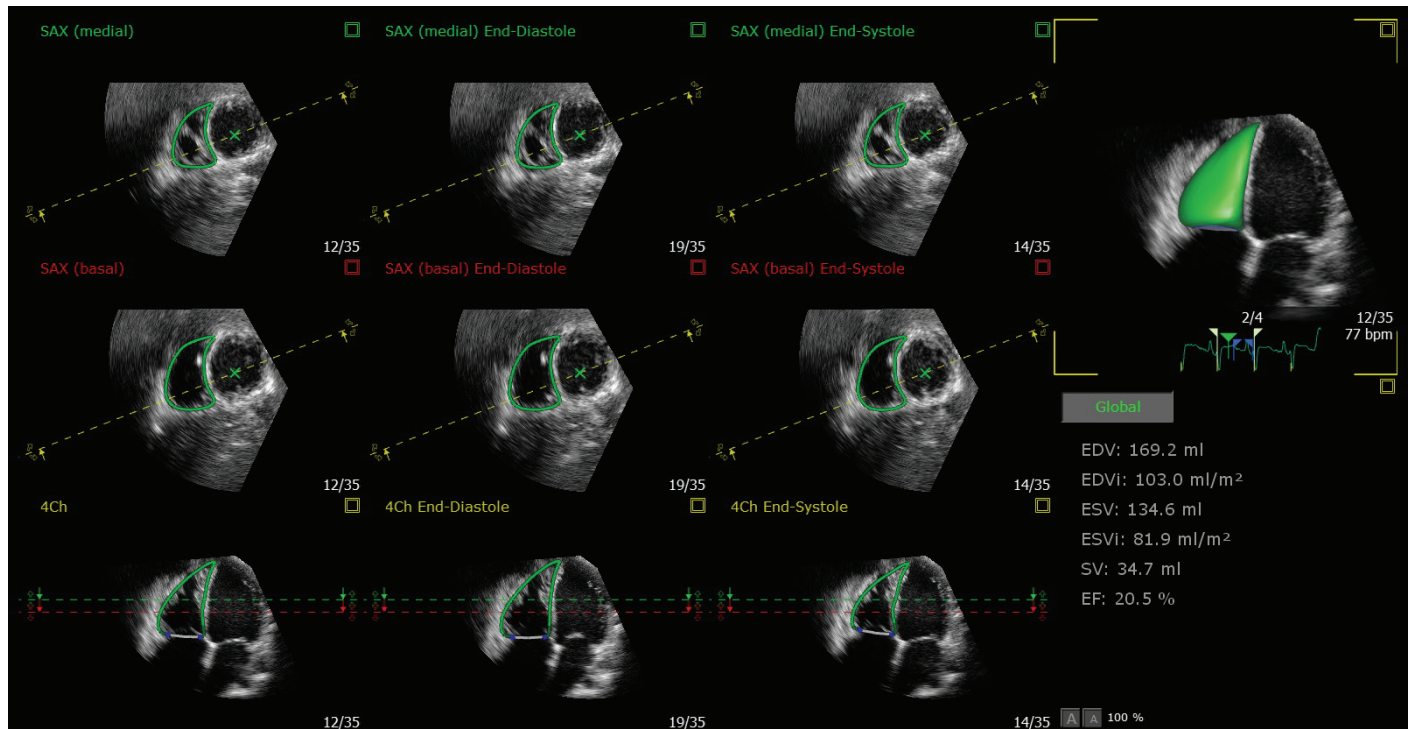


Figure 100. RV volumes and 3D-RVEF measurement.

only 12% of the patients with grade 0, 1, or 2 TR reached the endpoint. Patients with moderate or severe TR were nearly five times more likely to develop post-LVAD RV failure, highlighting the substantial impact of TR.⁵⁸⁶

Valve Diseases

Aortic stenosis (AS) presents a unique consideration in patients with advanced HF, particularly those with significantly reduced stroke volume. In such cases, relying solely on valve gradients may not accurately reflect the severity of AS. Interestingly, in patients undergoing LVAD implantation, severe AS might be well tolerated due to the ability of blood flow to bypass the aortic valve entirely. However, if obstructive LVAD dysfunction occurs in the presence of AS and cardiac output is solely dependent on the aortic valve, providing adequate cardiac output becomes challenging.⁵⁷²

Mitral stenosis, tricuspid stenosis and pulmonary stenosis: In patients with advanced HF, the measurement of mitral valve (MV) area using pressure half time (PHT) may be underestimated due to increased left ventricular end-diastolic pressure. In such cases, planimetric MV area measurement may offer a more accurate assessment. Additionally, moderate to severe stenosis of the mitral, tricuspid, and pulmonary valves can impede adequate inflow to the LVAD by decreasing left ventricular preload. Therefore, significant stenosis of these valves should be treated prior to LVAD implantation.⁵⁷²

Aortic regurgitation (AR) moderate or severe AR can often be underestimated due to poor color-flow Doppler images and slow AR velocities resulting from high left ventricular diastolic pressures and low systemic pressures. Additionally, despite a high regurgitant fraction, the AR volume may remain relatively low.

Suspensions of significant AR should be raised in cases of aortic root dilation, eccentric AR, calcific or rheumatic aortic valve degeneration, or the presence of a prosthetic aortic valve.

When TTE is inadequate, particularly in cases of eccentric or prosthetic regurgitation, TEE should be seriously considered. Prior to LVAD implantation, recent guidelines recommend perioperative TEE confirmation and surgical correction of AR greater than mild severity. Surgical options may include aortic valve replacement with a bioprosthesis, aortic valve patching, or a coaptation stitch at the center of the aortic cusps.⁵⁸⁷⁻⁵⁸⁹

Mitral regurgitation (MR) often sees significant improvement after LVAD support, attributable to decreased LV size, reduced filling pressures, and enhanced leaflet coaptation. Consequently, any degree of MR is generally deemed acceptable in LVAD candidates and it is not required surgical treatment.⁵⁷²

Tricuspid Regurgitation (TR) is commonly observed in patients with HF, and significant post-operative TR may contribute to RV dysfunction, leading to decreased LV preload and a low-output state. LVAD implantation introduces both beneficial and adverse effects on the severity of TR.

Factors that exacerbate TR after LVAD implantation include the leftward shift of the IVS, decreased RV function, and increased RV preload in an already compromised RV. Conversely, factors that mitigate or reduce TR include elevated RA pressure. In some cases, LVADs exert a favorable effect on TR by reducing LV and pulmonary artery pressures.

According to recent guidelines, considering surgical repair of the tricuspid valve at the time of LVAD implantation is recommended when significant TR is present.⁵⁶⁸

Table 32. Perioperative Echocardiographic Analysis

- Detection of air bubbles and de-airing prior to LVAD activation
- Inspection of the ascending and descending aorta using a midesophageal aortic valve long-axis view, and long- and short-axis views of the descending aorta
- Evaluate the location of the cannulas, anastomotic sites and LV apex
- LVAD flow and power interrogation

Pulmonary regurgitation (PR) in patients with advanced HF typically arises from elevated pulmonary vascular resistance. Moderate or severe PR in any patient may indicate preoperative RV dysfunction. In cases where RV function is adequate, PR may be well tolerated, especially with successful LV unloading achieved by LVAD.

However, if pulmonary vascular resistance increases for any reason following LVAD implantation, significant PR could potentially contribute to RV dysfunction.⁵⁷²

Evaluation of *prosthetic valves* with TTE and TEE when necessary is essential before surgery. Reduced flow through a mechanical aortic valve (AV) prosthesis inherently increases the risk of postoperative valve thrombosis and thromboembolic events following LVAD implantation. Therefore, even if the valve functions normally, replacing the mechanical valve with a bioprosthetic valve or performing valve closure during LVAD implantation is advisable.

Surgically replacing a normally functioning MV prosthesis (mechanical or bioprosthetic), even in the presence of significant MR, is generally not recommended, as the LVAD will increase forward transmitral flow. However, moderate or more prosthetic valve obstruction is a notable exception. In cases of moderate or more prosthetic valve obstruction during LVAD implantation, consideration should be given to MV replacement with a bioprosthesis.

Dysfunction of the tricuspid or pulmonary valve prosthesis is a significant finding as it may adversely affect postoperative RV function, and appropriate treatment should be pursued.⁵⁶⁸

Intracardiac Shunts

After LVAD implantation, left atrial (LA) pressure decreases as a result of LV unloading, while RA pressure increases, especially when RV dysfunction is present, due to heightened systemic venous return. In cases of cardiac shunts, these hemodynamic changes may lead to hypoxemia and paradoxical embolization.^{572,573}

Pre-LVAD echocardiography should thoroughly examine for a patent foramen ovale (PFO) or atrial septal defect (ASD), and elective repair during surgery is necessary to prevent complications. Diagnosis of PFO may pose challenges in intubated, uncooperative patients with respiratory distress. TEE with agitated saline and Valsalva maneuver, along with color flow Doppler, represents a highly sensitive and specific method for detecting PFO. However, elevated biatrial pressure in cases with biventricular failure can diminish or eliminate any gradient, rendering it difficult to identify PFOs using agitated saline and color-flow imaging.^{568,590}

Similar to interatrial shunts, ventricular septal defects (VSDs) can lead to hypoxemia and right-to-left shunting shortly after implantation, posing a risk of paradoxical embolization

during LVAD support. If detected, VSDs should be closed at the time of LVAD implantation, as they are typically an absolute contraindication to device implantation.⁵⁷²

Intracardiac Thrombus

A severely reduced LVEF and the presence of an apical aneurysm/akinesis elevate the risk of developing an apical thrombus at the site of inflow cannula insertion. While an intracardiac thrombus may increase the risk of stroke during LV inflow cannula insertion, it is not an absolute contraindication for LVAD implantation. Therefore, the presence of a LV thrombus must be assessed both before and after the procedure. TTE may have a higher screening yield than TEE in identifying LV apical thrombi. To enhance sensitivity during thrombus assessment, the use of intravenous microbubble contrast injection is strongly recommended.^{572,573}

Perioperative Echocardiography–Intraoperative and Early Postoperative Period

Perioperative TEE is an invaluable tool for evaluation both during LVAD implantation and after implantation. All images acquired following LVAD activation should be analyzed with the device name and the current pump speed. After implantation, it is imperative to check for adequate de-airing of the LV and the device, the location of the inflow and outflow cannulas, native valvular function, LV unloading, septal shift, RV function, the presence of shunts previously undetected by echocardiography and complications (Table 32).

Continuous TEE guidance is essential for subsequent de-airing maneuvers. Direct visualization and careful examination for signs of air should be conducted on the LA, LV (including the LV apex and inflow cannula), aortic root, ascending aorta, outflow graft-to-ascending aorta anastomosis, transverse, and descending aorta. Air exiting the LV often accumulates at the ostium of the right coronary artery (RCA). Suspected air embolization to the RCA may manifest as acute RV dysfunction or dilatation, and/or an exacerbation of TR severity.^{573,591}

Midesophageal (ME) four-chamber and two-chamber views assist in aligning the inflow cannula with the LV inlet and identify obstructions from IVS or side walls (Figure 101, Video 19). A color flow Doppler should be applied to the inflow cannula to visualize laminar blood flow through the cannula. When inflow cannula velocities exceed 1.5 m/s, a thorough examination of the insertion site, preferably using 3D echocardiography, is necessary to rule out potential tissue obstruction.

The outflow graft anastomosis and flow through the outflow graft into the ascending aorta are best visualized in the ME ascending aorta short or long axis, as well as upper esophageal views (Figure 102, Video 20). High velocities (>2.0 m/s) may indicate obstruction in the outflow graft.^{573,577}

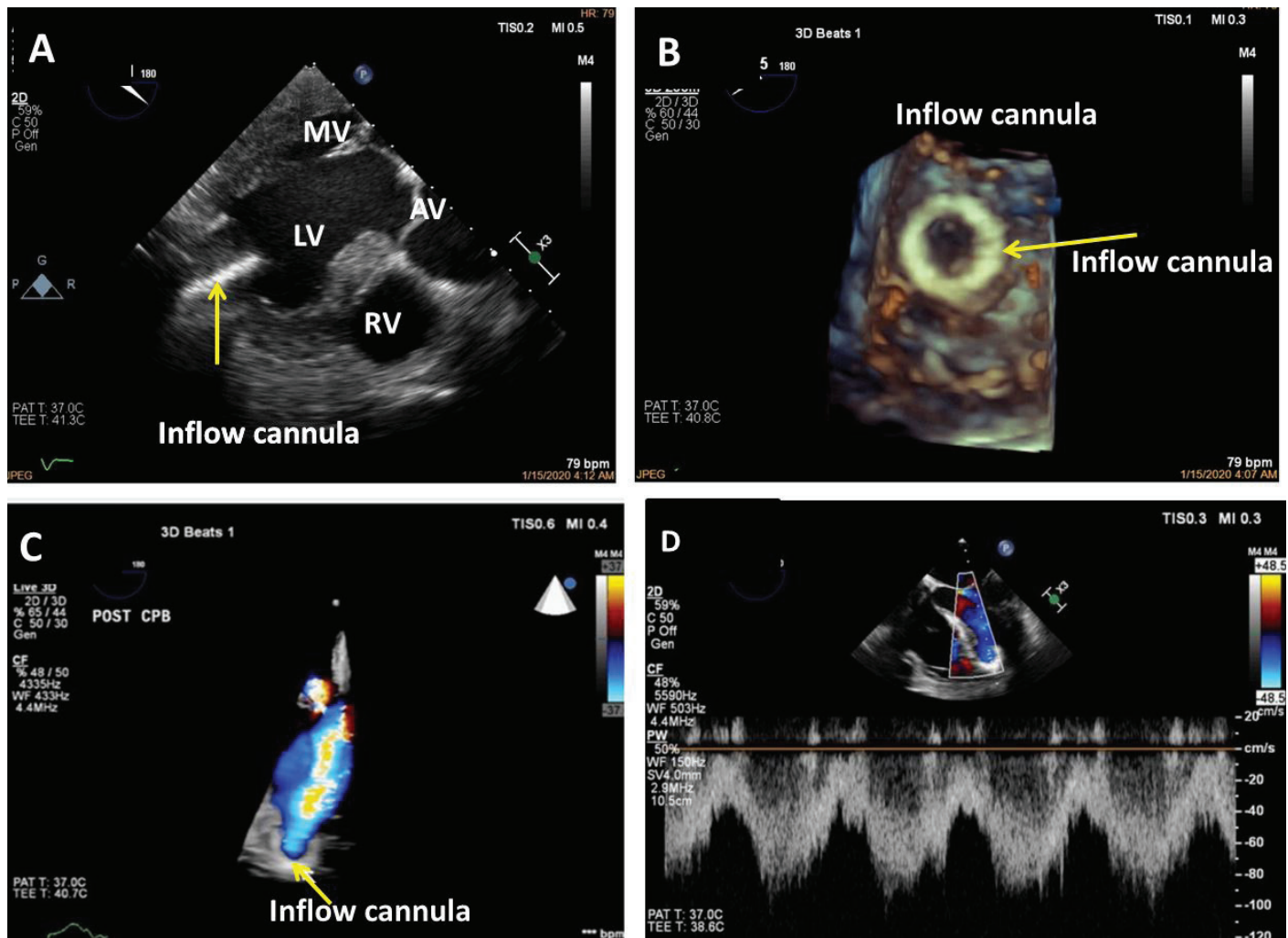


Figure 101. Inflow cannula; (A): Position; (B): 3D imaging; (C): color Doppler; (D): spectral Doppler of inflow cannula. AV; aortic valve, MV; mitral valve, LA; left atrium, LV; left ventricle.

When the LVAD is activated, the size of each chamber should decrease as the LV and LA are unloaded (Video 21, Video 22). Gradually increasing the LVAD speed requires regular examination of cardiac sizes and structures to optimize the LVAD speed. The appropriate LVAD speed should effectively unload the ventricle without causing suction, allow intermittent opening of the aortic valve, and maintain the average blood pressure between 60 and 85 mmHg.⁵⁷²

With adequate unloading of the LV and LA, the IVS and interatrial septum (IAS) may deviate slightly to the left. However, the lack of unloading following LVAD implantation, combined with rightward septum shifting, increases the likelihood of suboptimal LVAD support, abnormal device function, or outflow cannula occlusion. The presence of spontaneous echocardiographic contrast in the LV or LA can also indicate LVAD malfunction.⁵⁷²

In patients with high LVAD speed rates, excessive leftward septum shift may lead to "suction" (Figure 103, Video 23, and Video 24). Additionally, besides high speed, 'suction' can be caused by decreased LV preload due to hypovolemia, right ventricular failure, and severe TR. Moreover, suction itself can induce severe RV failure and exacerbate TR.

If suction is observed, the pump speed, LV and RV dimensions, AV opening, TR, flow velocities, and inflow cannula location should be checked. It is crucial that pump speed is constantly updated and monitored during perioperative TEE examination. Suction events can be promptly addressed by reducing pump speed to improve RV function and diminish TR (Figure 103, Video 24).

A suction event occurring at a relatively low pump rate (indicating severe RV dysfunction) is concerning and may necessitate biventricular support (Figure 103, Video 25).⁵⁹²⁻⁵⁹⁴

Both RV function and the severity of TR must undergo careful evaluation. The same guidelines can be utilized to assess pre- and post-LVAD RV function, as well as TR.

In cases of acute severe RV failure, the RV will undergo significant dilation, accompanied by severe TR and LV suction (Video 23). During acute heart failure episodes, fluid therapy should be increased, vasodilators should be discontinued, and the LVAD speed should be reduced (Video 24). However, if RV failure persists despite these interventions, right ventricular assist devices should be considered (Video 25).^{568,579}

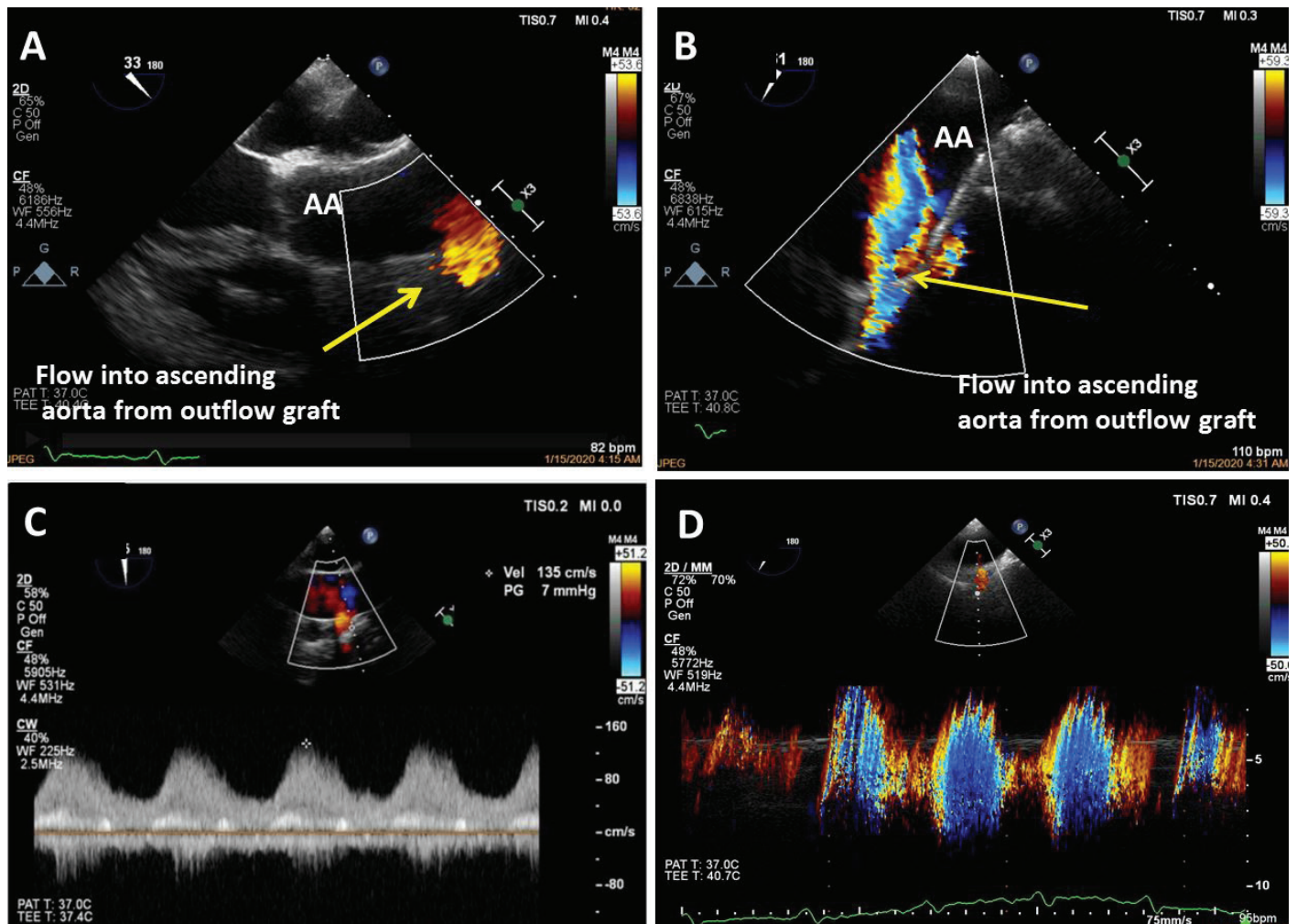


Figure 102. Color Doppler and spectral Doppler flow of outflow cannula. AA, Ascending aorta.

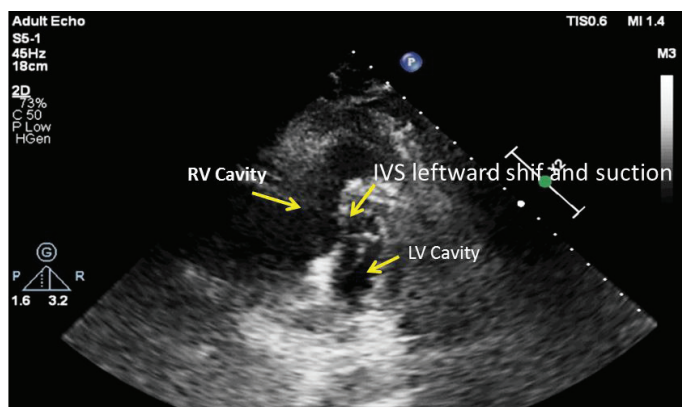


Figure 103. LV suction because of RV failure. IVS, interventricular septum; LV, left ventricle; RV, right ventricle.

Depending on the level of LVAD support (pump speed), AV opening may vary significantly or occur only intermittently in many cases. Due to pulsus alternans observed in LVAD patients, the AV may open intermittently when residual native left ventricular outflow tract (LVOT) flow is present. Conversely, the AV may not open at all when LV unloading is excessive (Video 26).

In cases of insufficient LV unloading, the AV may open during every cycle. Ideally, it should open every 3-4 cycles, and efforts should be made to adjust the pump speed accordingly to achieve this frequency as much as possible. The degree of AV opening can be assessed by M-mode evaluation of the AV from the long-axis window.^{572,573}

TEE evaluation for PFO following ventricular assist device VAD implantation should be conducted (if not previously determined) before weaning off cardiopulmonary bypass. Additionally, intraoperative examination should include assessment of the great vessels, valvular function, and potential iatrogenic complications such as aortic dissection or tamponade.

Longterm Follow-up Echocardiography

After device implantation, LVAD surveillance echocardiography should be scheduled approximately 2 weeks after the patient is stabilized. This stabilization entails the absence of heart failure symptoms, successful weaning from intravenous pharmacologic inotropic and vasopressor agents within days, absence of LVAD controller alarms, and no serologic evidence of hemolysis or infection. Alternatively, the surveillance echo can be conducted

Table 33. Post-operative and Follow-up Echocardiography

- Left ventricle and right ventricle chamber Dimensions of left ventricle and right ventricle chambers
- Left ventricle and right ventricle systolic function
- Left atrial volume, dimensions of mitral annulus, geometry of the leaflets and papillary muscles, and degree of mitral regurgitation
- Degree of tricuspid regurgitation, tricuspid valve annulus dimension, and pulmonary artery systolic pressure
- Aortic valve morphology, assessing for the opening of the valve, degree of aortic regurgitation, and size of the ascending aorta
- Evaluate for thrombus, particularly surrounding the inlet cannula
- Shunts
- Inflow cannula location, colour-flow pattern, and Doppler analysis assessing for laminar flow and normal velocities
- Outflow cannula location, colour-flow pattern, and Doppler analysis assessing for laminar flow and normal velocities
- Interventricular septal location and aortic valve opening assessing the adequacy of the LVAD function
- LVAD interrogation of flow and power

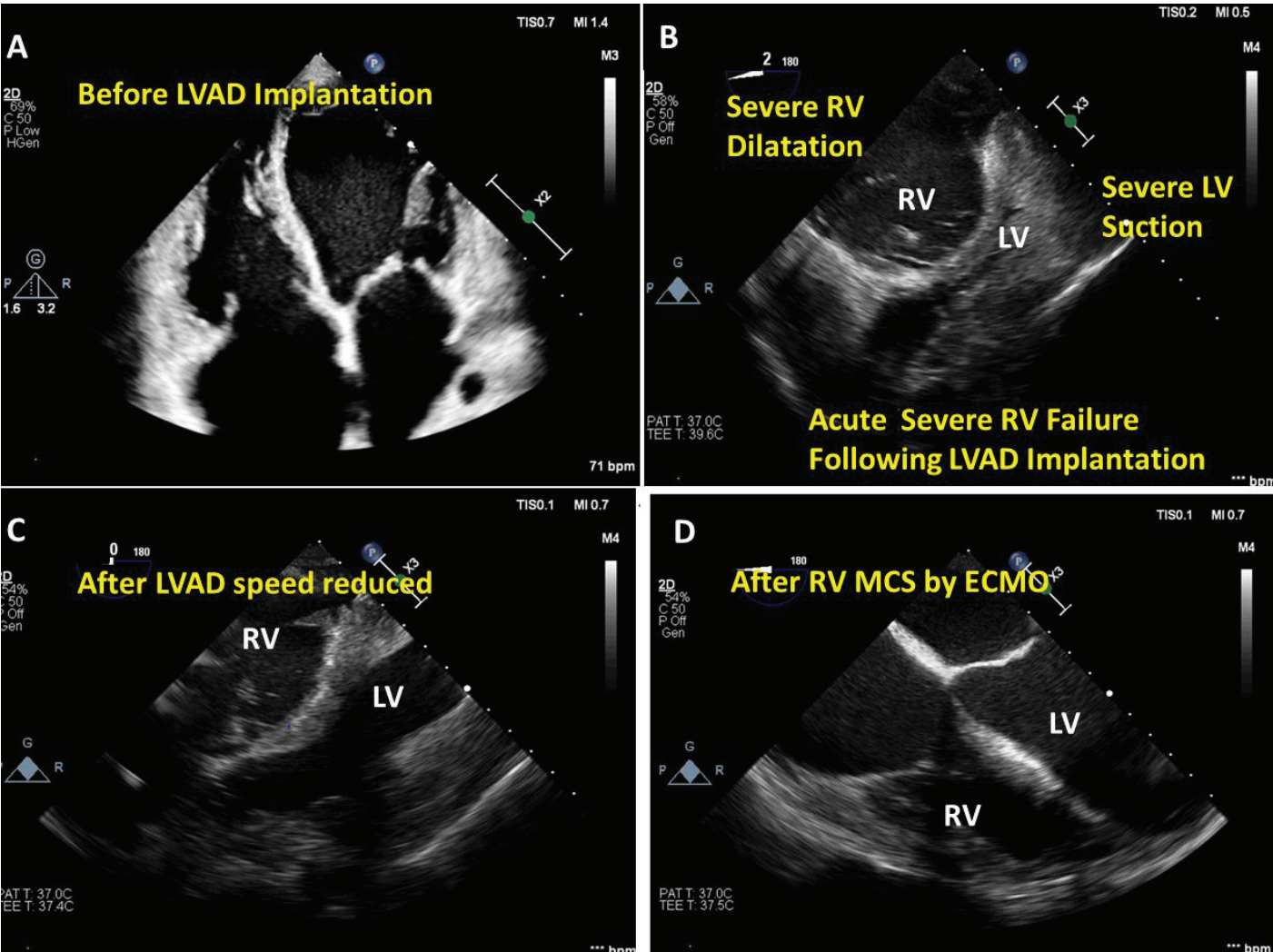


Figure 104. RV failure after LVAD implantation; (A): Before LVAD implantation; (B): acute RV failure after implantation and severe LV 'suction', (C): after LVAD speed decreased; (D): after ECMO support. ECMO, extracorporeal membrane oxygenation; LV, left ventricle; LVAD, left ventricular assist device; RV, right ventricle.

before discharge, whichever comes first. Subsequently, surveillance TTE should be planned for 1, 3, 6, and 12 months after implantation, with follow-up appointments scheduled every 6 to 12 months thereafter.⁵⁷²

Follow-up TTE serves two primary purposes: (i) conducting a comprehensive routine assessment of optimal LVAD function;

and (ii) evaluating potential causes of recurrent HF. Key variables to closely assess during follow-up TTE include the status of AV opening, degree of AR, LVAD setting in relation to hemodynamic findings, RV function and TR, as well as the position and flow of the inflow and outflow cannulas. Additionally, the structure and function of the left heart chambers and IVS position should be carefully evaluated (Table 33).

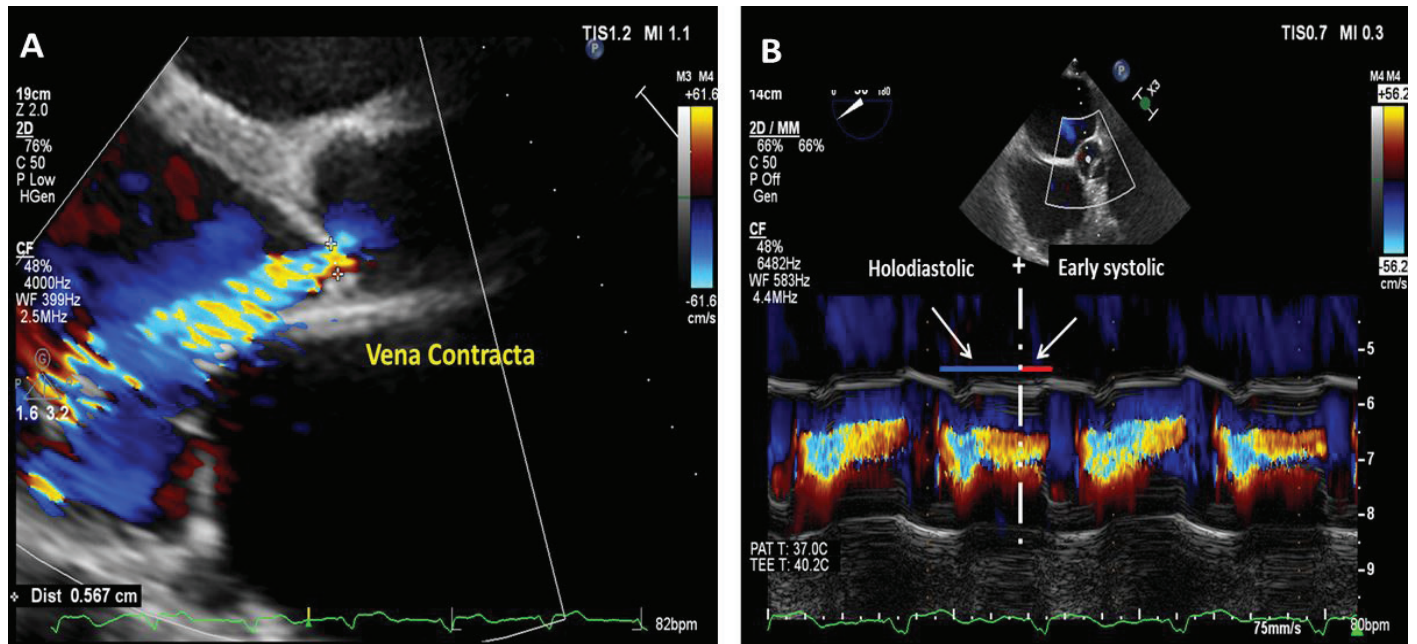


Figure 105. Aortic regurgitation (A): vena contracta; (B): Colour M mode duration of aortic regurgitation (holodiastolic and early-systolic).

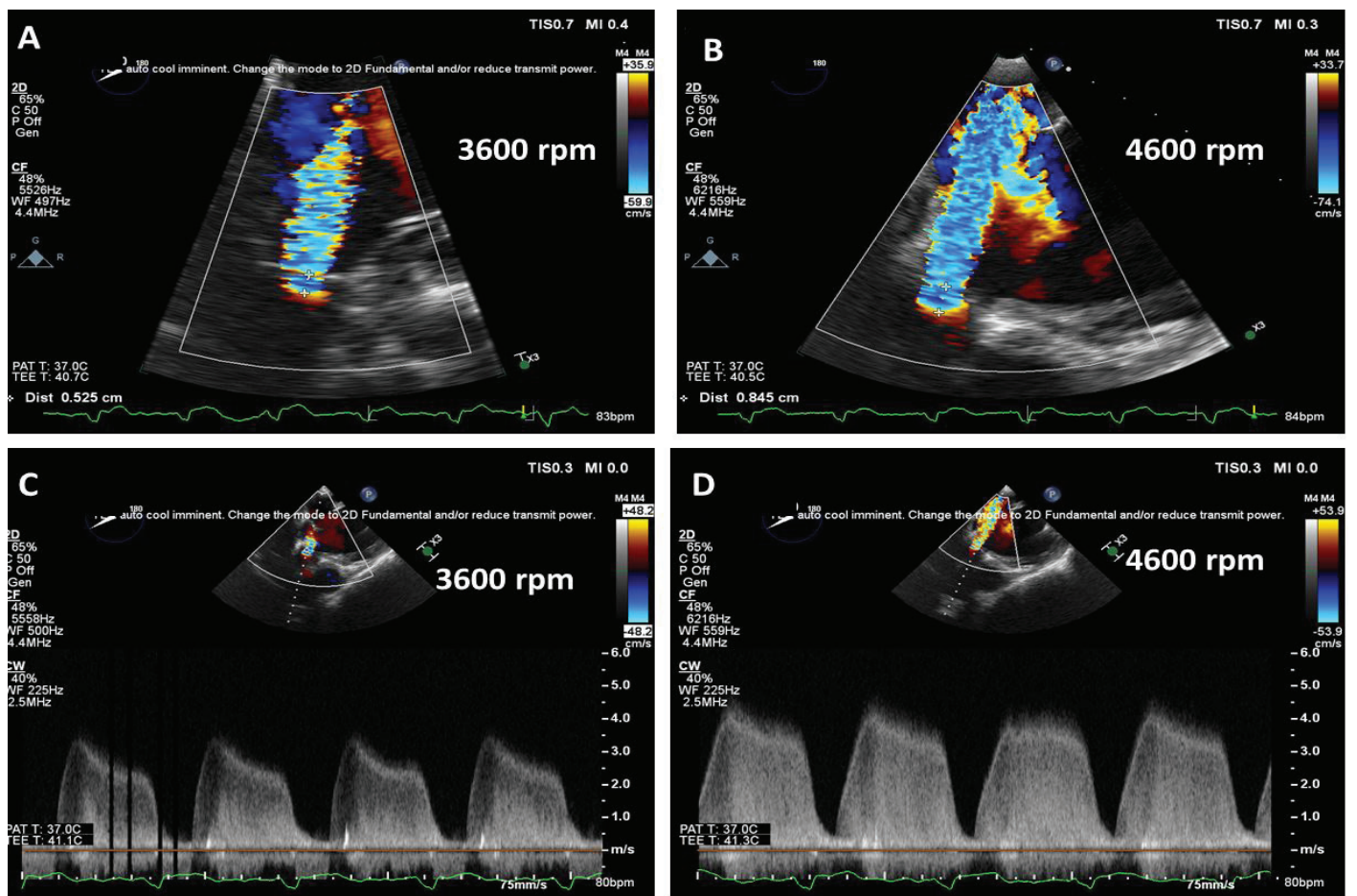


Figure 106. Increases in aortic regurgitation with LVAD speed increased (A): PISA of AR at 3600 rpm; (B): PISA of AR at 4600 rpm; (C): Continuous Doppler of AR at 3600 rpm; (D) Continuous Doppler of AR at 4600 rpm. AR, aortic regurgitation; LVAD, left ventricular assist device; PISA, proximal isovelocity surface area.

Function of Left Heart Chambers

To assess intrinsic LV function, measurements of the LVEF, LVEDd, and ejection period divided by ejection time should be conducted.^{573,595}

Due to left ventricular unloading, there should be a reduction in the dimensions of the LV cavity at the end of diastole and systole. An increase in dimensions should raise concerns about a possible malfunction. The LVEDd from the 2D parasternal long-axis image is considered the most reproducible measure of LV size following LVAD implantation. A decrease of at least 15% in the LVEDd relative to pre-implantation values can be anticipated 3 months following implantation.⁵⁹⁶

It is noteworthy that the finding of the LVEDd being paradoxically smaller than the LV end-systolic diameter (LVESd) is significant, as it may be indicative of either severe RV dysfunction or excessive LVAD unloading. Although LV volumes measured by Simpson's biplane or uniplane method more accurately represent LV size than linear measurements, technical difficulties may arise following LVAD implantation due to apical shadowing and inflow cannula-related dropout.⁵⁷²

After LVAD implantation, measurements of LVEF face both physiological and technical limitations. Challenges arise due to issues such as image quality and difficulties in delineating the endocardial border, often caused by apical foreshortening, apical shadowing from the device, or acoustic dropout (signal attenuation). Moreover, the LVEF may not accurately reflect LV function due to the non-physiological unloading imposed by the LVAD. Calculating LVEF, especially for assessing myocardial recovery, necessitates a temporary interruption of LVAD support.⁵⁹⁵

The preferred method for calculating LVEF is the biplane modified Simpson method, particularly in patients with optimal apical views. FAC of the LV and fractional shortening methods can serve as potential measures of LV systolic function in patients with suboptimal apical views that still offer adequate parasternal views; however, their accuracy in LVAD patients has not been conclusively confirmed. It is not recommended to use LVEF calculated by LV stroke volume, as many LVAD patients exhibit beat-to-beat variations in this parameter.⁵⁷²

Right Ventricular Size and Systolic Function

Measuring common metrics for RV size and systolic function in LVAD patients is feasible. These metrics include linear dimensions, RV FAC, TAPSE, and right-sided cardiac output.

Aortic Valve Opening and Aortic Regurgitation

The extent of AV opening indicates the flow through the native circuit. Lowering LVAD rpms can help maintain AV opening. The objective of LVAD programming should be to find an optimal balance between AV opening and providing adequate physiological support via the LVAD. Persistent AV closure may increase the risk of developing AR. Recent guidelines suggest adjusting the LVAD speed to ensure at least intermittent AV opening. The extent of AV opening can be assessed and documented using M-mode imaging of the AV in the long-axis view.

De novo AR is a common complication following permanent LVAD implantation, affecting 25% to 30% of patients within the first-year after-implantation.^{597,598} Reduced AV opening, local stasis, high shear stress, inversion of transvalvular gradient, thrombosis, fibrosis, and retraction or fusion of aortic cusps are among the factors contributing to AR. Calcification of the AV and eccentric regurgitant flow may also occur. Moderate or severe AR leads to the recirculation of antegrade blood flow from the aorta to the LV and compromises cardiac output. The severity of aortic regurgitation (AR) is highly dependent on the global hemodynamic status, including LV preload, residual LV contractility, and heart rate.⁵⁷²

In the continuous-flow LVAD condition, AR occurs throughout the cardiac cycle, predominantly during diastole (Figure 104). Traditional TTE parameters underestimate the severity of AR due to its continuous flow. Quantitative TTE parameters such as PHT, proximal isovelocity surface area, and diastolic flow reversal are inaccurate, and vena contracta (VC) measurements can underestimate AR. A VC width of 0.3 cm or a jet width/LVOT width ratio > 45 should indicate at least moderate (and possibly severe) AR due to the prolonged duration of AR during LVAD support (Figure 105).⁵⁷² High LVAD speeds exacerbate the severity of AR (Figure 106).

Novel echocardiographic parameters have been proposed to enhance the accuracy of AR assessment with continuous-flow LVADs. Diastolic acceleration of the outflow cannula is directly proportional to the severity of AR, and the peak systolic-to-diastolic (S/D) velocity ratio of the outflow cannula is inversely related to AR severity. Compared to conventional criteria, these innovative parameters demonstrate better correlation with LV filling pressures and AR fraction. A S/D ratio of <5.0 or a diastolic acceleration of >49.0 cm/s² indicates moderate to severe AR.⁵⁹⁹

The Position of Interventricular Septum

The interventricular pressure gradient plays a crucial role in determining the end-diastolic position of the IVS, which should be regularly assessed and reported as neutral, leftward-shifted, or rightward-shifted. Various factors can influence the position of the IVS.

Excessive LVAD speed, reduced LV preload, or elevated RV end-diastolic pressures can lead to leftward shifting due to LV over-decompression. Conversely, increased LV afterload, severe AR, malfunctioning pump, or inadequate LVAD speed setting can elevate LV end-diastolic pressures, resulting in a rightward shift. Regular monitoring of the IVS position is essential for optimizing LVAD support and preventing adverse outcomes.⁵⁷³

Functions of Inflow and Outflow Cannulas

High-velocity color Doppler or high-velocity spectral Doppler (>1.5 m/s) at the inflow orifice may indicate cannula misalignment, suction, or other inflow obstructions.⁵⁷³

Conversely, *low-velocity inflow* could suggest internal inflow-cannula thrombosis or a more distal obstruction in the system. In such cases, the Doppler flow velocity profile may exhibit a relatively "continuous" pattern with reduced phasic or pulsatile characteristics.⁵⁷³

High outflow-graft velocity typically indicates an obstruction or pump malfunction, such as a visible kink or thrombus. If the sample volume is close to the obstruction site, the peak outflow-graft velocity may exceed 2 m/s. However, if the sample volume is distant from the obstruction site, the spectral Doppler signal may be diminished or absent. In patients suffering from end-stage heart failure (HF), heart transplantation stands out as the gold standard therapy.⁵⁷³

Assessment of Recurrent HF Associated with LVAD Dysfunction

In general, LVAD malfunctions can be categorized into three main types: (i) low pump flow with increased power, (ii) low pump flow with normal power, and (iii) high pump flow with low cardiac output.

Low pump flow with increased power is typically attributed to heightened afterload. This condition may arise due to thrombosis or mechanical malfunction within the pump. Echocardiographic assessments often reveal a rightward deviation of the IVS, functional MR, and aortic valve opening in every cardiac cycle. Additionally, the presence of spontaneous echocardiographic contrast in the LV and/or LA, along with regurgitant flow through both cannulas, may be observed. It is crucial to differentiate between LVAD thrombosis or malfunction, as emergency pump replacement surgery may be necessary. When encountering a decreased or absent Doppler signal in the outflow cannula, considerations should include potential outflow cannula obstruction and increased afterload.^{600,601}

Low pump flow with normal power typically results from a diminished LVAD preload, which may arise due to conditions

such as RV failure, significant TR, or hypovolemia. Additionally, the possibility of an inflow cannula obstruction should be considered in such cases.⁵⁷³

In instances of *high pump flow coupled with low cardiac output*, a discrepancy between the total cardiac output and the LVAD output may suggest the occurrence of "futile cycles." This discrepancy could potentially indicate the presence of significant underlying AR.⁵⁷³

Summary

In patients for whom a LVAD is planned, appropriate candidate selection is the most crucial factor in determining long-term morbidity and mortality. The echocardiography is the most important and first-line imaging modality in preoperative evaluation for candidacy, guidance during LVAD insertion, detection of complications, and long-term monitoring.

Video 17. 3D LV volumes

Video 18. 3D RV volumes

Video 19. Inflow cannula position and flow

Video 20. Outflow graft flow to ascending aorta derived from upper esophageal window

Video 21. LV unloading

Video 22. LA unloading

Video 23. Acute RV failure –severe suction

Video 24. RV failure –after LVAD speed reduced

Video 25. RV failure–after ECMO implantation

Video 26. No AV opening

Imaging in Ischemic Cardiomyopathy

Coronary artery disease is one of the leading causes of death and mortality worldwide.⁶⁰² Ischemic cardiomyopathy, the most common heart disease defined by impaired pump functions of the heart due to myocardial damage caused by ischemia, is associated with reduced blood flow in the coronary arteries due to plaque formation in coronary artery disease (CAD).⁶⁰³ The definition of ischemic cardiomyopathy (ICM) varies in the literature, characterized as a severe decrease in left ventricular function with an ejection fraction (EF) below 35% in the presence of severe CAD, and in another as an EF below 50%.⁶⁰⁴

Ischemic cardiomyopathy includes clinical conditions ranging from myocardial ischemia and myocardial infarction to heart failure. The pathophysiological substrate of ICM is variable, ranging from hibernating myocardium to irreversible scar tissue. Hibernating myocardium refers to the temporary inactivity of the heart muscle due to insufficient oxygen supply for a specific period, with the potential for recovery of function. In this case, the heart muscle can return to normal function with appropriate treatment and restored blood flow.

Various diagnostic tests use alternative definitions to assess the presence of hibernating myocardium. These definitions differ, providing information about different aspects of the pathophysiology, such as various imaging techniques, metabolic imaging, scar imaging, or contractile reserve. Consequently, the outcomes of these tests may vary depending on the specific imaging technique selected for evaluation. It is important to consider the strengths and weaknesses of each imaging method in the diagnosis of myocardial hibernation.

Various imaging techniques, such as echocardiography (ECHO), single-photon emission computed tomography (SPECT), positron emission tomography (PET), coronary computed tomography angiography (CCTA), and cardiac magnetic resonance (CMR), can be used to obtain information about coronary anatomy, myocardial ischemia, myocardial perfusion, and tissue characterization.⁶⁰⁵ The preferred imaging method for confirming the diagnosis of acute and chronic coronary artery disease and determining treatment depends on the clinical condition, patient characteristics, local suitability in the clinic, and expertise.

This review aims to provide guidance on selecting the most appropriate imaging approach for individual patients.

Echocardiography

For all patients with suspected chronic coronary syndrome, a resting transthoracic echocardiogram (TTE) is recommended for evaluating wall motion and structural abnormalities.⁶⁰² Echocardiography is used to detect various aspects of CAD, such as wall motion abnormalities (WMA), impaired contractile response, microvascular perfusion, or flow in epicardial arteries during both resting and stress conditions induced by exercise or inotropic/vasodilator agents.

Imaging based on the assessment of myocardial perfusion is more sensitive in detecting ischemia, whereas imaging based on evaluating wall motion abnormalities has higher specificity.⁶⁰⁵ Echocardiography is a widely used and easily accessible method that provides multidirectional and clinically significant parameters such as ventricular volumes, ejection fraction, assessment of ischemia-

related valve insufficiencies, thrombus evaluation, evaluation of wall motion defects with stress ECHO, and assessment of cardiac function with strain imaging.

Global systolic function is commonly assessed through the measurement of left ventricular ejection fraction (LVEF), which can be quantified using two-dimensional (2D) or three-dimensional (3D) echocardiography. LVEF is a significant predictor for heart failure, arrhythmias, hospitalization, and mortality. It is utilized in determining treatment strategies and the need for an implantable cardioverter-defibrillator (ICD) for primary prophylaxis.^{537,606} Additionally, cardiac volumes have diagnostic and prognostic importance independent of EF. Left ventricular dilatation is associated with a poor prognosis.⁶⁰⁷

Recommended methods for evaluating left ventricular volumes and functions include the modified biplane Simpson method, the area-length method, and 3D echocardiography. The modified biplane Simpson method is the most widely used, where EF is calculated from left ventricular end-diastolic and end-systolic volumes derived from apical four- and two-chamber views.^{2,3} In cases of good image quality, 3D echocardiography provides volumes with higher accuracy compared to two-dimensional methods and similar values to CMR.^{3,608}

In addition to assessing global left ventricular function, regional systolic function should also be evaluated. Regional systolic function is typically assessed through visual interpretation of wall thickening. Ischemic cardiomyopathy frequently presents with segmental wall motion abnormalities. Although a 17-segment model is recommended for evaluating left ventricular segmental functions, a 16-segment model is commonly used in clinical practice due to challenges in assessing the thickening of the apex.

In ischemic cardiomyopathy, resting echocardiography may categorize segments as: 1) normal or hyperkinetic, 2) hypokinetic, 3) akinetic, and 4) dyskinetic-aneurysmal. A resting end-diastolic wall thickness of less than 6 mm reflects scar tissue with a low likelihood of recovery, and these regions are unlikely to regain function after revascularization.^{2,3,608,609} During rest, in cases of severe coronary stenosis or collateral dependency, hypokinesia and even akinesia may only occur in the endocardial part of the myocardium due to hypoperfusion. Akinesia or dyskinesia

during rest may be associated with transmural flow reduction or a previous myocardial infarction.⁶⁰²

In patients with ICM who have an implanted ICD for primary prevention, the tissue Doppler imaging (TDI) velocity (a') can provide valuable prognostic information regarding the likelihood of experiencing ventricular tachycardia, ventricular fibrillation, and cardiovascular mortality.⁶¹⁰

Left ventricular thrombi may develop in ischemic cardiomyopathy, which may lead to embolic events. Echocardiography is used to evaluate the presence of thrombus, but in challenging acoustic conditions or when there is suspicion, contrast echocardiography (contrast ECHO) is a useful option. Contrast ECHO also aids in the assessment of wall motion abnormalities where standard echocardiographic images are limited. Figure 107 illustrates the visualization of left ventricular thrombus using various modalities.

Myocardial contrast echocardiography is a non-invasive imaging method used to assess myocardial perfusion. In cases where visualizing two or more adjacent segments is challenging during rest or stress, the recommended approach involves utilizing approved ultrasound contrast agents (UCAs), specifically ultrasound contrast or microbubbles. This method has demonstrated superiority over SPECT in assessing hibernating myocardium and predicting functional recovery in patients with ischemic cardiomyopathy.⁶¹¹

Strain and strain rate are also recommended as supplementary parameters to EF for assessing left ventricular functions.² Myocardial strain is based on calculating the fractional change in deformation of the myocardium throughout the cardiac cycle, and the rate of this change is defined as the strain rate. This deformation occurs longitudinally, circumferentially, and radially, with longitudinal strain being dominant during systole. Global longitudinal strain (GLS) is the most sensitive parameter, particularly in ischemic cardiomyopathy, where endocardial ischemia is more pronounced, making GLS one of the earliest affected parameters.⁶¹²

The literature provides comprehensive data on GLS, leading to its incorporation into clinical practice.⁶¹³ Studies have shown that GLS is more beneficial than EF in identifying coronary artery

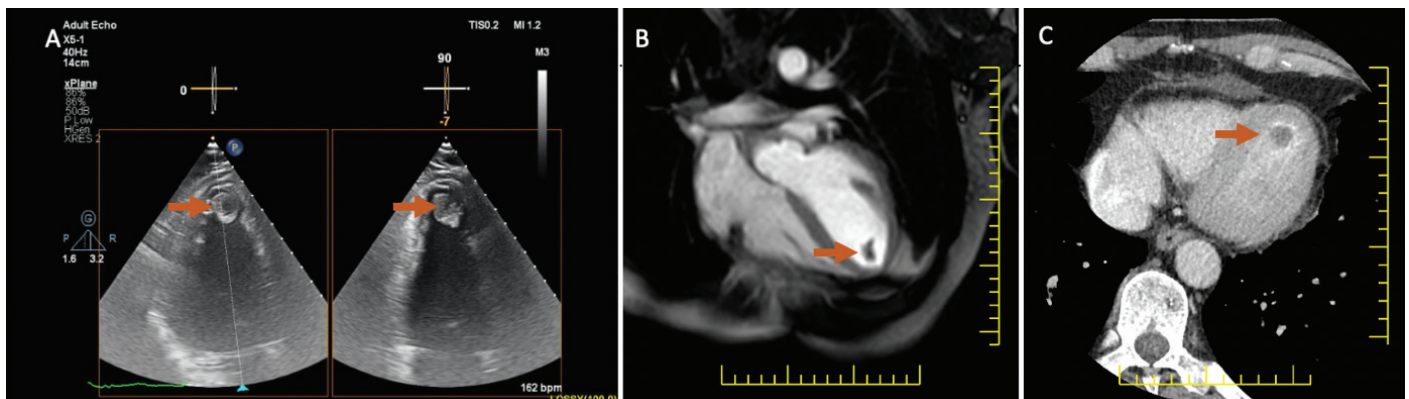


Figure 107. Demonstration of the akinetic and thinned segment with a thrombus at the apex of the left ventricle in a patient with ischemic cardiomyopathy using echocardiography (A), cardiac magnetic resonance (B), and coronary computed tomography (C).

disease in patients and is also associated with adverse outcomes such as mortality and heart failure.^{614,615} According to a meta-analysis of 24 studies, the average normal range for GLS was reported as -19.7% (with a 95% confidence interval of -20.4% to -18.9%).⁶¹⁶ Although clear thresholds are not specified in the guidelines, values above -20% are generally considered normal.³ The normal range for strain rate is reported to be between 1/second and 4/second.⁶¹³

In a study focusing on circumferential strain (CS), evidence has shown that CS may be a better determinant of cardiac events compared to EF, total myocardial scar determined by CMR, and GLS.⁶¹⁷ While strain is influenced by preload and afterload, strain rate is less affected.⁶¹³ Additionally, it should be noted that strain values can be influenced by test variability, technical factors, and clinical factors specific to the patient. In light of the available data, the assessment of strain alone does not seem sufficient for evaluating left ventricular function, but it is believed to be beneficial when used in conjunction with parameters like EF.

Illustrative echocardiography images associated with ischemic cardiomyopathy are presented in Figure 108.

Pharmacological/exercise stress echocardiography is recommended for the diagnosis of CAD by both American and European guidelines.^{603,618} It offers significant advantages such as easy accessibility, low cost, and radiation-free imaging. Unlike modalities that assess myocardial ischemia or perfusion, it identifies wall motion abnormalities, providing a distinct approach to diagnosis. This type of stress echocardiography can be performed using either physical or pharmacological agents.

The criteria for an abnormal response are not restricted solely to abnormal contraction; it is also crucial if a segment fails to demonstrate an appropriate increase in contractility during the stress response. Patients capable of exercise should undergo an exercise stress test, representing a genuine physiological response. Exercise stress provides more prognostic information than pharmacological stress, considering factors such as electrocardiogram results, exercise capacity, the time to symptoms, and blood pressure response. Pharmacological stress echocardiography is generally preferred for patients unable to exercise or in specific clinical conditions including the presence of left bundle branch block.⁶⁰²

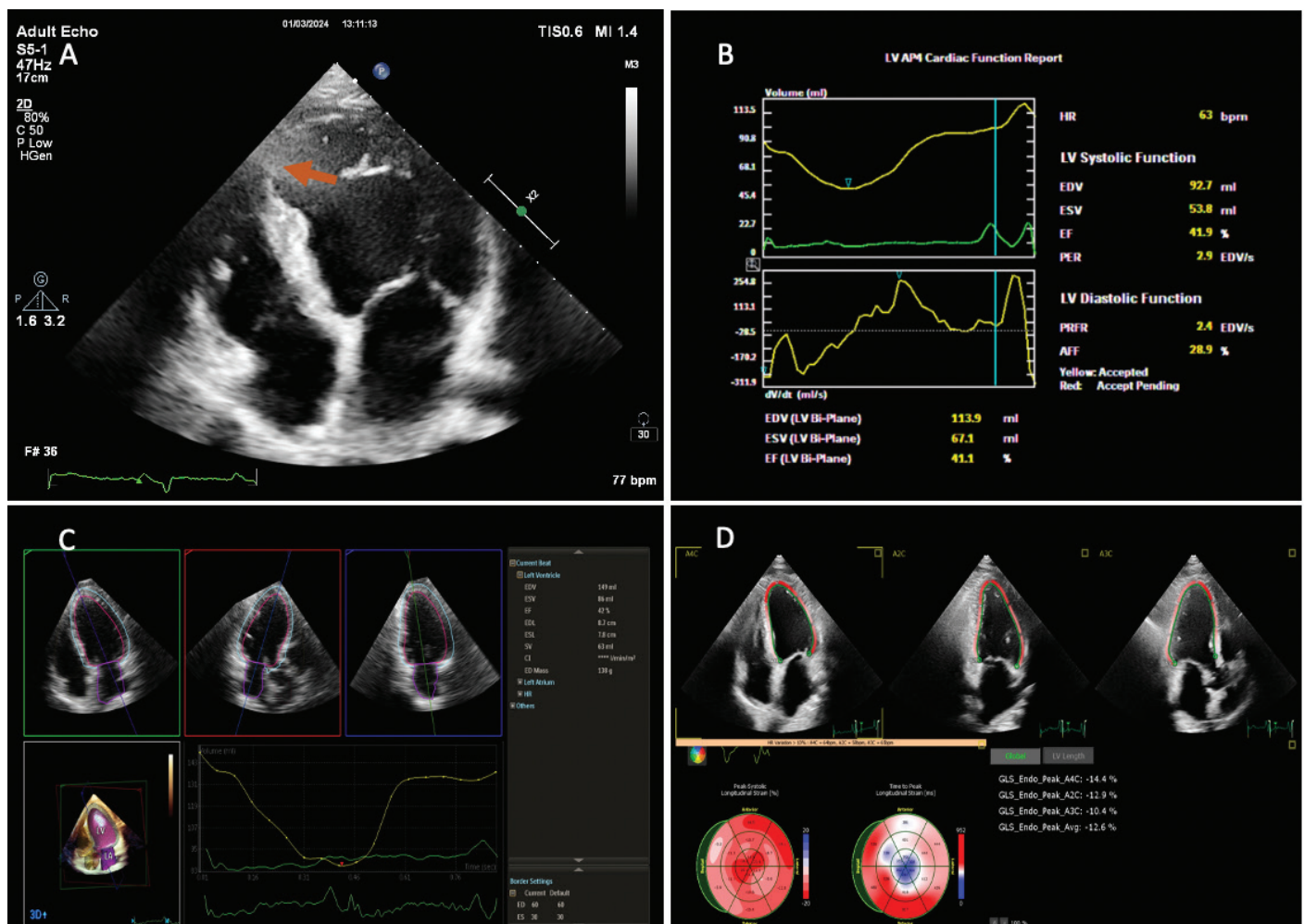


Figure 108. Echocardiography. (A) Aneurysm at the apicoseptum of the left ventricle in the apical 4-chamber view. Calculation of left ventricular ejection fraction using the modified biplane Simpson method (B) and three-dimensional echocardiography (C) in a patient with ischemic cardiomyopathy, and measurement of left ventricular global longitudinal strain (D).

Dobutamine can be used as an inotropic agent, while adenosine or dipyridamole can be utilized as vasodilator agents. Blood pressure and electrocardiogram changes during the procedure provide additional prognostic data. Significant limitations include poor acoustic windows, suboptimal imaging, and operator dependency. Dobutamine is infused at low doses for the assessment of contractile reserve, but in many cases, it can be applied at moderate and high doses to evaluate ischemia. Improved function with low-dose dobutamine suggests hibernating myocardium, while the development of new wall motion abnormalities or a biphasic response at high stress levels may indicate inducible myocardial ischemia.⁶⁰⁴

Beyond detecting coronary artery disease, stress echocardiography plays a crucial role in predicting patients at risk and prognosis. This is based on quantifying the global ischemic burden, utilizing multiple scores: (i) the number of segments showing an abnormal response; (ii) the percentage of myocardium showing an abnormal response (>20%); (iii) global myocardial ischemic severity (wall motion score index (WMSI) >1.4); (iv) abnormal response in multiple coronary regions; and (v) development of wall thickening abnormalities during early stress.⁶⁰²

Research efforts have been dedicated to augmenting the diagnostic and prognostic capabilities of stress echocardiography through the incorporation of additional parameters for wall motion defects. The development of the ABCDE protocol has played a crucial role in enhancing the prognostic accuracy of stress echocardiography.⁶¹⁹ In this protocol, A evaluates wall motions at rest and during stress, assessing the WMSI. A positive change, where Rest WMSI < Stress WMSI, is considered in favor of ischemia. Conversely, a negative change, indicating no alteration in viability or reserve, is evaluated in favor of scar tissue. The duration of stress without ischemia has been associated with the severity of coronary artery stenosis and adverse outcomes. Stress WMSI has been shown to be associated with mortality in patients with coronary artery disease.^{620,621}

B involves the transformation of normal A-lines in lung ultrasonography into B-lines, with the presence of at least two B-lines. This provides information about pulmonary congestion and diastolic dysfunction. An increase in B-lines is also linked to mortality.

C involves evaluating parameters providing information about left ventricular contractile reserve. An expected response to stress includes an increase in EF and a decrease in end-systolic volume. An increase of 10% or more in end-systolic volume is associated with a poor prognosis.

D assesses coronary microvascular dysfunction by measuring coronary flow velocity reserve (CFVR) using color Doppler and pulse wave Doppler. A normal response is CFVR > 2.0, and values below this threshold are considered abnormal. CFVR has been identified as a robust predictor of mortality in individuals with CAD.

E evaluates heart rate reserve (HRR), with a normal response being >1.80 during exercise and dobutamine stress echocardiography. Reduced HRR has been found to be a significant predictor of morbidity in patients with CAD.⁶²¹

An example of dobutamine stress echocardiography in a patient with suspected CAD is illustrated in Figure 109.

Direct echocardiographic assessment of epicardial arterial flow is feasible with Doppler ultrasound. However, the widespread clinical use of this method is significantly limited by the difficulty in reliably imaging only the larger primary vessels and the challenges in simultaneously visualizing all three main coronary arteries.⁶⁰²

Due to the apical and posterior displacement of papillary muscles associated with left ventricular remodeling, the coaptation of mitral valve leaflets is disrupted, leading to the development of mitral regurgitation. Despite the normal anatomical structure of the mitral valve, this regurgitation is referred to as secondary or functional mitral regurgitation. Secondary mitral regurgitation has been shown to be associated with mortality.

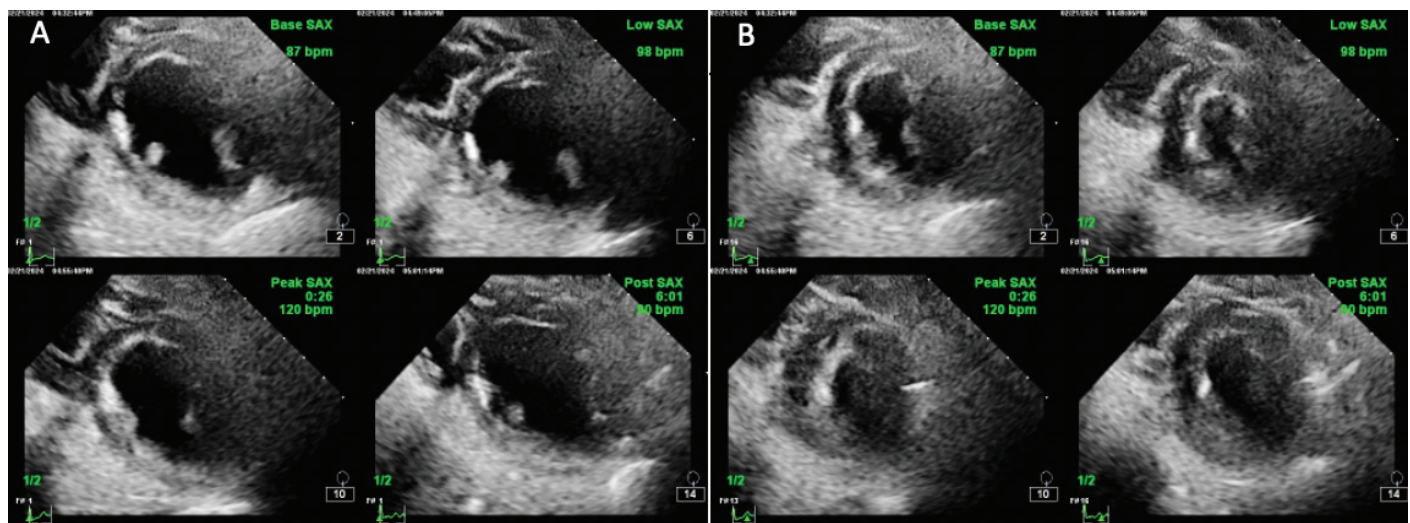


Figure 109. Dobutamine stress echocardiography was performed to evaluate myocardial ischemia, capturing short-axis images during diastole (A) and systole (B) at various stages, including baseline, low-dose dobutamine, peak dobutamine, and post-stress moments.

When assessing the severity of secondary mitral regurgitation, the effective regurgitant orifice area (EROA) and regurgitant volume (RV) have been found to be prognostically relevant. The proximal isovelocity surface area (PISA) method is the most commonly used technique for grading regurgitation. Severe secondary mitral regurgitation is defined as an EROA of 0.3 cm² or more, or an RV of 45 ml or more. Additionally, the morphological features of the mitral valve, left atrium, and left ventricle sizes should be taken into consideration. Parameters such as tenting area, coaptation gap, coaptation depth, and leaflet lengths, which are useful in planning the treatment strategy for mitral regurgitation, are also evaluated. In cases where image quality is good, three-dimensional imaging can provide more accurate measurements.⁶²²

Despite limitations in image quality, echocardiography remains a fundamental diagnostic tool for evaluating patients with ischemic cardiomyopathy due to its accessibility, versatility, and cost-effectiveness.

Coronary Computed Tomographic Angiography

Conventional angiography remains the reference method for detecting CAD.^{603,618} Coronary Computed Tomographic Angiography (CCTA) is an imaging modality that provides information on the prevalence of atherosclerosis, plaque characterization, and severity of stenosis.⁶²³ It can also be used in patients who have undergone percutaneous coronary intervention (PCI) and coronary artery bypass grafting (CABG). Its sensitivity in diagnosing CAD is reported to be quite high, with a specificity of 89%.⁶²⁴ It is included in the diagnostic algorithms for stable coronary artery disease in European and American guidelines.^{603,618}

The most common and prognostically reliable method for measuring the coronary artery calcium burden is the Agatston score. In this score, the calcified atherosclerotic area for each slice is multiplied by a density weighting factor (higher density yields a higher score), and the total is summed across the entire coronary artery tree.⁶⁰² The CAD-RADS score in CCTA has been shown to be useful in determining the burden and prognosis of

CAD. However, its clear benefit in assessing the progression of ischemic cardiomyopathy has not been demonstrated.^{625,626}

CCTA's ability to provide information on plaque characterization is a significant advantage. It allows the assessment of factors associated with poor prognosis, such as plaque burden and non-calcified plaque volume.^{627,628} In symptomatic patients, CCTA enables the unique and direct three-dimensional visualization of coronary arteries, assessing the presence, extent, and severity of stenosis.⁶⁰² However, it should be kept in mind that these findings may be influenced by the technical specifications of the computed tomography device. Additionally, CCTA is a helpful modality in detecting the presence of ventricular thrombus.

An example of detecting coronary artery stenosis with CCTA is shown in Figure 110.

CCTA provides information about coronary anatomy with its current features, but its utility in understanding the hemodynamic characteristics of CAD severity is limited. Additional tests are required to demonstrate myocardial ischemia. Fractional Flow Reserve (FFR) is the ratio of pressure difference between the distal and proximal parts of a stenosis.⁶²⁹ CCTA facilitates the calculation of FFR_{ct} using flow simulations, enabling a thorough evaluation of the anatomical and functional characteristics of the observed plaque. This contributes to a more comprehensive assessment of the severity of CAD. Studies have demonstrated that FFR_{ct} contributes to a reduction in short-term and one-year adverse outcomes.^{630,631}

Perfusion computed tomography (CTP) aims to assess myocardial ischemia by evaluating the hemodynamic impact of stenotic plaques using a hyperemic agent. CTP evaluations may utilize both static and dynamic protocols to perform measurements. Studies have demonstrated that CTP measurements enhance diagnostic accuracy compared to CT angiography alone. Despite demonstrating higher specificity and positive predictive value in contrast to FFR_{ct}, it is essential to consider increased radiation exposure.⁶³²⁻⁶³⁵

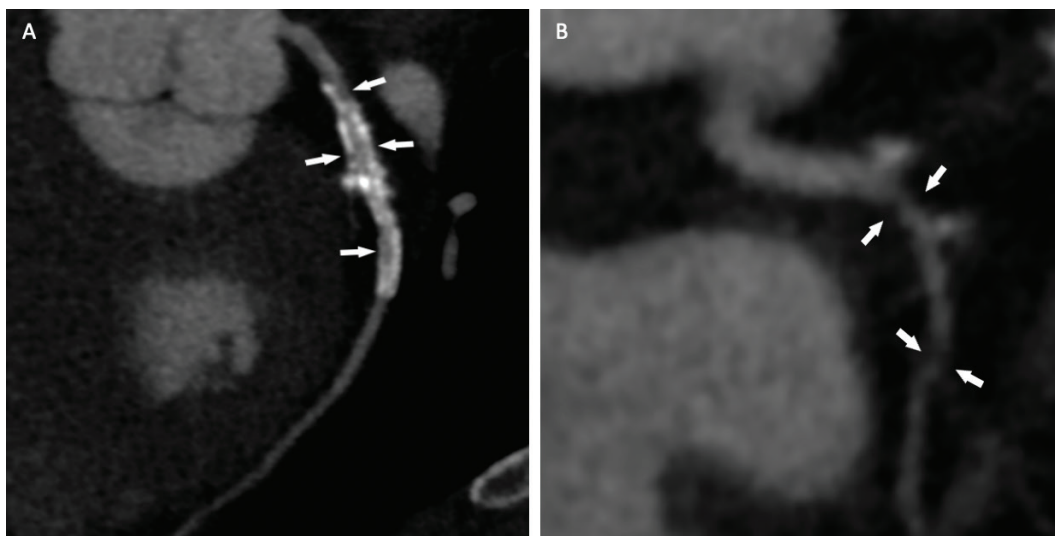


Figure 110. Coronary Computed Tomographic Angiography. (A) Demonstration of moderate to severe stenosis within the stent in the left anterior descending coronary artery and (B) critical stenosis in the circumflex coronary artery.

Performing myocardial perfusion with CT during rest and vasodilator stress is a promising but not widely used technique in the clinical setting. This method extends beyond the fundamental coronary CTA study, necessitating additional contrast and increasing exposure to radiation.⁶⁰²

Nuclear Imaging

It is known that the degree of stenosis in the coronary arteries alone is not a sufficient parameter in the management of treatment, and it is beneficial to evaluate the hemodynamic significance of the narrowing of the coronary arteries.^{603,618} SPECT and PET are the most commonly used imaging methods for functional assessment.

SPECT evaluates myocardial perfusion during rest and stress using radioactive agents such as Tc99m and Tl201. It has been

reported to have a sensitivity of 86% and a specificity of 74%.⁶³⁶ Negative SPECT results have been associated with a reduction in adverse cardiac events. Additionally, high-risk SPECT results have been found to be more strongly associated with cardiovascular events.^{635,637,638}

Studies have shown that SPECT is valuable not only in the diagnosis of CAD but also in risk stratification, treatment evaluation, and prognosis assessment.^{605,639} However, its diagnostic utility is limited in cases of multi-vessel coronary artery disease, microvascular disease, and high body mass index (BMI).⁶⁰⁵ An example of myocardial perfusion imaging is shown in Figure 111.

PET provides a better evaluation of myocardial ischemia compared to SPECT due to its higher spatial and temporal resolution. With these advantages, PET offers higher diagnostic accuracy in cases

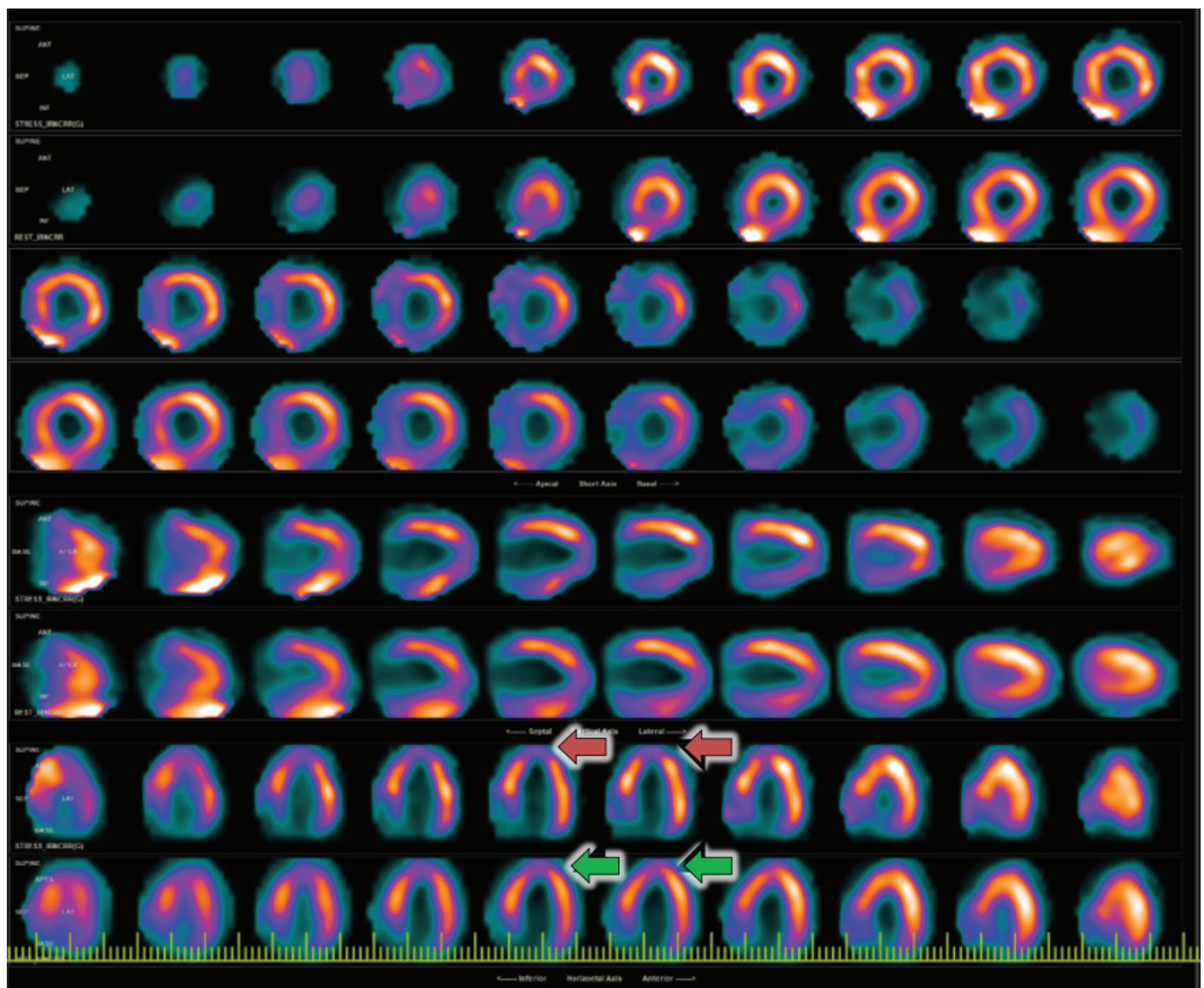


Figure 111. Myocardial Perfusion Scintigraphy. Images of myocardial perfusion scintigraphy demonstrating apical wall ischemia. Lines of images arranged in pairs depict stress in the upper lines and rest stages in the lower lines. In the transverse sections, the improvement (green arrow) in the area corresponding to the apical segment in rest images compared to the reduced uptake during stress (red arrows) which suggests the presence of ischemia.

of multi-vessel disease and main coronary lesions where SPECT may have diagnostic limitations.^{640,641} It has been reported to have a sensitivity of 90% and a specificity of 89%.⁶⁴² The most commonly used radiotracers to detect a decrease in myocardial blood flow are 82Rubidium and 13N-Ammonia, with 15O-H₂O being the gold standard.^{640,643} Demonstrating the association of abnormal PET results with poor cardiovascular outcomes has also highlighted its prognostic value.⁶⁴⁴

In addition to assessing ischemia, the 18F-fluorodeoxyglucose (18F-FDG) PET method is employed for evaluating myocardial viability. Assessing the presence of viable tissue is a critical parameter for revascularization in advanced CAD with left ventricular dysfunction. Existing data in the literature suggest that PET surpasses dobutamine stress echocardiography and SPECT in investigating viable tissue.⁶⁴⁵ A meta-analysis has demonstrated that 18F-FDG has the highest sensitivity for myocardial viability, while dobutamine stress echocardiography exhibits the highest specificity.⁶⁴⁶

All contemporary camera-computer systems are equipped with fully automated software capable of obtaining high-reproducibility of LVEF values. Radionuclide ventriculography, also known as gated blood pool imaging, can be performed using either first-pass or equilibrium-gated techniques.⁶⁰² However, its

routine use is restricted due to limitations in accessibility and cost. Additionally, radiation exposure should be considered when comparing it to stress echocardiography and CMR.

Cardiac Magnetic Resonance

CMR imaging provides a broad range of methods for evaluating patients with known or suspected coronary artery disease. These include assessing global and regional ventricular function, myocardial perfusion, scar tissue, and viability. While CMR imaging serves as a functional test to detect ischemia, it can also provide information about myocardial viability through the evaluation of late gadolinium enhancement.

CMR datasets allow independent volumetric analysis of both the left and right ventricles without relying on geometric assumptions. In the context of coronary artery disease, cine imaging is used during rest to determine regional and global ventricular function, wall thickness, and left ventricular mass, providing a high level of repeatability.⁶⁰²

The stress CMR protocol commonly aims to assess myocardial perfusion using stress vasodilator agents such as adenosine or dipyridamole, or an inotropic agent like dobutamine, often with short-axis images.⁶⁴⁷ One advantage of CMR is the high repeatability of imaging planes, consistently providing high

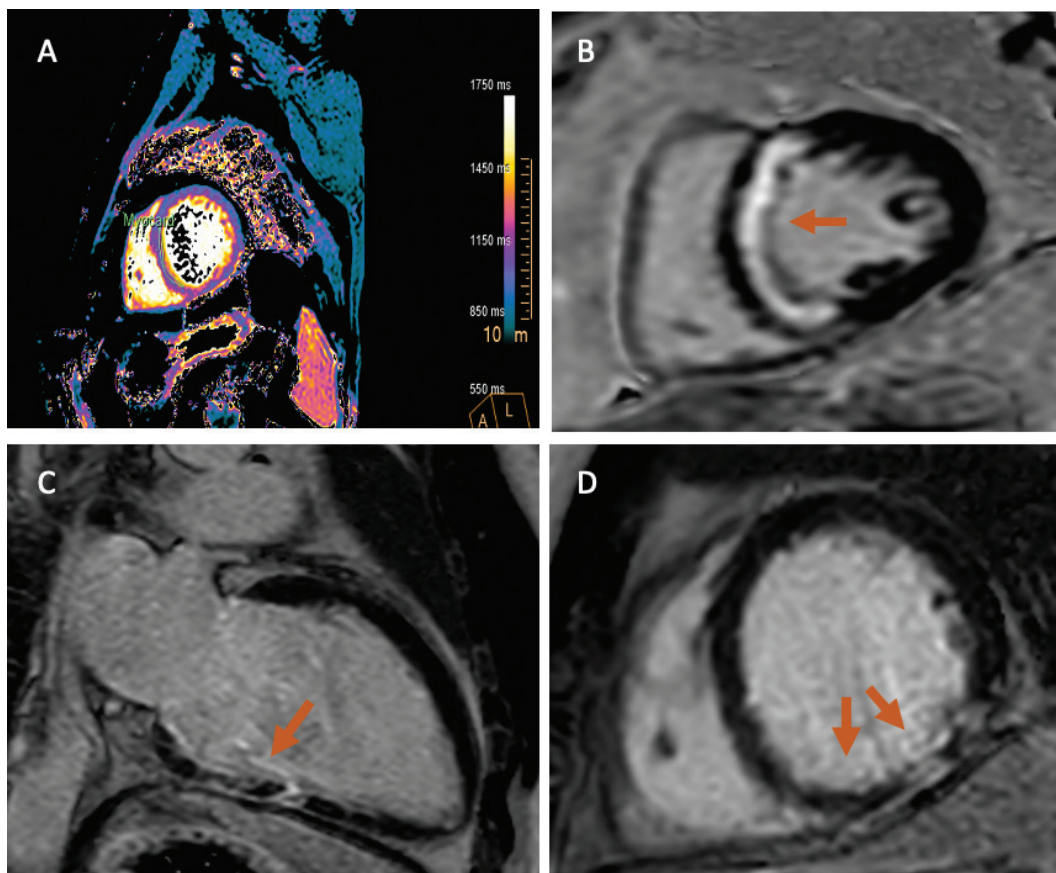


Figure 112. Cardiac Magnetic Resonance Imaging. (A) Increased T1 signal revealing myocardial injury. Subendocardial LGE in septal wall in short axis view (B), subendocardial to transmural LGE in posterior wall in two chamber view (C), and transmural LGE in inferior-inferoseptal wall in short-axis view (D), representing myocardial scar. LGE, late gadolinium enhancement.

image quality and endocardial border definition. According to the European Cardiology Guidelines, having more than two segments with perfusion defects increases the cardiovascular event risk for the patient.⁶⁰³ Comparative studies have shown that stress CMR yields similar results in terms of cardiovascular events when compared to invasive FFR.⁶⁴⁸ Furthermore, evidence suggests that it is diagnostically superior to SPECT in another study.⁶⁴⁹

According to the results of a meta-analysis, stress CMR demonstrates a sensitivity of 87% and a specificity of 89%.⁶⁵⁰ The significance of stress CMR lies in its important prognostic contributions, as negative results are associated with a reduced need for invasive interventions and lower costs without an increase in adverse cardiovascular events.⁶⁵¹ In addition to the visual assessment of ischemic areas, efforts are being made to develop semi-quantitative or fully quantitative methods. Further research is needed for the integration of these new techniques into daily practice. The limitations of this technique include long acquisition times, high costs, and challenges in unstable patients.

CMR presents the benefit of characterizing tissue. With late gadolinium enhancement (LGE) assessment, it is possible to distinguish between ischemia and scar in the perfusion defect seen on CMR. The absence of LGE indicates ischemia. LGE provides the best determination of scar with prognostic value.⁶⁵² In ischemic cardiomyopathy, the underlying myocardial damage and necrosis leading to ventricular remodeling involve collagen accumulation due to fibroblast activity and an increase in extracellular volume.⁶²³ The LGE pattern in ischemic cardiomyopathy extends from transmural to subendocardial.

T1 mapping methods assess the amount of fibrosis, defining transmural involvement when myocardial involvement is >75%.^{653,654} The absence or <50% myocardial LGE supports myocardial viability and is associated with improvement in left ventricular function after PCI or CABG.⁶⁵⁵ According to the results of a meta-analysis encompassing 24 studies assessing myocardial viability, LGE has been found to have the highest sensitivity at 95% in predicting improvement in left ventricular systolic

functions.⁶⁵⁶ Simultaneously, extracellular volume measurement is also a significant parameter. In a study, increased extracellular volume was associated with frequent hospitalizations due to heart failure, all-cause mortality, and was found correlated with LVEF.⁶⁵⁷

An example of CMR imaging in ICM is illustrated in Figure 112.

In addition to assessing myocardial ischemia and viability, CMR contributes to the detection of left ventricular thrombus. The presence of a left ventricular thrombus is a significant condition in ischemic heart patients due to its association with embolic events and the need for anticoagulation. CMR, with its tissue characterization advantage, helps overcome limitations in evaluating left ventricular thrombus with echocardiography. Studies have demonstrated that CMR is more sensitive in detecting left ventricular thrombus compared to TTE.^{658,659} Furthermore, cine imaging enables the identification of valvular pathologies associated with coronary artery disease, such as functional mitral regurgitation.⁶⁰²

Despite the significant contributions of CMR in tissue characterization, assessing myocardial ischemia and scar, and detecting left ventricular thrombus, the technique faces notable limitations, including long acquisition times, high costs, and challenges in unstable patients.

Conclusion

All imaging methods can provide information about the structure and function of the left ventricle, but echocardiography and CMR have clear advantages. Revascularization can improve regional and global left ventricular function in patients with inducible ischemia and hibernating myocardium. Various tests are available to identify hibernating myocardium. Among them, SPECT is sensitive in detecting cellular integrity and has a wide range of applications. Dobutamine stress echocardiography also has broad applications but lower sensitivity. In patients with severe left ventricular dysfunction, PET imaging may be more beneficial in evaluating hibernating myocardium. Contrast-enhanced CMR with low-dose dobutamine stimulation is considered the most accurate technique.

Peripartum Cardiomyopathy

Peripartum cardiomyopathy (PPCM) is defined as an idiopathic cardiomyopathy that manifests with heart failure (HF) due to left ventricular (LV) systolic dysfunction towards the end of pregnancy or during the months following childbirth, in the absence of any other cause of HF.^{660,661} According to the diagnostic criteria, the LV ejection fraction (EF) is less than 45%, and the LV may or may not exhibit dilation.^{660,661} PPCM is primarily diagnosed post-delivery and represents a diagnosis of exclusion, considered when there is no alternative cause. The symptoms and signs of PPCM can mimic those of late pregnancy and the peripartum period, often resulting in a delay in diagnosis until after childbirth. Patients typically present with symptoms of acute HF. However, ventricular arrhythmias and/or sudden cardiac death may also be initial manifestations of the condition.^{660,662}

Epidemiology

PPCM occurs in approximately 1 in 2,000 births worldwide.⁶⁶³ Incidence rates of PPCM vary significantly by region, influenced by environmental and genetic factors, cultural differences, and variations in perinatal care, leading to distinct regional distributions. Reports indicate incidence rates as high as 1 in 100 births in Nigeria, 1 in 300 births in Haiti, and as low as 1 in 20,000 births in Japan.⁶⁶² In the United States, the reported incidence ranges from 1 in 1,000 to 1 in 4,000 births,^{664,665} with a trend toward increasing incidence. This rise may be attributed to older maternal ages, higher rates of multiple pregnancies due to advanced fertility treatments, and possibly improved recognition of the condition. Additionally, many cases may go undiagnosed, making the true incidence of PPCM difficult to ascertain.

Pathophysiology and Risk Factors

The etiology of PPCM is not fully understood but is believed to be multifactorial. Evidence from animal models and epidemiological studies supports the notion that PPCM is predominantly a vascular disease, often triggered by the hormonal milieu of the peripartum period.^{666,667} Studies suggest that vascular damage may be due to prolactin-mediated oxidative stress on the myocardium.⁶⁶² If PPCM occurs together with preeclampsia, it is thought that placental angiogenic factors may also provide a common pathophysiological mechanism.⁶⁶² Proposed mechanisms for PPCM, though not definitively proven, include nutritional deficiencies, viral myocarditis, and autoimmune processes.^{660,663} The hemodynamic stress of pregnancy has also been considered a potential contributing factor. However, the most significant cardiovascular changes occur in the second trimester, a period when women with pre-existing heart disease might start to exhibit symptoms of HF.⁶⁶⁸ Conversely, many women with PPCM do not develop symptoms until late in pregnancy or after childbirth. This discrepancy indicates that the timing of PPCM symptom onset does not align with the hemodynamic shifts associated with pregnancy.

Multiparity, multiple pregnancies, African ethnicity, smoking, diabetes, hypertension, preeclampsia, malnutrition, advanced maternal age, and adolescent pregnancy are identified as significant predisposing factors.^{660,662} Studies have shown that PPCM is 3 to 16 times more common in African-American women than in white women.⁶⁶⁹ Preeclampsia and hypertension have a strong association with PPCM, with preeclampsia present in 22% of women with PPCM.⁶⁷⁰ In the United States, multiple pregnancies are reported in 7% to 14.5% of women with PPCM.^{662,663} Advanced maternal age also appears to be linked to PPCM, with half of the cases occurring in women over the age of 30.

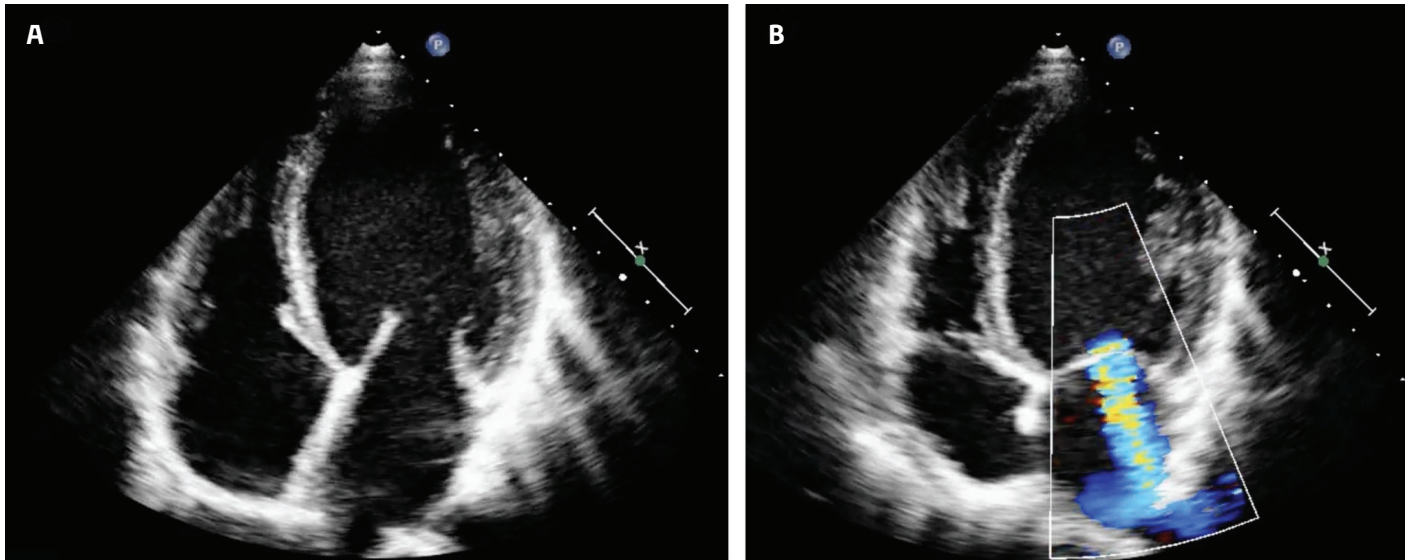


Figure 113. Transthoracic echocardiography apical four-chamber view of PPCM; (A) Dilated left ventricle, (B) Functional mitral regurgitation jet with color Doppler.

Women over 40 years of age are reported to be 10 times more likely to develop the condition than those younger than 20 years of age.^{664,671}

The most widely accepted theory regarding the pathogenesis of PPCM is the vasculohormonal model, which is supported by studies focusing on pregnancy hormones. According to this model, imbalances in peripartum hormones lead to cardiovascular dysfunction and, subsequently, HF in susceptible women.⁶⁶⁷

Genetics

The familial occurrence of PPCM and its 6% co-occurrence with dilated cardiomyopathy (DCM) suggest a genetic predisposition to the disease.⁶⁷²⁻⁶⁷⁴ A German cohort study found that 15% of women with PPCM had a first-degree relative with a history of heart disease, including PPCM, DCM, sudden death, or arrhythmias.⁶⁷⁵ Subsequent genetic studies have supported the notion that genetics play a role in PPCM⁶⁷⁶ and have identified potential pathogenic variants in genes known to contribute to DCM, such as *TTN* and *BAG3*, highlighting the genetic overlap between PPCM and DCM.⁶⁷⁷

Truncating variants in genes like *TTN*, *FLNC*, *BAG3*, and *DSP* have been found to be disproportionately represented in nearly 15% of PPCM patients. *TTN* truncating variants, the most common among these, are present in almost 10% of patients.^{1,660} The *TTN* gene encodes titin, the largest human protein, which is a vital structural component of the sarcomeres in cardiac and skeletal muscles.⁶⁶² In the Investigations in Pregnancy-Associated Cardiomyopathy (IPAC) cohort, *TTN* variants were associated with lower LVEF at one year, suggesting that the presence of *TTN* truncating variants may predict worse outcomes.⁶⁷⁷ However, it is important to note that more than 90% of individuals with *TTN* truncating variants do not develop DCM or PPCM,⁶⁷⁸ indicating that other environmental, genetic, or epigenetic factors also contribute to disease development. The observation that most women with PPCM do not have a family history of cardiomyopathy and that PPCM does not consistently recur in subsequent pregnancies implies that no single genetic factor is fully penetrant, and additional elements influence the onset of the disease. Further research in diverse populations is

needed to explore how genetic variants interact with comorbidities and the vascular, hormonal, and hemodynamic changes of late pregnancy. Understanding genetic differences may help explain why only a minority of women develop HF in response to vascular damage secondary to hormonal changes during late pregnancy.

In accordance with the 2023 European Society of Cardiology (ESC) Cardiomyopathy guideline, genetic consultation and testing may be beneficial and should be considered for patients with PPCM (Recommendation Class 2a, Level of Evidence C).¹

Diagnosis

PPCM is characterized by acute and sometimes severe clinical HF during pregnancy or in the early postpartum period. It is defined as maternal HF with systolic dysfunction (LVEF less than 45%) occurring in the last month of pregnancy or within the first five months after childbirth, in the absence of previously diagnosed cardiac dysfunction.^{660,661} However, on rare occasions, the disease has been reported to manifest early in pregnancy or more than five months postpartum.^{679,680}

Most women with PPCM are diagnosed after childbirth, typically within the first month postpartum.⁶⁷⁹ Diagnosis often faces delays due to limited awareness of the disease and the overlap of normal pregnancy symptoms with those of HF. A high degree of clinical suspicion is required for diagnosis. Unfortunately, delayed diagnosis is linked to an increased risk of preventable complications and poorer outcomes.^{681,682}

Most patients present with signs and symptoms of HF, such as fatigue, weakness, shortness of breath, orthopnea, paroxysmal nocturnal dyspnea, edema, and chest tightness. During physical examination, findings often include tachypnea, tachycardia, jugular venous distention, an S3 heart sound, lung rales, and peripheral edema. Less commonly, patients may present with cardiogenic shock, malignant arrhythmias, and thromboembolic complications.⁶⁸⁰

Echocardiography is the preferred initial imaging method for diagnosing PPCM. The diagnosis is generally made through echocardiography, documenting systolic dysfunction in the

absence of other structural heart diseases.^{660,677} LV dilatation is common (Figure 113A) but not universally present. In addition to systolic dysfunction, echocardiography may reveal LV and right ventricular dilatation and/or dysfunction, functional mitral (Figure 113B) and/or tricuspid regurgitation, pulmonary hypertension, and enlargement of the left atrium or both atria. Intracardiac thrombus formation can occur, especially when the LVEF is significantly reduced.⁶⁸³

Sinus tachycardia may be observed on an electrocardiogram (ECG) and can indicate nonspecific abnormalities. However, it is important to note that a normal ECG does not exclude the diagnosis of PPCM.⁶⁸⁴ Additionally, findings such as pulmonary venous congestion may be detected on chest radiography, but these are not specific to PPCM.

Brain natriuretic peptide (BNP) and N-terminal pro-BNP levels, which generally do not vary significantly throughout a normal pregnancy, are often markedly elevated in patients with PPCM.⁶⁸⁵ Cardiac magnetic resonance imaging (MRI) provides detailed structural evaluation, including accurate EF and cavity measurements, for cases where the echocardiogram is inadequate. However, the use of gadolinium contrast is avoided during pregnancy. Endomyocardial biopsy is generally not required for the diagnosis of PPCM and is seldom performed. It is only indicated when an alternative diagnosis that would necessitate a different treatment approach, such as giant cell myocarditis, is suspected.^{662,663,683}

Differential Diagnosis

PPCM is a diagnosis of exclusion. The differential diagnosis includes pre-existing structural heart disease, pulmonary edema induced by preeclampsia without systolic dysfunction, pulmonary embolism, spontaneous coronary artery dissection, and exposure to toxins, such as chemotherapeutic agents (Table 34).^{662,663,683}

Prognosis

The clinical outcomes of patients with PPCM vary significantly, and the prognosis is generally more favorable in developed countries. While some women experience a relatively mild disease course and fully recover, others suffer from severe morbidity and mortality. PPCM is a significant cause of maternal death.^{671,686} As a result, PPCM can lead to devastating consequences in the lives of the affected individuals, their families, and their newborn infants.

PPCM has been associated with a higher recovery rate compared to other forms of HF with reduced LVEF, and recovery is often observed within the first 3 to 6 months post-diagnosis.^{687,688} There are cases, such as a patient diagnosed with PPCM immediately after delivery with severely reduced LV systolic function (Videos 27a and 27b), where nearly a 50% improvement in LVEF was observed by the fifth month after delivery (Videos 28a and 28b).

Recovery can continue up to 2 years after the initial diagnosis.^{663,689} The rates of recovery vary among different patient populations. Approximately 50% of affected patients experience a recovery in cardiac function, yet the morbidity and mortality associated with PPCM remain high. Some patients may require the support of a LV assist device (LVAD) or undergo cardiac transplantation.

Table 34. Differential diagnosis of heart failure throughout pregnancy
Pre-existing cardiomyopathy
Preeclampsia
Takotsubo cardiomyopathy
Heart valve diseases, including rheumatic diseases
Congenital heart disease
Chemotherapy-associated cardiomyopathy
Spontaneous coronary artery dissection
Other causes of myocardial infarction, including MINOCA
Myocarditis
Hypertensive heart disease
Tachycardia-arrhythmia-associated cardiomyopathy
Pulmonary congestion due to prolonged tocolysis
Other high-flow causes of sepsis, thyrotoxicosis, and heart failure
Aortic dissection
Pulmonary or amniotic embolism
Systemic disease-induced cardiomyopathy (SLE, hemochromatosis)
MINOCA, Myocardial infarction with non-obstructive coronary arteries; SLE, Systemic lupus erythematosus

PPCM is linked to a range of adverse outcomes, including brain injury, cardiopulmonary arrest, pulmonary congestion, thromboembolic complications, the need for mechanical circulatory support, cardiac transplantation, and mortality. It accounts for nearly 60% of cardiogenic shock cases during pregnancy or in the early postpartum period.⁶⁹⁰ Up to 10% of cases may necessitate the implantation of a LVAD or heart transplantation.⁶⁹¹ LV thrombus was identified in 10% to 17% of patients with PPCM on initial echocardiograms, and thromboembolic complications were reported in 5% to 9% of women.^{662,692} The increased risk of thromboembolic events in PPCM is likely related to the hypercoagulable state of pregnancy, LV dilation and dysfunction, venous stasis, and the immobilization following postpartum.

Mortality predictions for PPCM vary significantly across racial groups, geographic regions, and follow-up durations. In the United States, mortality rates range from 7% to 20%.^{686,693} A 24-month prospective study conducted in Turkey reported a mortality rate of 24%.⁶⁹⁴ These rates tend to be higher among Black women and women in underdeveloped countries.⁶⁶⁹

Prognostic Factors

Among the different prognostic factors evaluated, LVEF at the time of diagnosis emerges as the most reliable predictor of adverse events or long-term recovery.^{661,662,691} A baseline LVEF of less than 30%, significant LV dilatation (end-diastolic diameter equal to or greater than 6.0 cm), the presence of an LV thrombus, and right ventricular involvement are associated with poorer outcomes.⁶⁶¹ Other factors indicating worse prognosis include delayed presentation (more than one week after childbirth) and late enhancement with gadolinium on MRI.^{688,695}

African American ethnicity is strongly associated with lower recovery rates, longer recovery periods, more adverse outcomes, and higher mortality.⁶⁶⁹ Concurrent preeclampsia has been linked to better LV recovery but a higher incidence of adverse cardiovascular outcomes.⁶⁹⁶ Troponin and N-terminal pro-B-type natriuretic peptide (NT-proBNP) are biomarkers associated with poorer outcomes.^{697,698} The presence of late gadolinium enhancement on cardiac MRI may signal fibrosis, which is associated with reduced myocardial recovery; however, late gadolinium enhancement is not observed in most patients with PPCM.

Management and Treatment

There are limited randomized studies evaluating treatments for PPCM, and no definitive conclusions have been drawn from these studies. Currently, there are no proven disease-specific treatments for PPCM. Therefore, the management primarily involves medical treatment following the guidelines recommended for DCM and HF with reduced EF.⁶⁹⁹ Diuretics and nitrates are used to manage hypervolemia, but care must be taken to avoid causing hypotension during pregnancy.

Angiotensin-converting enzyme (ACE) inhibitors, angiotensin II receptor blockers (ARBs), and aldosterone receptor antagonists can be used after delivery but are contraindicated before childbirth.

Hydralazine plus isosorbide dinitrate serves as an alternative regimen for reducing afterload during pregnancy. Beta-blockers are commonly prescribed and are considered safe throughout pregnancy. Currently, there is no data on the safety and efficacy of recently developed HF pharmaceutical agents, such as sacubitril-valsartan and sodium-glucose co-transporter 2 inhibitors, during or after pregnancy. However, these agents are increasingly utilized post-partum. Most standard HF medications are compatible with breastfeeding, but there is a lack of safety information for newer agents.⁶⁹⁹

The hypercoagulability associated with pregnancy increases the risk of thrombotic complications, including LV thrombus and thromboembolic events, occurring in 5% to 20% of cases.⁷⁰⁰ Consequently, there should be a low threshold for initiating anticoagulant therapy. The American Heart Association recommends anticoagulation for cases with a LVEF less than 30%,⁷⁰¹ while the ESC advises anticoagulation when LVEF is less than 35%.⁷⁰² Currently, there is no published data to guide the choice between therapeutic or prophylactic anticoagulation.

Warfarin, which can cross the placenta, is generally avoided during pregnancy except for the anticoagulation of mechanical heart valves due to its potential teratogenic effects. Low molecular weight heparin (LMWH) does not cross the placenta and is considered safe for use during pregnancy.⁶⁶¹ Both warfarin and LMWH are deemed safe during lactation. Newer anticoagulants have not been studied for use during pregnancy or lactation and are typically avoided.

The use of bromocriptine to inhibit prolactin release from the pituitary gland is under investigation and may be considered for patients with LVEF below 35%. The 2018 ESC guidelines weakly recommend considering bromocriptine therapy to

halt breastfeeding and potentially accelerate recovery of LV function in patients with PPCM (Recommendation Class IIb, Level of Evidence: B).⁶⁶¹ Due to its association with thrombotic complications, therapeutic anticoagulation alongside bromocriptine therapy is suggested.^{661,662} The implications of discontinuing breastfeeding because of bromocriptine use should be thoroughly discussed with the patient.

Ventricular arrhythmias are common in patients with PPCM, and when a defibrillator is warranted, the use of a temporary, wearable defibrillator should be considered over an implantable cardioverter-defibrillator (ICD), given the frequent improvement in cardiac contractility. Due to the significant rate of spontaneous recovery following delivery, the threshold for early ICD implantation should be higher in PPCM patients than in those with other conditions.¹

PPCM is the leading cause of cardiogenic shock during or shortly after pregnancy.⁶⁹⁰ In severe cases of PPCM, temporary mechanical circulatory support options such as the intra-aortic balloon pump, percutaneous ventricular assist devices, and extracorporeal membrane oxygenation have been successfully employed and should be considered early in patients with hemodynamic instability despite inotropic support.^{1,703} Temporary or permanent LVADs may also be necessary. Approximately 10% of cardiogenic shock cases resulting from PPCM necessitate LVAD implantation or heart transplantation.⁶⁹¹

Delivery and Lactation

Delivery and management in patients with PPCM during pregnancy can be complex and requires a multidisciplinary team approach, including an obstetrician, anesthesiologist, cardiologist, and an advanced HF specialist with expertise in maternal-fetal medicine, particularly when the patient is hemodynamically unstable. The priority is to stabilize the mother to minimize potential fetal complications associated with prematurity. Despite medical treatment, if hemodynamic instability persists, it may necessitate preterm birth or termination before fetal viability. Stable patients may undergo vaginal delivery unless there are specific obstetric reasons for a cesarean section, given that cesarean delivery is linked to a higher risk of bleeding, infection, and thromboembolic complications.⁶⁶² Unless there are obstetric indications for cesarean section, such as severe HF (LVEF less than 30% or NYHA class III-IV) or the use of oral anticoagulants, vaginal delivery is recommended for most women with PPCM (Recommendation Class 1, Level of Evidence: C).¹

Breastfeeding offers numerous benefits for both infants and mothers, and is not contraindicated in PPCM.⁶⁶¹ Recent findings from the Investigations of IPAC study have shown that breastfeeding is not associated with adverse outcomes, elevated inflammatory markers, or lasting myocardial dysfunction.⁶⁸⁸ This evidence suggests that breastfeeding, which entails continued stimulation of prolactin secretion, may not be harmful in the context of PPCM. Most heart failure medications are considered safe for use during breastfeeding, and there should be no hesitancy in recommending breastfeeding to women with PPCM. For patients considering the initiation of bromocriptine therapy, the implications of not breastfeeding should be thoroughly discussed with the patient.

Postpartum patients should be considered for genetic consultation and testing even in the absence of a family history of PPCM or DCM.¹ If a pathogenic variant is identified, cascade testing of family members may be beneficial for facilitating prevention, early diagnosis, and treatment.

Contraception

Contraception should be addressed at the time of diagnosis or before hospital discharge. For women with permanent LV dysfunction, the risks posed by future pregnancy may outweigh the thromboembolic risks associated with estrogen-containing contraceptives. Thus, women should be encouraged to choose the contraceptive method they will use most reliably. Both the obstetrician/gynecologist and the cardiologist should emphasize the importance of contraception.⁶⁶²

Treatment Period

In cases of persistent cardiac dysfunction, medications should be continued indefinitely. The optimal duration of treatment following recovery of LV function remains uncertain. Diuretic drugs may be discontinued unless the patient exhibits congestive symptoms. HF medications should be tapered off gradually, accompanied by frequent clinical assessments and echocardiographic monitoring of LVEF, ideally every 3 to 6 months. It is recommended that LV function be re-evaluated after medication cessation, followed by annual clinical and echocardiographic evaluations.^{662,683}

Future Pregnancies

The safety of future pregnancies is a significant concern for patients with PPCM and their families, making proper and informed counseling crucial. The risks associated with subsequent pregnancies largely depend on whether myocardial function has fully recovered, with pre-pregnancy LVEF being the strongest predictor of outcomes.⁶⁹¹ Women with evidence of permanent myocardial dysfunction should be advised about the risks of recurrent HF, ongoing impairment of cardiac function, and increased mortality. Furthermore, fetal outcomes, including the risks of stillbirth, miscarriage, and preterm birth, are worse in women with permanent LV dysfunction. Based on these considerations, the 2018 ESC guidelines for managing cardiovascular diseases during pregnancy advise against subsequent pregnancies unless the LVEF is greater than 50–55%.⁶⁶¹ Women who achieve a recovery of LVEF to more

than 50% after PPCM face a lower risk of complications in future pregnancies but still have a heightened risk of recurrent PPCM and HF.⁷⁰⁴ Pre-pregnancy counseling should include discussions about the potential for recurrent myocardial dysfunction, which may persist after pregnancy.

Conclusion

The diagnosis of PPCM should be considered in any pregnant or postpartum woman presenting with symptoms indicative of HF. Echocardiography is essential for evaluating systolic dysfunction, especially after an elevated level of BNP is detected. Early diagnosis and timely initiation of appropriate medical therapy can mitigate adverse outcomes. While research is limited, evidence suggests that breastfeeding is safe for women diagnosed with PPCM. These women should be cared for by specialized multidisciplinary teams and may require ongoing HF management. Women contemplating future pregnancies should receive comprehensive counseling regarding PPCM and undergo thorough monitoring. Long-term follow-up is crucial for managing PPCM, though the ideal duration for continuing medication after recovery remains uncertain.

Despite significant progress in understanding PPCM, many questions about its pathogenesis and the complex interplay of genetics with the vascular and hormonal changes in late pregnancy remain unanswered. The therapeutic role of bromocriptine in PPCM is still uncertain, highlighting the need for randomized clinical trials to clarify its risks and potential benefits. There are also substantial gaps in knowledge regarding the optimal anticoagulation strategy, appropriate timing for ICD implantation, risk prediction and management in subsequent pregnancies, and the duration of medication after myocardial recovery. These uncertainties underscore the need for continued research and clinical studies to improve outcomes for women with PPCM.

Video 27. Transthoracic echocardiography performed due to heart failure at the first week after delivery showing mild dilatation, global hypokinesia, and severe systolic dysfunction of the left ventricle in the apical 4-chamber (a) and parasternal long-axis (b) views.

Video 28. In the control transthoracic echocardiography performed at the 5th month after delivery, left ventricular systolic function and size were normal in the apical 4-chamber (a) and parasternal short-axis (b) views.

Syndromic and Metabolic Cardiomyopathies: Rare Variants for Adults (Glycogen Storage Diseases, Friedreich's Ataxia)

Glycogen Storage Diseases

Glycogen storage diseases (GSD) arise from the abnormal storage and/or use of glycogen due to deficiencies in enzymes or transporters involved in the synthesis or degradation of glycogen. Each mutation in glycogen storage diseases may present with a different phenotypic pattern. GSD particularly affects the liver, skeletal muscle, heart, and, less commonly, the central nervous system and kidneys.^{705,706}

In glycogen storage diseases, cardiac events occur in types GSD 0b, GSD II (Pompe disease, Danon disease, and PRKAG2), GSD III (Cori-Forbes disease), GSD IV (Andersen disease), GSD XV, and PGM1–CDG (previously called GSD XIV). Involvement occurs.^{705,707} Among these, only the initial clinical presentation of PGM1–CDG is dilated cardiomyopathy, while in the others, the initial presentation is usually hypertrophic cardiomyopathy.

Glycogen Storage Disease 0b

GYS1 (muscle-specific glycogen synthase) is vital for glycogen synthesis in cardiac and skeletal muscle, providing critical energy reserves during rapid muscle contraction, sustained muscle work, and hypoxia. In GYS1 mutation, the glycogen content within the muscle cell decreases, leading to Type 1 muscle fibers and cellular mitochondrial proliferation in the skeletal muscle. The clinical presentation of GSD 0b includes exercise intolerance, hypertrophic cardiomyopathy, sudden cardiac death during exercise, and adult-onset peripheral myopathy without cardiomyopathy. Due to an innate metabolic error, there is zero muscle glycogen storage, and the diagnosis is made by histochemical examination.^{707–709}

Glycogen Storage Disease II

Pompe Disease

In acid α -glucosidase deficiency, intralysosomal glycogen accumulation occurs in all tissues, especially in skeletal muscle. Infantile-onset Pompe disease has a poor prognosis and is fatal in infancy if left untreated. The main symptoms are hypertrophic cardiomyopathy, hypotonia, and motor developmental delay. Late-onset Pompe disease (LOPD) affects more than one organ, with its primary symptom being muscle weakness. LOPD can occur at any age, typically without cardiomyopathy in the early years of life. In LOPD, cardiovascular symptoms may occur in adulthood, although this is rare.⁷¹⁰

In the infantile form of Pompe disease, severe hypertrophy is always observed in both ventricles. Myocardial hypertrophy rarely occurs in the adult form. Left ventricular systolic dysfunction may be rare. Right ventricular involvement is not seen in LOPD. Rhythm disorders such as sinus arrhythmias, supraventricular tachycardia, Wolff-Parkinson-White syndrome, or atrioventricular block requiring pacemaker implantation may occur in adult patients.^{710–712} Vascular involvement is rare in LOPD and is usually extracerebral. Due to glycogen accumulation in small vessels, vascular compliance may deteriorate, leading to dilated arteriopathy and dissection in the thoracic aorta.^{711,713}

Danon Disease

Danon disease is a rare X-linked disorder characterized by cardiomyopathy with either a hypertrophic or dilated phenotype, cognitive disability, and proximal myopathy. It is caused by the deficiency

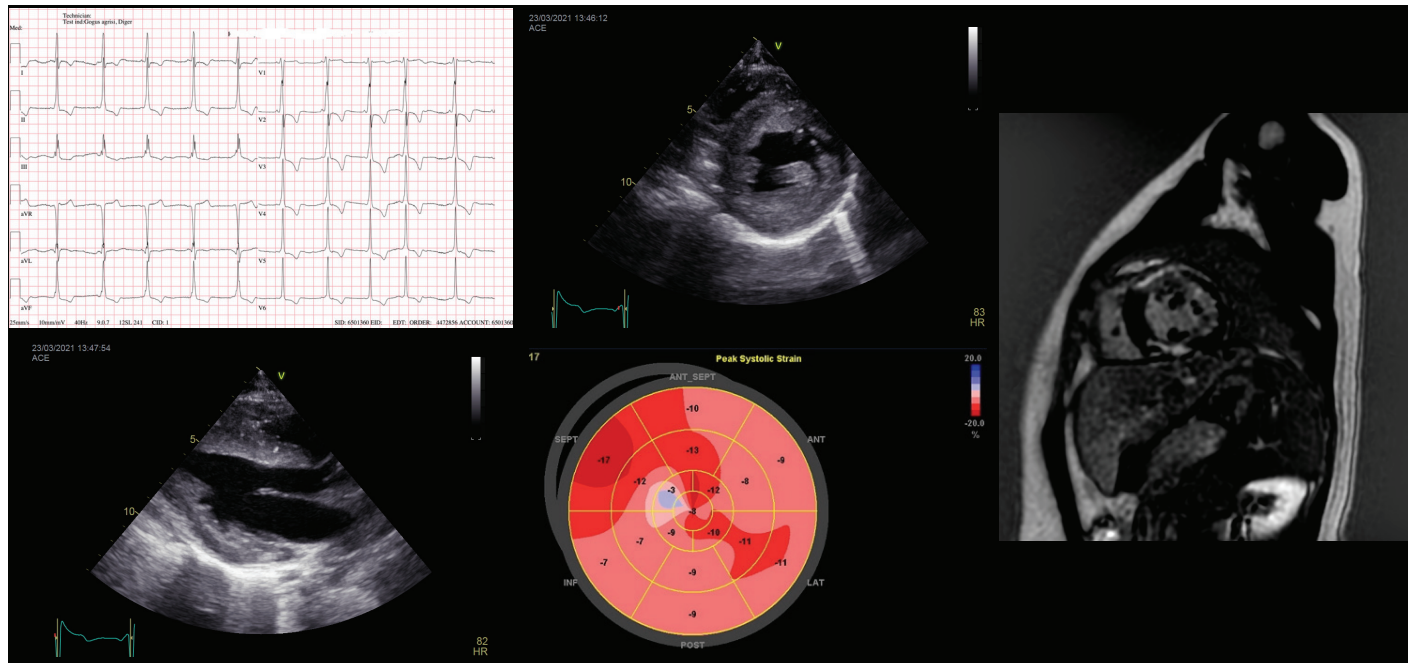


Figure 114. Danon disease; WPW appearance on ECG, concentric left ventricular hypertrophy, global longitudinal strain reduction in the left ventricle, and mid-ventricular diffuse fibrosis with preserved septum on MRI.

of lysosome-associated membrane protein-2 (LAMP2), which lines the inner surface of the lysosomal membrane and acts as a receptor for proteins to be exported and degraded through lysosomes in chaperone-mediated autophagy. The LAMP2 gene is located on chromosome Xq24. The dilated cardiomyopathy phenotype is often fatal. Danon disease is present in 1-6% of patients with left ventricular hypertrophy of unexplained etiology and in 17% of patients with hypertrophy accompanied by elevated serum creatine kinase or Wolff-Parkinson-White syndrome.⁷⁰⁶ Men are more severely affected than women. Affected women typically have milder and later-onset cardiac symptoms, with no male-to-male transmission of the disease. Male patients with Danon disease exhibit lower cognitive abilities and higher creatine kinase levels. Cardiomyopathy progresses more rapidly in males, who may require a pacemaker, left ventricular assist device, or heart transplantation in their second and third decades. This poor clinical course generally occurs a decade later in female patients. Female patients usually have better cognitive abilities and lower creatine kinase levels.

In the multicenter European registry study, 53% of patients with Danon disease were male, with the age at diagnosis ranging from birth to 42 years in men and from 2 to 65 years in women. Cardiac involvement is seen in 96% of cases, with extracardiac findings being more prominent in men than in women.

Left ventricular hypertrophy was reported in 73% of male patients and 74% of female patients. Left ventricular systolic dysfunction was noted in 40% of men and 59% of women. The age at first hospitalization for heart failure was younger in men than in women (18 ± 6 years versus 28 ± 17 years). Heart failure was the leading cause of death in most patients (59%). Left ventricular systolic dysfunction is the strongest predictor of a negative prognosis. Eight men and eight women received a heart

transplant or a left ventricular assist device. Female patients who underwent heart transplantation had a better prognosis than male patients.⁷¹⁴

In the early stages of Danon disease, there is severe concentric hypertrophy of the left ventricle, while in the final stage, the ventricle becomes dilated and thin. On magnetic resonance imaging (MRI), the hypertrophy appears relatively concentric and is more pronounced in male patients than in females. Additionally, in male patients, late gadolinium uptake is not distributed homogeneously. MRI shows widespread late gadolinium enhancement with a preserved mid-ventricular septum. This finding distinguishes Danon cardiomyopathy from other cardiomyopathies (Figure 114).^{715,716}

PRKAG2

PRKAG2 is an autosomal dominant glycogen storage disease caused by mutations in the PRKAG2 gene. The affected protein, 5'-AMP-activated protein kinase subunit gamma-2, is a protein kinase that increases AMP production and ATP catabolism in response to various cellular stressors.⁷¹⁷ The most common ECG abnormality is a short PR interval (68%), followed by right bundle branch block. QRS depolarization disturbances, delta waves (slurs), and clinically significant AV or sinoatrial blocks are also common. Secondary repolarization abnormalities, high-voltage QRS complexes can often be seen without significant left ventricular hypertrophy on echocardiography. Sometimes, this is accompanied by left axis deviation.⁷¹⁸ On echocardiography, hypertrophy is typically limited to the left ventricle, with the right ventricle rarely involved. In PRKAG2, left ventricular hypertrophy is usually eccentric. In the early stages of the disease, it involves the mid-infero-lateral segments, while in advanced cases, more widespread hypertrophy occurs. In very advanced stages, thickening of the interventricular septum becomes more evident. Generally, hypertrophy does not

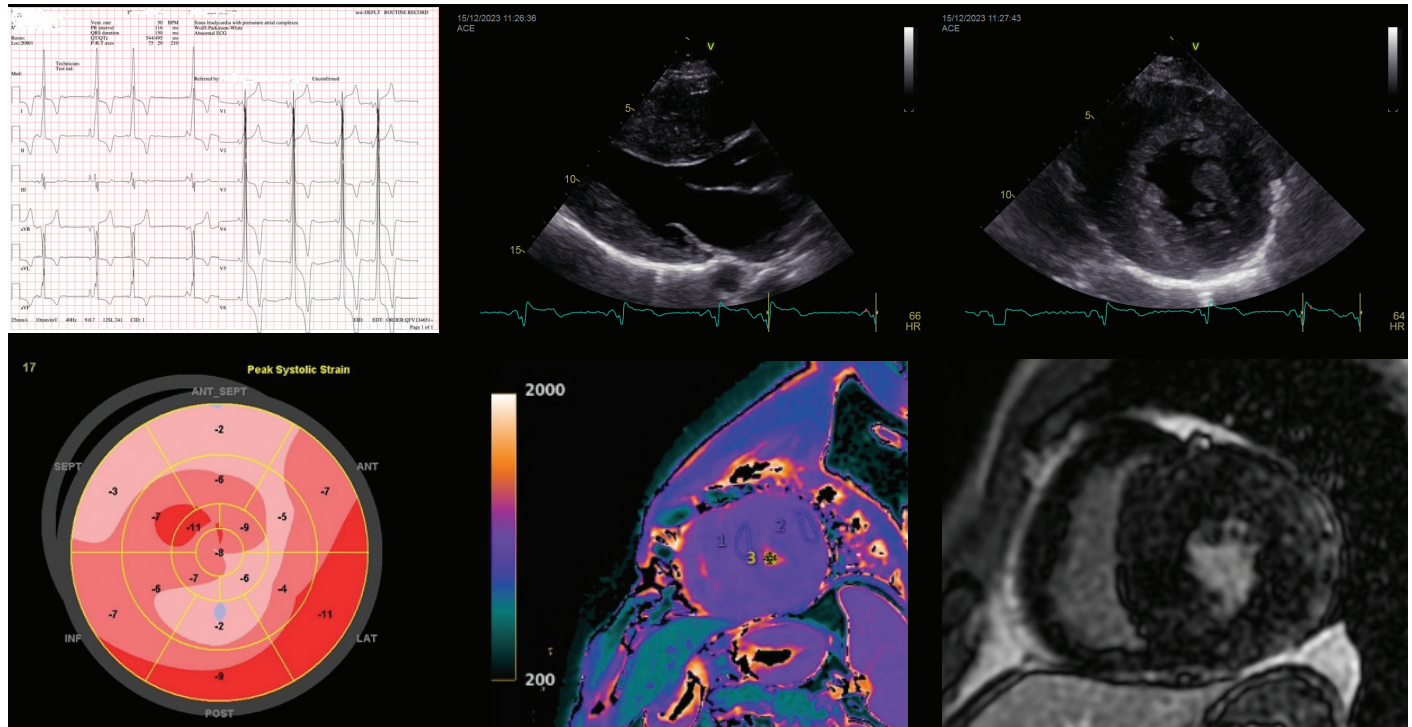


Figure 115. PRKAG 2; WPW appearance on ECG, concentric left ventricular hypertrophy, global longitudinal strain decrease in the left ventricle, thick trabeculae in the apical region, widespread native T1 decrease in MRI, and the beginning of fibrosis in the postero-lateral region.

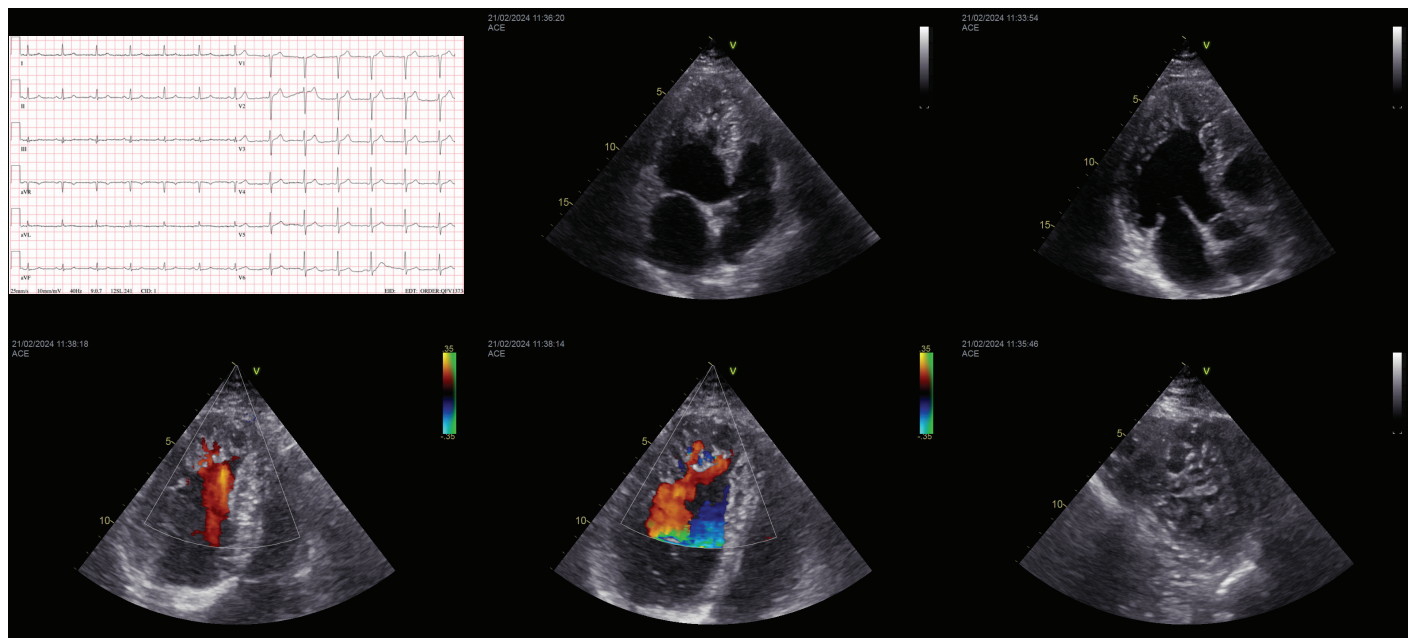


Figure 116. PRKAG 2; Doppler niquist limit is reduced to visualize non-specific ECG, concentric severe left ventricular hypertrophy, significant increase in trabeculation in the apical part of the left ventricle, and the filling of the trabeculae with Color Doppler.

correlate with the ECG, and the wall thickness is often ≤ 1.5 cm. An important echocardiographic finding is apical hypertrabeculation. However, as in non-compaction, a clear distinction between compact and non-compact layers cannot be made, and they appear as coarser trabeculae.⁷¹⁸ In a color Doppler study, the recesses between the trabeculae seen in PRKAG2 cardiomyopathy

are filled with blood from the ventricle. In magnetic resonance imaging (MRI), the native T1 value is low in patients without late gadolinium uptake in the early stages of the disease. In advanced disease, native T1 increases due to fibrosis, and gadolinium uptake becomes widely evident (Figures 115–116).⁷¹⁹

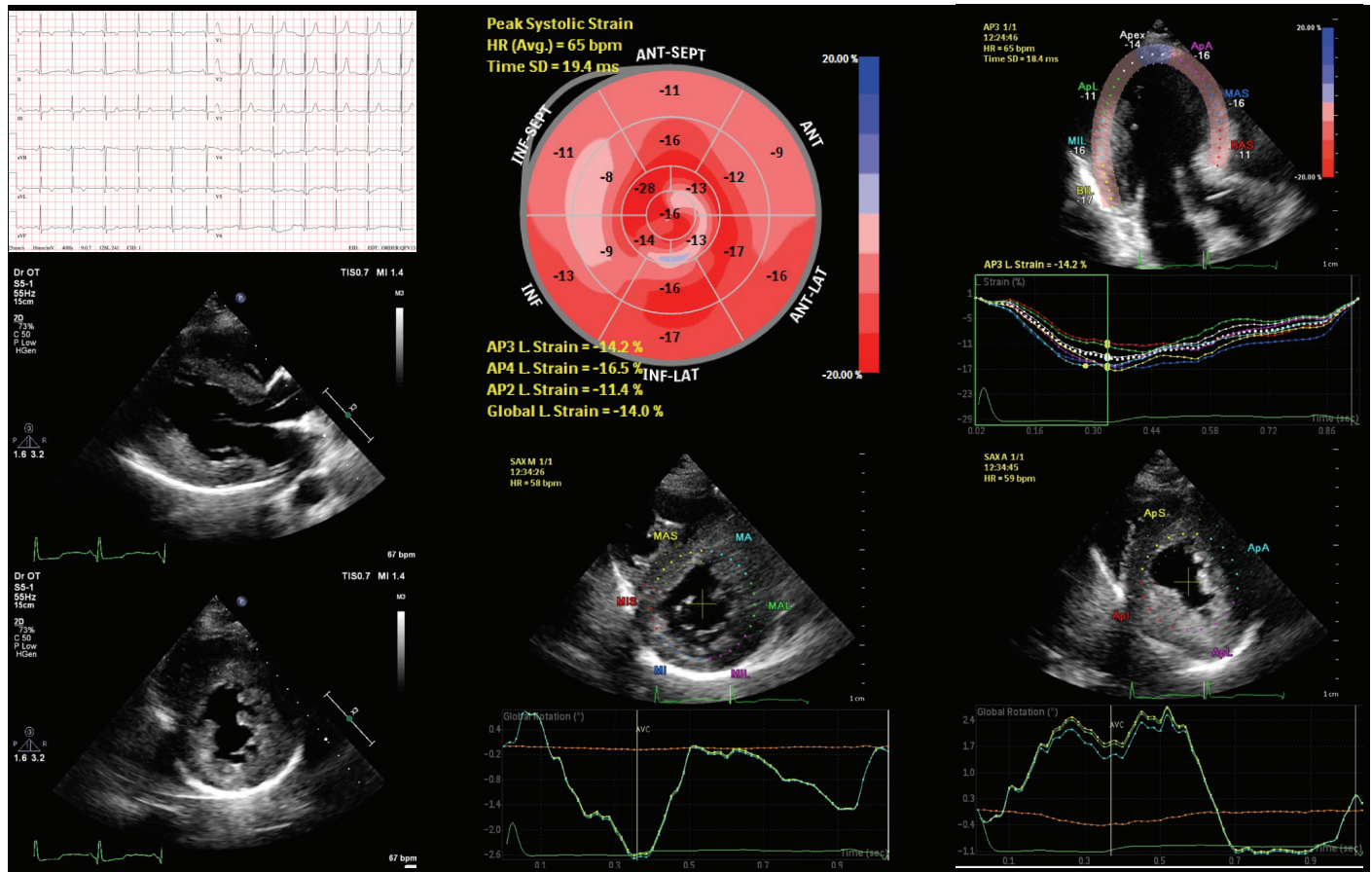


Figure 117. Glycogen Storage Disease III (Core-Forbes disease); ECG left ventricular hypertrophy, fragmented short PQ, concentric severe left ventricular hypertrophy, global longitudinal strain reduction in the left ventricle (longitudinal dysfunction), normal left ventricular circumferential twisting (preserved circumferential function).

Glycogen Storage Disease III (Cori-Forbes Disease)

Cori-Forbes disease is an autosomal recessive disorder caused by a deficiency of the debranching enzyme. Without this enzyme, glycogen cannot be fully broken down, leading to abnormal intracellular glycogen accumulation in the liver and cardiac/skeletal muscle. Symptoms include hepatomegaly, hypoglycemia, hyperlipidemia, and growth retardation. The severity of clinical symptoms varies depending on the age of onset and the rate of disease progression.⁷²⁰ Postmortem cardiac examinations reveal fibrosis, vacuolation of myocytes, glycogen accumulation in the atrioventricular node, and glycogen accumulation in intramyocardial arteries associated with smooth muscle hyperplasia.⁷²¹ Left ventricular hypertrophy is observed in GSD Type III, although its prevalence is unknown. Heart failure is rare. There is no direct correlation between the severity of myopathy, creatine kinase elevation, and cardiac involvement, but left ventricular hypertrophy increases with age. Echocardiography shows varying frequencies of left ventricular hypertrophy and heart failure, while MRI findings indicate fibrosis (Figure 117).

Glycogen Storage Disease Type IV

Andersen disease, or GSD Type IV, is caused by mutations in the GBE1 gene located at 3p12, which encodes the

glycogen branching enzyme (GBE). GSD Type IV accounts for approximately 3% of all GSDs.^{717,723,724} Loss of function of GBE1 leads to the accumulation of abnormal glycogen chains with fewer branch points, known as polyglucosans. These polyglucosans accumulate in metabotoxic polyglucosan bodies, disrupting the function of organs and tissues, particularly the neuromuscular system and liver. GSD IV exhibits various clinical phenotypes, characterized by different mutations, tissue involvement, and clinical manifestations. The age of onset ranges from newborn to adulthood, with initial symptoms typically appearing in childhood. Liver involvement is prominent, often leading to cirrhosis and premature death. However, some patients may experience milder liver involvement and reach adulthood without requiring a liver transplant. Cardiac findings generally result from the accumulation of amylopectin-like polysaccharides in the myocardium.^{717,722,723} Clinically, GSD IV may present as either hypertrophic or dilated cardiomyopathy.⁷²³

Glycogen Storage Disease Type XV

Glycogen storage disease type XV is a rare disease caused by heterozygous mutations in the glycogenin type 1 (GYG1) gene on chromosome 3q24. The prevalence is estimated to be less than 1/1,000,000. The disease predominantly affects

Table 35. Recommended staging system for hypertrophic cardiomyopathy in Friedreich's ataxia

Stage	
0	No Friedreich ataxia cardiomyopathy ECG, echocardiography, MRI and hsTNT are normal
I	Mild Friedreich ataxia cardiomyopathy T-wave inversion, posterior wall thickness < 11 mm, no fibrosis on MRI, Ejection fraction ≥ 55%, hsTNT normal
II	Middle Friedreich ataxia cardiomyopathy T-wave inversion, posterior wall thickness ≥ 11 mm, no fibrosis on MRI, Ejection fraction ≥ 55%, hsTNT normal
III	Severe Friedreich ataxia cardiomyopathy Fibrosis on MRI, high hsTNT
IV	End-stage Friedreich ataxia cardiomyopathy Ejection fraction < 55%

*Modified from Weidemann F, Liu D, Hu K, et al. The cardiomyopathy in Friedreich's ataxia – New biomarker for staging cardiac involvement. *Int J Cardiol.* 2015;194:50–57.

the heart and skeletal muscles. Seven patients with cardiac symptoms, including hypertrophic cardiomyopathy, heart failure, and late-onset coronary artery disease, have been reported. Endomyocardial biopsy often reveals hypertrophic cardiomyocytes with enlarged nuclei, large centrally located vacuoles containing periodic acid–Schiff–positive material, and glycogen depletion in the cytoplasm.^{717,724,725}

Phosphoglucomutase 1 Deficiency

Phosphoglucomutase 1 deficiency (PGM1–CDG), previously known as glycogen storage disease type XIV, presents with two main phenotypes: myopathic and multisystemic. The multisystemic phenotype includes congenital malformations such as cleft palate, bifid uvula, heart valve anomalies, anal atresia, and vertebral anomalies, along with endocrine and hematological abnormalities, and involvement of the heart, muscles, and liver. In PGM1–CDG, the age of onset varies, and cardiac involvement is common. The most frequent cardiac finding is dilated cardiomyopathy, while conduction and other structural heart abnormalities are less common. On ECG, a long QT interval, ST wave elevation, T wave inversion, sinus tachycardia, and minor incomplete intraventricular conduction disorders may be observed.⁷²⁶

Friedreich's Ataxia Hypertrophic Cardiomyopathy

Friedreich's Ataxia is an autosomal recessive neurodegenerative disease caused by mutations in the Frataxin gene, affecting the central and peripheral nervous systems and the heart. Frataxin is a protein that acts as an iron chaperone and is essential for energy metabolism. Its levels increase in proportion to the energy metabolism requirements of the tissue. Irregularities in the frataxin protein result in involvement of cardiac muscle cells and neurons.^{727,728} In the classical type, the first signs of involvement begin before the age of 20 and the disease progresses aggressively. When symptoms start after the age of 25, it is referred to as Late Onset Friedreich Ataxia (LOFA), and when they start after the age of 40, it is called Very Late–Onset Friedreich Ataxia (VLOFA). LOFA and VLOFA are very rare, progress more slowly, and have a better prognosis.

The most prominent neurological findings in Friedreich's Ataxia include ataxia, dysarthria, lower extremity areflexia, lower extremity muscle weakness, auditory neuropathy, neurogenic bladder, gastropathy, optic nerve atrophy, and sleep apnea. Scoliosis, pes cavus, insulin resistance, and diabetes are also common orthopedic and endocrinological issues. Major cardiac findings include hypertrophic cardiomyopathy, progressive left ventricular dilatation, and heart failure. Cardiac involvement indicates a poor prognosis, particularly in cases where the disease begins early.⁷²⁹ Friedreich's Ataxia is one of the leading causes of hypertrophic cardiomyopathy in early childhood and adolescence. Left ventricular hypertrophy begins with mitochondrial proliferation due to the Frataxin protein disorder. This disrupts the cellular energy chain, leading to intracellular iron accumulation, fibrosis, and subsequent loss of contractile elements.^{730,731}

In Friedreich's Ataxia patients, concentric left ventricular hypertrophy is common; asymmetric hypertrophy is very rare. Diastolic wall thickness is usually less than 15 mm, the ejection fraction is preserved, and outflow tract obstruction is typically absent. Early cardiac involvement often indicates early neurodegenerative deterioration, though there is generally no specific relationship between the degree of neurological pathology and cardiac involvement. Diastolic dysfunction is rare in the early stages of the disease. In the advanced stage, the left ventricle dilates and significant systolic dysfunction develops. Left ventricular global longitudinal strain loss is one of the first findings and may begin before hypertrophy. However, there is no pathognomonic Bull's Eye pattern for the disease; strain loss affects all segments similarly. As the disease progresses, the strain deteriorates further. Ventricular dilation is one of the first findings indicating disease progression.^{732–734} Fibrosis increases with ventricular dilation, resulting in increased late gadolinium accumulation. Generally, fibrosis is patchy and irregular, affecting different left ventricular wall segments. Its typical location is the middle part of the myocardium, but a specific site for late gadolinium uptake in the left ventricle has not been identified. Due to iron accumulation in the pathophysiology of the disease, the native T1 value initially decreases slightly. However, in the later stages of the disease, with the development of widespread fibrosis in the left ventricle, the native T1 value begins to increase

again.⁷³⁵ Coronary vascular disease is rare, but microvascular damage due to insulin resistance and diabetes, along with associated perfusion disorders, is common on nuclear imaging. Weidemann et al.⁷³⁶ proposed a staging system for Friedreich's Ataxia cardiomyopathy (Table 35). However, this staging is not sufficient to determine prognosis due to the lack of evidence for its prognostic usefulness.

Negative T waves, especially in the inferolateral leads, are present in almost all patients with Friedreich's Ataxia and are the earliest ECG finding of cardiomyopathy. Many patients also exhibit hypertrophy, left axis deviation, and other repolarization abnormalities. Particularly supraventricular arrhythmias are more common (supraventricular tachycardia, atrial fibrillation, and flutter).⁷²⁸

Cardiotoxicity-associated Cardiomyopathy

Objective: When should we use the term cardiotoxicity? How should we evaluate it? What is the role of imaging in patient follow-up?

Numerous definitions have been proposed in the past to describe the range of cardiovascular toxicity related to cancer treatment. However, a standardized definition was established in the 2022 Cardio-Oncology guideline. This guideline was developed in collaboration with the European Society of Cardiology (ESC), the European Haematology Association (EHA), the European Society for Therapeutic Radiology and Oncology (ESTRO), and the International Cardio-Oncology Society (IC-OS). While it was once believed that cardiotoxicity was solely a consequence of chemotherapy, the discovery of new treatment methods and a deeper understanding of cardiovascular side effects have broadened this concept. It is now referred to as cancer therapy-related cardiovascular toxicity (CTR-CVT). In clinical settings, the term "cancer therapy-related cardiac dysfunction (CTR-CD)" is used interchangeably to denote the same condition. These terms are preferred because they more accurately convey the etiological connection between conditions related to cardiac injury and the broad spectrum of cancer treatments. This spectrum includes conventional chemotherapy, immunotherapy, targeted therapies, and radiotherapy.⁷³⁷ CTR-CVT is categorized based on the clinical presence or absence of heart failure and the severity of the condition. Table 36 provides a summary of cardiotoxicity based on clinical and echocardiographic findings.

Pathogenesis of Cancer Therapy Associated Cardiovascular Toxicity

The "multiple hit" model suggests that heart failure arises from a multifactorial etiology. When this model is applied to CTR-CVT, it indicates that patients with either overt or subclinical cardiovascular (CV) disease are at a higher risk of myocardial damage and cardiotoxicity from cancer treatment,

Table 36. Diagnosis of Cancer Treatment-Related Cardiovascular Toxicity⁷³⁷

Symptomatic (HF)	
Very Severe	HF necessitating inotropic support, mechanical circulatory support, or consideration of transplantation
Severe	Hospitalization due to HF
Moderate	Requirement for outpatient intensification of diuretic and HF therapy
Mild	Presence of mild HF symptoms, with no need for intensification of therapy
Asymptomatic	
Severe	New LVEF reduction to <40%
Moderate	New LVEF reduction by ≥10 percentage points to an LVEF of 40–49% or New LVEF reduction by <10 percentage points to an LVEF of 40–49% AND either new relative decline in GLS by >15% from baseline or New rise in cardiac biomarkers
Mild	LVEF ≥50 and new relative decline in GLS by >15% from baseline and/or new rise in cardiac biomarkers

HF, Heart failure; LVEF, Left ventricular ejection fraction; GLS, global longitudinal strain.

Table 37. Classification and Characteristics of Cancer Therapy–Related Cardiotoxicity⁷⁴²

	Type 1	Type 2
Characteristic Agents	Anthracyclines	Anti-HER2 Antibody, Tyrosine Kinase Inhibitors
Mechanism of Cardiac Dysfunction	• Direct cardiomyocyte necrosis • Free radical formation • Oxidative stress/damage	• Cardiomyocyte dysfunction • Blocked ErbB2 signaling
Clinical Course and Response to Treatment	• Permanent cardiomyocyte damage from the initial drug administration • Persistent and irreversible cardiac dysfunction	• Typically, reversible cardiomyocyte dysfunction • Good prognosis • High likelihood of recovery in 2–4 months
Myocardial Biopsy Findings	• Vacuoles • Myofibrillar disarray • Necrosis	• No characteristic changes

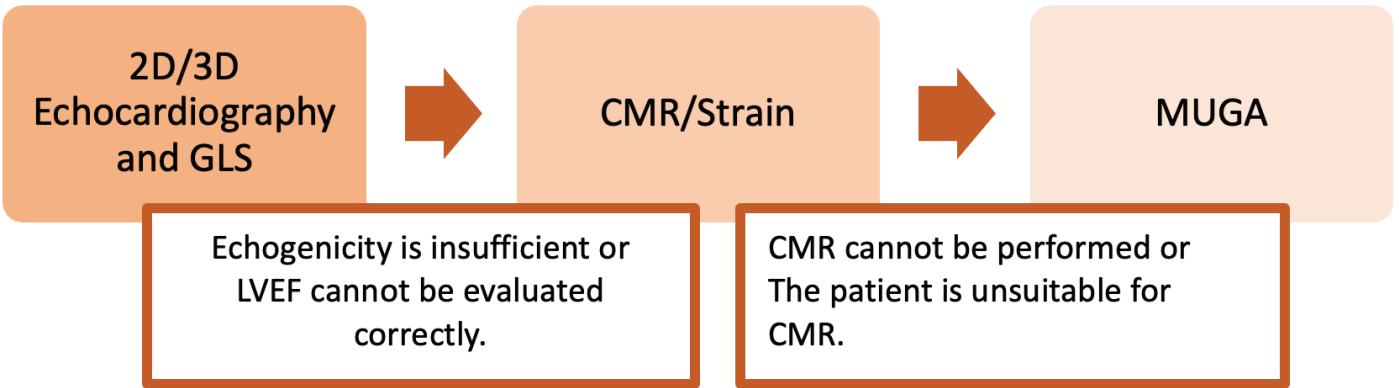


Figure 118. Ranking of Imaging Modalities for Monitoring Cancer Therapy–Induced Cardiomyopathy. The timing and frequency of surveillance should be determined based on the type of chemotherapy and baseline cardiac risk.

due to their already diminished cardiac reserves. The presence of each modifiable and non-modifiable CV risk factor further elevates the risk of toxicity.⁷³⁸

Risk markers for cardiotoxicity related to cancer include the site of the cancer such as pancreatic, renal, lung, or lymphoma and its stage for instance, advanced. Factors associated with cancer that may elevate the risk of cardiovascular disease include increased coagulability, invasion of the cardiovascular system, and high output states. Additionally, risk factors tied to cancer treatment encompass previous radiotherapy, especially when targeted at the heart and mediastinum, and prior exposure to anthracycline or hormone therapy.⁷³⁹

Molecular Characteristics of Cancer Therapy Associated Cardiotoxicity

The mechanisms of action of anthracycline and HER2 inhibitors including trastuzumab and its derivatives are among the most common causes of cardiotoxicity. Anthracycline cardiotoxicity is thought to result from free radicals produced by the inhibition of topoisomerase-II β and an increase in oxidative stress. This leads to a phenotype of chronic dilated cardiomyopathy characterized by cellular damage, myocyte death, and myocardial fibrosis. The risk of cardiotoxicity from anthracyclines is dose-dependent and can be reversible if detected early and treated properly.⁷⁴⁰

The pathogenesis of cardiotoxicity associated with HER2 inhibitors, such as trastuzumab, remains poorly understood. However, it is believed to involve pathological changes in cardiomyocyte structure and alterations in gene expression that

regulate cardiac and mitochondrial function, as well as DNA repair.⁷⁴¹ Table 37 details the characteristics of cardiotoxicity associated with both types of agents.

Radiotherapy-induced Cardiomyopathy

Exposure to radiation in the thoracic region can significantly increase the risk of non-ischemic cardiomyopathy for several reasons. These reasons encompass direct fibrosis of the myocardium, hypertrophy as a secondary response to valvulitis, restrictive cardiomyopathy, and constrictive pericarditis. Recent studies have shown that the prevalence of restrictive cardiomyopathy following radiotherapy to the mediastinum is approximately 10%. Radiotherapy can lead to cardiotoxicity through mechanisms such as myocardial and epicardial fibrosis, capillary narrowing due to endothelial damage, and infiltration of smooth muscle cells triggered by inflammatory cytokines and cell proliferation. Primarily, radiation contributes to diastolic dysfunction and restrictive cardiomyopathy by increasing myocardial stiffness.⁷⁴³

Imaging in Cancer Therapy Associated Cardiotoxicity

Assessing the CV risk of cancer patients using clinical and imaging methods, along with biomarkers, is crucial for continuing cancer treatments without interruption and minimizing adverse effects on the CV system. Cardiovascular imaging plays a pivotal role in detecting subclinical diseases and evaluating the extent of pre-existing cardiac comorbidities before making treatment decisions. Furthermore, a multimodal approach is essential for surveillance, identifying changes during treatment, and, importantly, for the long-term follow-up of these patients.⁷⁴⁴ (Figure 118).

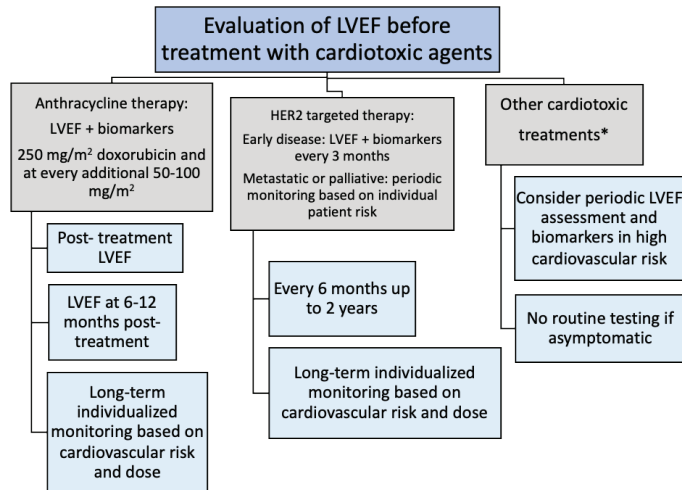


Figure 119. Timing of LVEF Assessment in Asymptomatic Patients Before, During, and After Treatment with Agents Known to Cause CTR-CVT, Based on ESC Guidelines.⁷³⁷

*Other cardiotoxic therapies include tyrosine kinase inhibitors, proteasome inhibitors, BRAF inhibitors, MEK inhibitors, immune checkpoint inhibitors and antimetabolites.

● Before treatment ● During treatment ● After treatment

Transthoracic Echocardiography

Echocardiography stands as the preferred imaging method in the management of cancer patients due to its accessibility, reproducibility, cost-effectiveness, lack of radiation, and safety for individuals with chronic kidney disease. However, emerging literature and clinical practice indicate that the ejection fraction (EF), which is the primary measure of left ventricular (LV) systolic function and recommended for monitoring cardiotoxicity, exhibits considerable variability, approximately 10%. In this context, EF measured by three-dimensional (3D) echocardiography is seen as more accurate and reproducible, with reduced inter-observer variability (around 5-6%). Three-dimensional echocardiography represents the most consistent method for assessing LVEF, though its precision relies on a clear definition of the endocardial border. This requirement may restrict its applicability in patients with a history of mastectomy and chest radiotherapy or in obese patients.⁷⁴⁵ When 3D echocardiography is not an option due to availability issues or poor image quality, the linear method (Teicholz) should not be employed for EF measurement in two-dimensional (2D) echocardiography. Instead, the Biplane Simpson method is preferred for calculating EF with 2D echocardiography.⁷⁴⁶ For patients with subpar image quality, where two or more LV segments are indistinct, contrast agents are recommended.⁷⁴⁷ Unfortunately, the use of echo-contrast agents is impractical in some regions, such as Türkiye, due to accessibility issues.

The monitoring schedule for left ventricular ejection fraction (LVEF) recommended by ESC guidelines, before, during, and after treatment with agents known to cause cardiomyopathy, is outlined in Figure 119. Imaging protocols may vary based on the patient's changing risk status throughout the treatment process. Furthermore, the imaging schedule can be tailored to the individual characteristics of the patient, ensuring a personalized approach to monitoring and managing the risk of cardiotoxicity.

Research has demonstrated that relying solely on LVEF assessment for managing cardiotoxicity is inadequate for detecting early cardiac damage, particularly in younger patients.⁷⁴⁸ Consequently, more sensitive measures that focus on myocardial deformation and the characterization of myocardial tissue have been recommended for the early identification of cardiac injury. Recent studies on cardiotoxicity highlight that changes in myocardial deformation precede alterations in LVEF.⁷⁴⁹ For patients undergoing treatment with anthracycline and/or trastuzumab, 2D strain echocardiography using the speckle tracking technique has revealed myocardial dysfunction even when LVEF remains within normal ranges.⁷⁵⁰

Global longitudinal strain (GLS) is the most frequently utilized parameter in strain imaging. When possible, it should be incorporated into all echocardiographic imaging protocols for patients in cardio-oncology. A decline in GLS greater than 15% is indicative of subclinical left ventricular systolic dysfunction. Prompt initiation of cardioprotective therapy and diligent monitoring of these patients are crucial for ensuring the uninterrupted continuation of cancer treatment. Moreover, GLS offers significantly improved intra- and interobserver reproducibility and accuracy compared to 2D LVEF measured by the biplane Simpson method.⁷⁵¹ Given that there can be technical variations in measuring strain across different equipment brands, it is essential to perform serial GLS monitoring for the same patient using the same echocardiography machine.

The primary challenge in routinely reporting GLS through echocardiography lies in the necessity of clearly defining the endocardial border to guarantee an accurate measurement of GLS, similar to the precision required for an accurate LVEF assessment. As a result, strain echocardiography might not be feasible for all patients, particularly those who have undergone mastectomy. Myocardial deformation imaging can also be conducted using non-contrast cardiac magnetic resonance imaging (CMR), with the technique's specifics elaborated upon in the CMR section.

Cardiac Magnetic Resonance Imaging

CMR is recognized as the gold standard for the non-invasive assessment of LV volumes and LVEF due to its superior accuracy and reproducibility. CMR sequences that assess LVEF do not require exposure to radiation or the use of gadolinium-based contrast agents. CMR serves as the preferred alternative for confirming LVEF measurements when echocardiography provides inconsistent or inaccurate results, or when patients present with insufficient echogenicity. Vallabhaneni et al.⁷⁵² highlighted in their review the significant role of CMR in the early detection of cardiac toxicity, as it is capable of identifying even minor changes in myocardial tissue and offers detailed tissue characterization. Figure 120 illustrates the use of multimodality imaging to evaluate a patient with CTR-CVT. The primary drawbacks of CMR include its limited availability and high cost. It may also pose challenges for patients with claustrophobia; however, the process can be expedited using rapid non-contrast CMR protocols that focus on assessing the function of the left and right ventricles, typically taking only 10-20 minutes.^{27,753,754}

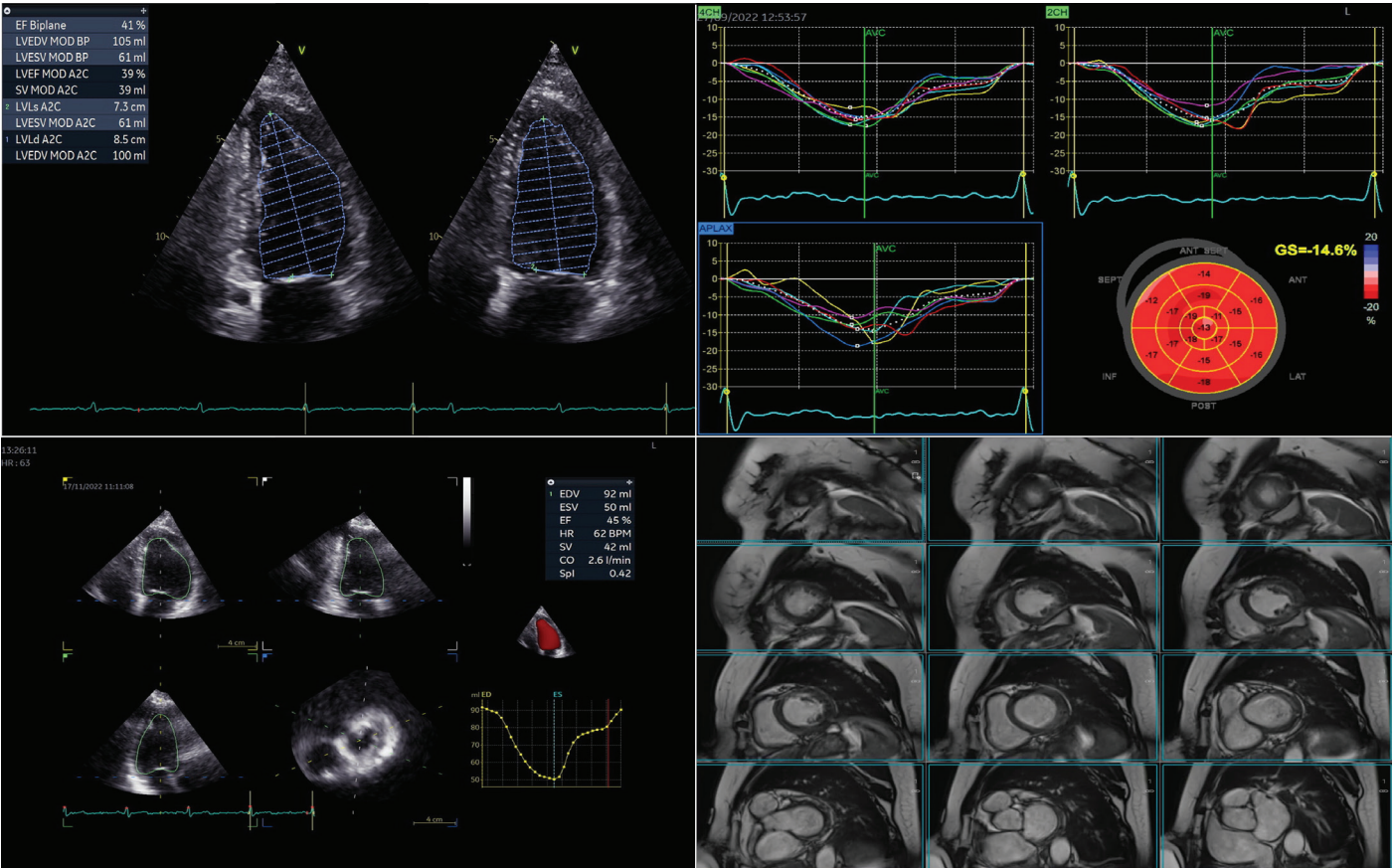


Figure 120. Multimodal Imaging of Cancer Therapy-Related Cardiac Dysfunction in a 52-Year-Old Patient Undergoing Trastuzumab Treatment for Breast Cancer. Initial LVEF (60%) and GLS (-20%) values decreased following trastuzumab therapy. Upper left panel: LVEF (41%) measured using the 2D echocardiography biplane Simpson method. Lower left panel: Volumetric LVEF measured at 45% by 3D echocardiography. Upper right panel: GLS (-14%) determined by strain echocardiography. Lower right panel: Volumetric LVEF (45%) assessed by CMR.

Table 38. CMR Protocol in Cardiotoxicity		
Scout/Anatomy Function	● Axial T1 weighted TSE black blood ● bSSFP (bright blood) long axis, 2,3, and 4 chambers ● bSSFP biventricular short axis	● Localization of cardiac planes ● Evaluation of morphology and functional parameters as LVEF ● Strain analysis for GLS and GCS
Tissue Characterization	● T1 Native (MOLLI) ● T2 STIR or SPAIR (black blood) short axis and long axis 4 chambers. ● T2 mapping	● Interstitial remodelling ● Evaluation of GLS, oedema and inflamed areas
Tissue Characterization After Contrast/Scar Imaging	● T1 weighted TSE and phase-sensitive inversion recovery gradient echo (early and delayed enhancement) ● T1 enhanced (MOLLI) in biplane short axis for base, middle and apex of ventricles	● Evaluation of hyperemic and flogistic areas ● Macroscopic and interstitial fibrosis

GLS, Global Longitudinal Strain; GCS, Global Circumferential Strain; TSE, Turbo Spin Echo; bSSFP, Balanced Steady-State Free Precession

Non-contrast CMR also facilitates myocardial deformation imaging. Strain measurement can be accurately performed using either existing cine arrays or custom strain-coded arrays and feature tracking, eliminating the need for intravenous gadolinium. Nonetheless, like echocardiographic GLS, CMR strain measurement programs are brand-specific, and serial follow-ups should ideally be conducted using the same machine. The recommended CMR protocol for assessing cardiotoxicity is outlined in Table 38.

Nuclear Imaging

Multiple gated acquisition (MUGA) scan is a scintigraphic technique that utilizes technetium-99m-pertechnetate-labelled red blood cells to evaluate LV function. ESC guidelines recommend the use of MUGA when echocardiography does not yield diagnostic results and CMR is not available. MUGA offers advantages over transthoracic echocardiography (TTE) in

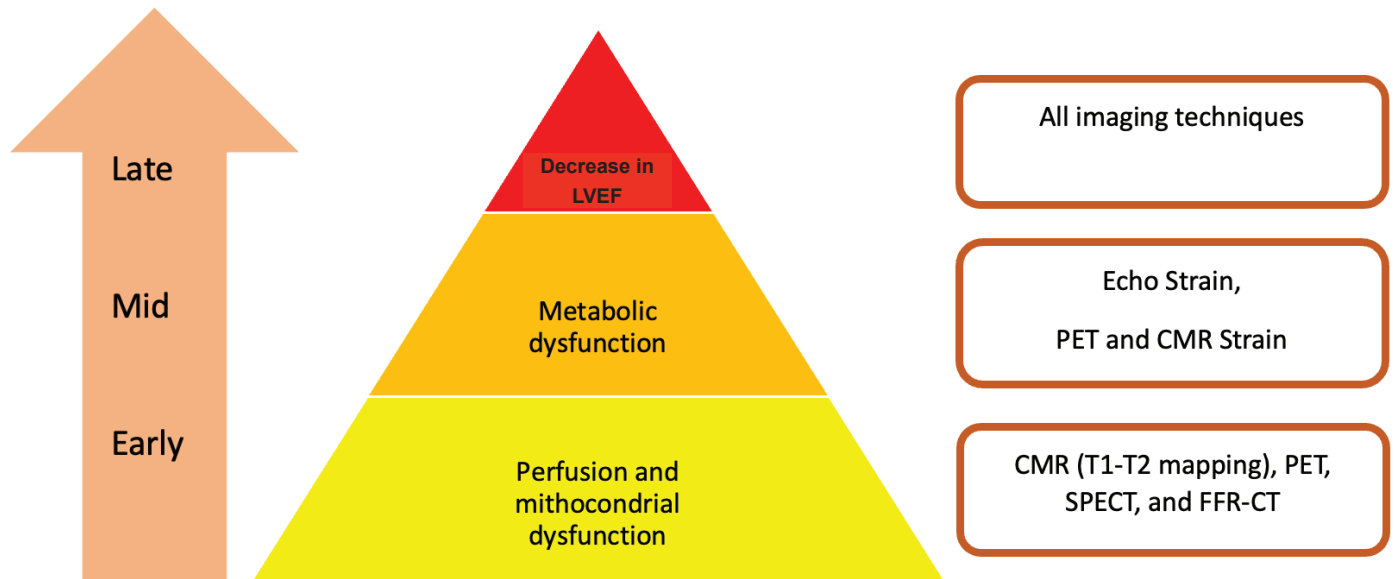


Figure 121. Detection of CTR-CMP (Cancer Therapy-Related Cardiovascular Toxicity) Using Non-Invasive Imaging Techniques.⁷⁵⁶

situations where patients may not tolerate echocardiography well, such as following recent radiation therapy or mastectomy. However, the limitations of MUGA, including its ECG-triggered nature, high cost, and significant radiation exposure, restrict its routine application. It is important to consider the potential for cumulative radiation exposure with MUGA, particularly in young women.⁷⁵⁵

Dynamic Multimodality Imaging in the Development of Chemotherapy-associated Cardiotoxicity

The progression of cancer therapy-related cardiomyopathy (CTR-CMP) is categorized into three stages: early, mid, and

late, as illustrated in Figure 121. The early phase is marked by perfusion and mitochondrial dysfunction. At this stage, CMR is instrumental in providing tissue characterization for edema and fibrosis—particularly through T1 and T2 mapping—and in determining microvascular dysfunction via perfusion CMR (Rest/Stress). The mid phase is characterized by metabolic dysfunction, resulting in impaired diastolic and strain parameters, which can be effectively assessed using echocardiography and CMR techniques. In the late phase, a reduced LVEF is observed, indicating the onset of myocardial damage. This reduction in LVEF is considered merely the “tip of the iceberg” in the context of underlying myocardial damage (Figure 121).

Takotsubo Cardiomyopathy

Takotsubo cardiomyopathy (TCM) is a type of non-ischemic cardiomyopathy first described by Dote et al.⁷⁵⁷ in Japan in 1991. The term "Takotsubo" (Tako: Octopus, Tsubo: Pot) refers to the end-systolic appearance of the left ventricle on echocardiography or left ventriculography, which resembles the pot used by Japanese fishermen to catch octopuses.^{757,758} TCM is also known as stress cardiomyopathy, broken heart syndrome, apical ballooning, and happy heart syndrome. It primarily affects postmenopausal women.

TCM is a reversible cardiomyopathy characterized by transient wall motion abnormalities in the left or right ventricle, or sometimes both.⁷⁵⁹ While it was previously considered benign and self-limiting, recent studies have shown that TCM is associated with adverse cardiovascular outcomes in both the short and long term.

Five patterns of TCM have been described in the literature. The typical pattern, which accounts for approximately 80% of TCM cases, involves ballooning and akinesia in the mid and apical segments of the left ventricle, with hyperkinesis in the basal segments. This pattern resembles the octopus-catching pot from which the syndrome derives its name. The second pattern is characterized by ballooning confined to the mid-ventricle, giving it a "Hawk's beak" appearance. In the third pattern, also known as reverse TCM, only the basal ventricle balloons and becomes akinetic or hypokinetic. The fourth pattern involves focal ballooning and akinesia of any segment. The fifth pattern affects the right ventricle either alone or in combination with the classic pattern.^{760–763}

Most patients experience a triggering physical (acute illnesses, elective or emergency surgical interventions, subarachnoid hemorrhage, stroke, etc.) or emotional (receiving news of death, losing someone close, economic difficulties, panic attacks, extreme fear or joy, etc.) stress before symptoms appear. However, a small number of patients do not exhibit these triggering stress factors.

Although the prognosis for TCM patients is generally positive and systolic function returns to normal within a few weeks or months, severe complications such as hypotension, cardiogenic shock, ventricular rupture, thrombus at the left ventricular apex, and ventricular arrhythmias, including torsade de pointes, have been reported in some cases.^{764,765}

Epidemiology

TCM constitutes 1–2% of patients presenting with acute coronary syndrome. It accounts for 0.02% of all hospitalizations in the United States. While it affects both genders, it is predominantly seen in women, occurring 10 times more frequently in women than in men. Although most affected women are postmenopausal and over the age of 50, there is no significant correlation between age and incidence in men.^{760,761} However, male gender is associated with higher mortality rates compared to female gender.

A significant increase in TCM incidence was observed during the COVID-19 pandemic, likely linked to social isolation, economic challenges, and heightened anxiety. Additionally, rare cases of TCM have been reported following COVID-19 mRNA vaccines.⁷⁶⁶

Pathophysiology

Although various hypotheses have been proposed regarding the pathophysiology of TCM since its first description, a definitive and clear mechanism has yet to be identified. The most current hypothesis

suggests that endothelial damage, microvascular dysfunction, and coronary vasospasm, triggered by reactive oxygen species and inflammatory cytokines, result from excessive catecholamine release and increased sympathetic activity following acute physical or emotional stress. This cascade leads to the production of the classic TCM pattern due to the high density of beta-adrenoreceptors (catecholamine receptors) in the apical region.

In a study by Witstein et al.,⁷⁶⁷ high catecholamine levels were found in TCM patients at the time of admission. Endomyocardial biopsies revealed endocardial band necrosis, indicative of catecholamine toxicity, along with localized inflammatory cell infiltration. These findings suggest that epicardial or microvascular coronary artery spasms, or direct myocyte damage due to intracellular calcium overload, could be responsible. However, coronary angiographies of TCM patients did not reveal any epicardial coronary artery spasms. Coronary artery spasms in response to the acetylcholine provocation test were detected in only a small number of patients.

In addition to elevated endogenous catecholamines, animal experiments have shown that administering exogenous catecholamines can induce TCM-like conditions. Similarly, cases of TCM have been reported in patients who received high doses of catecholamines.^{767–769} Other possible mechanisms include estrogen deficiency and chronic stress.

Clinical Features

Patients with TCM typically present with symptoms resembling acute coronary syndrome. Postmenopausal women often come to the emergency department complaining of chest pain, shortness

of breath, and palpitations. Rarely, patients may also present with syncope or cardiac arrest. A history of stressful physical or emotional events often precedes the onset of symptoms.⁷⁷⁰

The 12-lead electrocardiogram (ECG) of these patients may show findings such as ST segment elevation (usually in the chest leads), ST segment depression, T-wave inversion, and QT prolongation.^{771,772} Along with elevated troponin and CK-MB levels, an increase in B-Natriuretic Peptide (BNP) can also be detected.

Given these symptoms and findings, almost all patients are taken to the catheterization laboratory with a preliminary diagnosis of acute coronary syndrome (STEMI or Non-STEMI). When coronary angiography does not reveal significant coronary artery disease to explain the clinical presentation, further diagnostic investigations are conducted under the category of myocardial infarction without obstructive coronary artery stenosis (MINOCA).⁷⁷³

Diagnosis

When symptoms, signs, abnormal ECGs, and laboratory results are combined it is difficult to distinguish TCM from acute coronary syndrome. As a result, various diagnostic criteria have been developed. The first diagnostic criteria were proposed by Abe et al.⁷⁷⁴ in 2003. Subsequently, other criteria have been established, including the John Hopkins criteria, European Society of Cardiology Heart Failure Association criteria, Mayo Clinic criteria, and InterTAK criteria.^{165,770,775,776} Among these, the Mayo Clinic and InterTAK criteria are the most commonly used. The Mayo and InterTAK diagnostic criteria are summarized in Table 39.

InterTAK researchers developed the InterTAK diagnostic score to

Table 39. Diagnostic Criteria of Takotsubo Cardiomyopathy^{165,770}
Revised Mayo Clinic Diagnostic Criteria
➤ Transient hypokinesis, akinesis, or dyskinesis of the left ventricular mid segments with or without apical involvement; the regional wall motion abnormalities extend beyond a single epicardial vascular distribution; a stressful trigger is often, but not always, present
➤ Absence of obstructive coronary artery disease or acute plaque rupture
➤ New electrocardiographic abnormalities (ST elevation and/or T wave inversion) or modest troponin elevation
➤ Absence of pheochromocytoma and myocarditis
InterTAK Diagnostic Criteria
➤ Patients show transient left ventricular dysfunction (hypokinesia, akinesia or dyskinesia) presenting as apical ballooning or mid-ventricular, basal or focal wall motion abnormalities. Right ventricular involvement can be present. Besides these regional wall motion patterns, transitions between all types can exist. The regional wall motion abnormality usually extends beyond a single epicardial vascular distribution; however, rare cases can exist where the regional wall motion abnormality is present in the subtended myocardial territory of a single coronary artery
➤ An emotional, physical or combined trigger can precede a Takotsubo event, but this is not mandatory
➤ Neurologic disorders (subarachnoid haemorrhage, stroke/transient ischaemic attack or seizures) as well as pheochromocytoma may serve as triggers for takotsubo
➤ New ECG abnormalities are present (ST-segment elevation, ST-segment depression, T-wave inversion). Rare cases exist without any ECG changes
➤ Levels of cardiac biomarkers (troponin and creatine kinase) are moderately elevated in most cases; significant elevation of brain natriuretic peptide is common
➤ Significant coronary artery disease is not a contradiction in Takotsubo
➤ Patients have no evidence of infectious myocarditis
➤ Postmenopausal women are predominantly affected

assess the probability of TCM. This diagnostic score consists of seven parameters:

1. Female Gender (25 points)
2. Emotional Trigger (24 points)
3. Physical Trigger (13 points)
4. Absence of ST-Segment Depression (12 points)
5. Psychiatric Disorders (11 points)
6. Neurological Disorders (9 points)
7. QT Prolongation (6 points)

An InterTAK score of 70 or less indicates a low-to-medium probability of TCM, while a score above 70 indicates a high probability. Besides diagnostic criteria, invasive and non-invasive imaging methods such as ECG, echocardiography, invasive coronary angiography, coronary CT angiography, and cardiac magnetic resonance imaging (MRI) can assist in the diagnosis and differential diagnosis.

Diagnostic Methods

Electrocardiography

In the acute phase, various abnormalities are observed in the ECGs of TCM patients. The most common include ST elevation, ST depression, T-wave inversion, and QT prolongation.^{771,772} In a study evaluating 59 TCM patients from the Minneapolis Heart Institute, 56% of patients exhibited ST elevation (predominantly in the precordial leads), 17% had diffuse T-wave inversion, 10% had signs of improved anterior myocardial infarction (Q wave or R progression), and 17% had a normal ECG.

In the subacute or later stages, ECG findings can progress through different stages, similar to the patterns observed in pericarditis. Mitsuma et al. described four phases of ECG changes in TCM:

1. Phase 1: ST elevation, typically in the precordial leads and less frequently in the inferior or lateral leads.
2. Phase 2: T-wave inversion (days 1-3).
3. Phase 3: Return of the T-wave to normal (days 3-6).
4. Phase 4: QT prolongation with giant T-wave inversion (2-3 weeks).

These evolving ECG changes can provide valuable clues for diagnosing TCM in different stages of the condition.

Coronary Angiography

Since most TCM patients exhibit ST elevation on their ECG, they often undergo invasive catheter angiography. Typically, the coronary arteries appear normal, or mild stenosis (<50%) caused by atherosclerotic plaque may be observed. If TCM is suspected, performing left ventriculography during the same session can be highly beneficial for diagnosis.

Echocardiography

In patients who present to the emergency department with chest pain or shortness of breath, echocardiography (ECHO) is often the first imaging method used after obtaining a detailed history, performing a physical examination, and evaluating the ECG. ECHO plays a crucial role in assessing left ventricular systolic

function and regional wall motion abnormalities. Additionally, it is valuable for distinguishing TCM patterns and identifying potential right ventricular involvement.⁷⁷⁷

ECHO also allows for the evaluation of left ventricular outflow tract obstruction secondary to hyperkinesis in the basal segments and systolic anterior motion (SAM) of the mitral valve in the classical TCM pattern (Type 1). Diastolic dysfunction, which may occur in the acute phase of TCM patients, can be detected using Doppler ECHO parameters.

Cardiac Computed Tomography

Advancements in computed tomography (CT) technology over the past 20 years have enabled imaging of the coronary arteries with a very low radiation dose. The negative predictive value of cardiac CT is approximately 99%, making it highly effective for ruling out coronary artery disease. Although its use in TCM patients is limited, cardiac CT can be particularly useful for excluding coronary artery disease in TCM patients without ST segment elevation and those at low risk for acute coronary syndrome.

Cardiac Magnetic Resonance Imaging

Cardiac magnetic resonance (MR) imaging is the gold standard method for assessing the functions and volumes of both ventricles. Cardiac MR is increasingly used in daily practice to evaluate regional wall motion abnormalities, valve insufficiencies, myocardial tissue characterization (edema, fibrosis, infiltrative accumulation, etc.), and functional and anatomical assessment of the right ventricle. It does not require ionizing radiation and is not limited by acoustic window constraints.

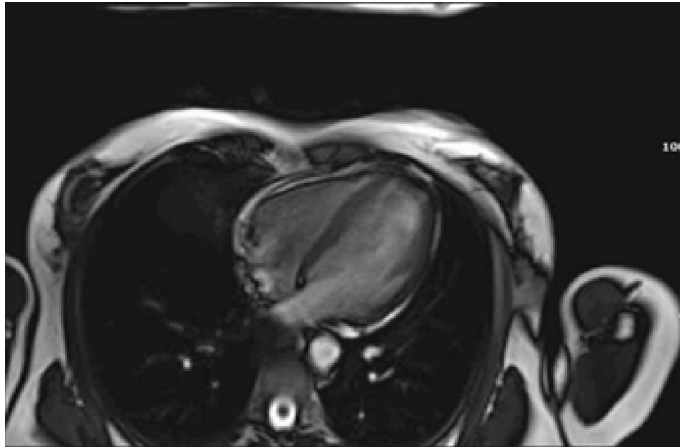
Cardiac MRI is particularly recommended in the differential diagnosis of patients with myocardial infarction with MINOCA.⁷⁷³ Cine imaging can easily evaluate hyperkinetic segments along with akinetic segments (Figure 122), detect outflow tract acceleration in the classical pattern, and identify mitral regurgitation secondary to systolic anterior motion.

Furthermore, cardiac MR can identify myocardial edema, a sign of inflammation, in ballooned and akinetic segments. Short Tau Inversion Recovery (STIR) sequences provide a qualitative assessment of edema, while T2 mapping offers a more quantitative measurement of its severity.

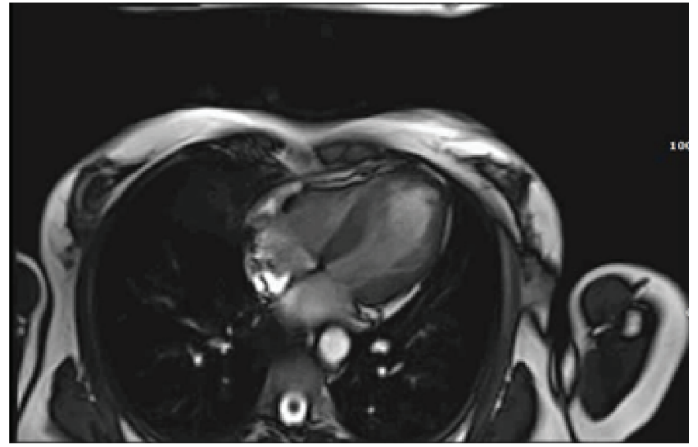
A crucial advantage of cardiac MR is its ability to differentiate TCM from acute myocardial infarction (MI). The late gadolinium enhancement (LGE) sequence typically shows subendocardial or transmural enhancement in patients with acute MI, while such enhancement is usually absent in TCM patients.⁷⁷⁸ Additionally, cardiac MR is frequently used to help exclude myocarditis, another potential cause of similar symptoms.

Prognosis

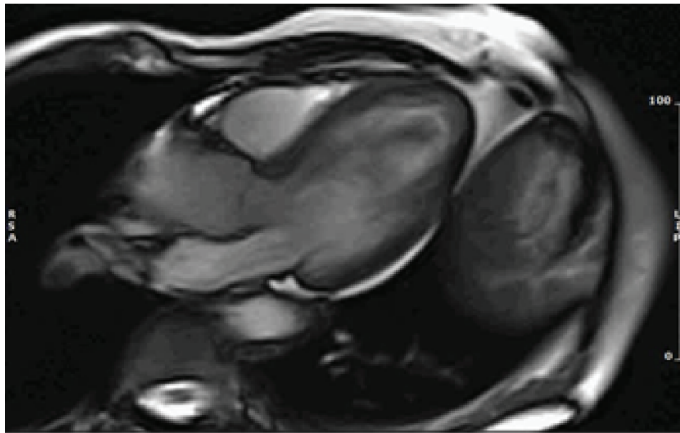
Generally, patients with TCM have a favorable prognosis. In approximately 95% of cases, left ventricular dysfunction improves within a few weeks. Recent studies estimate in-hospital mortality at around 5%, with most deaths occurring in hemodynamically unstable patients.⁷⁷⁹ Although men are less likely to develop TCM than women, their mortality rates are higher. Additionally, TCM triggered by physical stress has a higher mortality rate compared to TCM triggered by emotional stress.



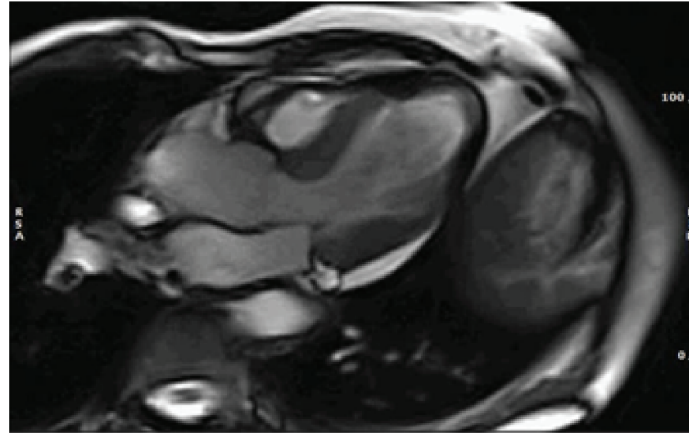
HLA end-diastole



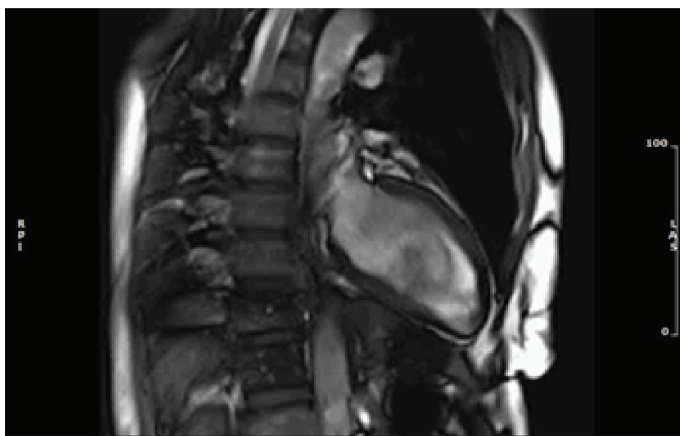
HLA end-systole



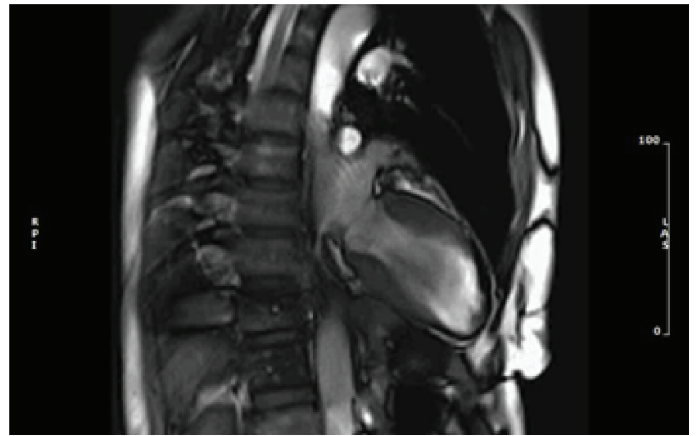
LVOT end-diastole



LVOT end-systole



VLA end-diastole



VLA end-systole

Figure 122. A case from my CMR archive for Takotsubo cardiomyopathy. HLA, VLA, LVOT views demonstrates mid and apical ballooning.

Atrial fibrillation (AF) is also an independent risk factor for mortality in TCM patients. Therefore, male gender, physical stress, and AF are important factors that should be considered in risk stratification for TCM patients.

Treatment

Due to the lack of randomized controlled trials for TCM, specific treatment protocols have not been established. Treatment approaches are generally tailored to the severity of

heart failure symptoms and are often based on case series or expert opinions.

Patients with TCM in cardiogenic shock should first be evaluated for left ventricular outflow tract obstruction. In these patients, catecholaminergic drugs such as adrenaline, noradrenaline, dobutamine, dopamine, and isoprenaline should be avoided, as their use has been associated with a 20% increase in mortality. Levosimendan may be beneficial in these patients.^{780,781}

In hemodynamically stable patients, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, beta-blockers, and mineralocorticoid receptor antagonists, used to treat systolic heart failure, may be considered. Diuretic and vasodilator drugs should be used in patients with pulmonary edema.⁷⁸²

Although beta-blockers have not been shown to reduce mortality in long-term TCM treatment, they should not be discontinued until left ventricular ejection fraction (EF) improves due to the elevated catecholamine levels in these patients. Patients with severe systolic dysfunction should be

evaluated for oral anticoagulant treatment if an apical thrombus is present.

Conclusion

TCM is detected in 1-2% of patients presenting with signs and symptoms of acute coronary syndrome. Although it was previously considered benign, in-hospital mortality is approximately 5%. Therefore, TCM should be considered in the differential diagnosis of MINOCA.

TCM should be suspected, particularly in postmenopausal women who present with new-onset chest pain and shortness of breath and have no significant stenosis on coronary angiography. Echocardiography (ECHO) and cardiac MR imaging play a crucial role in the diagnosis, assessment of complications, prognosis determination, and follow-up of TCM patients.

Video 29. <https://youtu.be/Hg-DUk39nQg>

Video 30. <https://youtu.be/V1RzHYwr7Wo>

Video 31. <https://youtu.be/MzpfKBuZF3o>

Left Ventricular Hypertrabeculation

Although left ventricular non-compaction (LVNC) was defined as a primary cardiomyopathy by the American Heart Association (AHA) in 2006,⁷⁸³ the 2023 European Society of Cardiology's 'Management of Cardiomyopathies' guideline classifies this condition not as a cardiomyopathy, but as a phenotypic feature characterized by prominent left ventricular trabeculae and deep recesses. This feature can occur in isolation or in conjunction with other abnormalities, including ventricular hypertrophy, dilatation, and/or systolic dysfunction. The guideline recommends using the term "hypertrabeculation (HT)" instead of LVNC, particularly in cases where the phenomenon is reversible or clearly initiates in adulthood.¹

While previous studies have suggested that hypertrabeculation arises due to an interruption in the transformation of non-compacted myocardium into compacted myocardium, recent evidence contradicts this hypothesis.⁷⁸⁴ Left ventricular hypertrabeculation is known to be associated with hereditary, developmental, or congenital heart diseases.⁷⁸⁴ It can manifest as a normal variant or result from a remodeling response to increased preload and afterload, secondary to factors such as pregnancy, sports activities, or ventricular dysfunction.^{785,786} The association of hypertrabeculation with left ventricular dilatation and dysfunction sparks significant debate. The question remains whether hypertrabeculation is a secondary response to changes in preload and afterload in ventricular dysfunction or represents a very rare cardiomyopathy that triggers this dysfunction, posing a perplexing dilemma.^{787,788}

Definition of Left Ventricular Hypertrabeculation

The diagnosis of left ventricular hypertrabeculation (LVHT) relies on cardiac imaging modalities. Despite the establishment of various diagnostic criteria for different modalities, which derived from studies involving small patient cohorts, these criteria lack standardization and definitive consensus. Typically, these criteria primarily emphasize morphological evaluation, disregarding functional assessment, which may result in the overdiagnosis of LVNC.⁷⁸⁹

While echocardiography serves as the primary imaging modality, cardiac magnetic resonance (CMR) with high resolution plays a crucial role in diagnosis, particularly in patients with limited echocardiographic windows. The role of cardiac computed tomography (CT) in diagnosis remains uncertain. However, it provides an opportunity to assess hypertrabeculation in patients who undergo CT for other indications, such as coronary artery or congenital anomaly examination.

Evaluation of Hypertrabeculation with Multimodality Imaging Methods

Echocardiography

Three separate echocardiographic criteria for diagnosing LVHT are outlined in Table 40. First, Chin et al.⁷⁹⁰ established a criterion based on the ratio derived from the short axis view at end-diastole, obtained by dividing the distance between the epicardial surface and the intertrabecular recesses (X) by the distance between the epicardial surface and the peak of the trabeculation (Y), where a ratio of less than 0.5 is diagnostic (Figure 123). However, this criterion, developed from a study involving only 8 cases, lacks clarity regarding the level at which the measurement should be taken and is not commonly preferred in daily clinical practice.

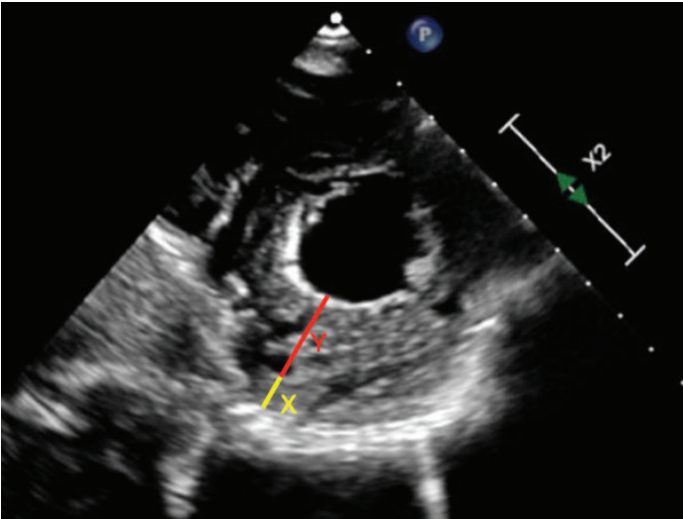


Figure 123. Chin criterion with transthoracic echocardiography: X (yellow line) / Y (red line) ≤ 0.5 in the short-axis view at end-diastole.

The second criterion, defined by Jenni et al.,⁷⁹¹ comprises four parameters measured from the short axis view at end-systole: 1. a ratio of thick noncompacted endocardial layer (NC) to thin compacted epicardial layer (NC/C) > 2; 2. predominance of NC in mid-lateral, mid-inferior, and apical segments; 3. blood flow in the deep intertrabecular recesses detected with color Doppler; and 4. absence of accompanying cardiac abnormalities (Figure 124). It's worth noting that the Jenni criteria are often applied regardless of the absence of accompanying cardiac abnormalities.⁷⁹²

Lastly, Stöllberger et al.⁷⁹³ published criteria involving five parameters observed at end-diastole in the apical four-chamber view: 1. more than three prominent trabeculations distal to the papillary muscles at the apex in a single imaging plane; 2. blood flow or perfusion in the trabecular recesses with color Doppler; 3. trabeculation and myocardium exhibiting the same echogenicity; 4. trabecular movement synchronous with ventricular contraction; and 5. NC/C ≥ 2 (Figure 125).

Table 40. Echocardiographic diagnostic criteria of left ventricular hypertrabeculation			
Criteria	Chin ⁷⁹⁰	Jenni ⁷⁹¹	Stöllberger ⁷⁹³
Cardiac Cycle	End-diastole	End-systole	End-diastole
View	Short axis	Short axis	Apical
Cut-off Value for Hypertrabeculation	X/Y ≤ 0.5	NC/C ≥ 2; predominance of NC in mid-lateral, mid-inferior, and apical segments; blood flow in the recesses with color Doppler; No accompanying cardiac anomalies	NC/C ≥ 2; more than three trabeculation distal to the papillary muscles; flow in the trabecular space with color Doppler; trabeculation and myocardium have the same echogenicity; trabecular movement synchronous with ventricular contraction

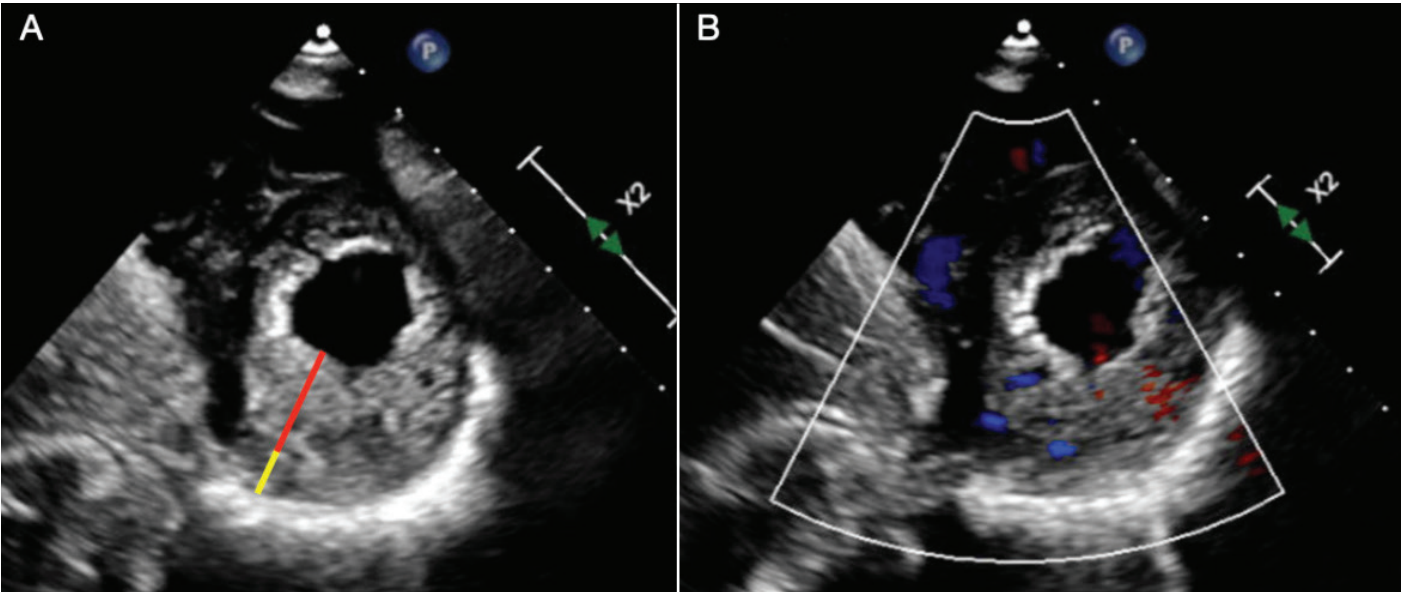


Figure 124. Jenni Criterion with Transthoracic echocardiography: (A) Noncompacted layer (red line) / compacted layer (yellow line) > 2 in the short-axis view at end-systole, with trabeculation predominance in the mid and apical segments. (B) Blood flow in intertrabecular recesses visualized with color Doppler.

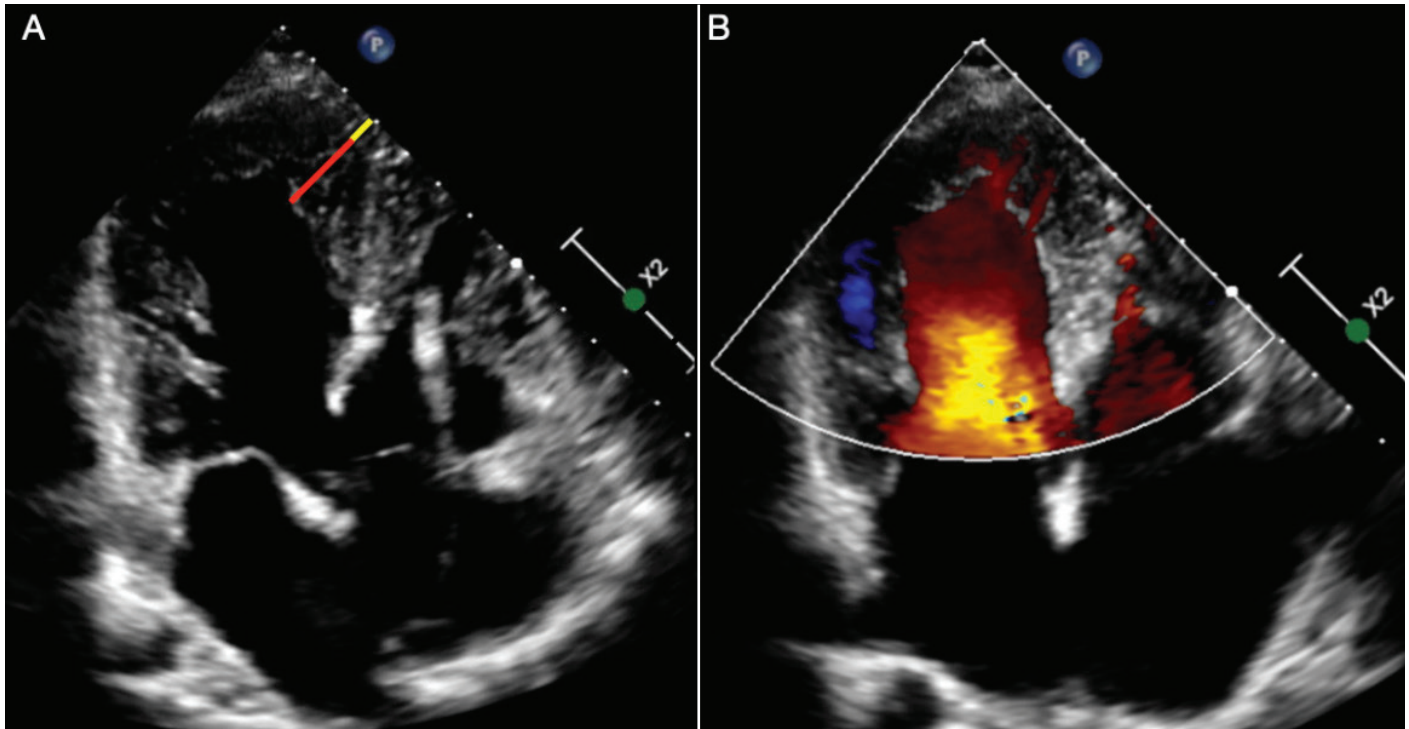


Figure 125. Stollberger criterion with transthoracic echocardiography in a 35-year-old male patient with biventricular hypertrabeculation and systolic dysfunction who had an implantable cardioverter-defibrillator due to ventricular tachycardia. (A) In the apical view at end-diastole, the noncompacted layer (red line) / compacted layer (yellow line) ≥ 2 , and trabeculations and myocardium move simultaneously with the same echogenicity. (B) Blood flow in intertrabecular recesses visualized with color Doppler.

Table 41. CMR diagnostic criteria for left ventricular hypertrabeculation

Criteria	Petersen ⁷⁹⁴	Jacquier ⁷⁹⁶	Stacey ⁷⁹⁸	Grothoff ⁷⁹⁹	Captur ⁸⁰⁰
Cardiac Cycle	End-diastole	End-diastole	End-systole	End-diastole	End-diastole
View	Long axis	Short axis stack	Short axis	Short axis stack	Short axis stack
Cut-off Value for Hypertrabeculation	NC/C > 2.3	NC mass > 20% of total LV mass	NC/C ≥ 2	Trabeculation mass > 15 g/m ² ; > 25% of total LV myocardial mass; NC/C ≥ 2 in segments 4-6; NC/C ≥ 3 in segments 1-3, 7-16	Maximum apical fractal dimension ≥ 1.30

In cases with low image quality, contrast echo can enhance the evaluation efficacy and reliability by rendering trabeculations and intertrabecular recesses more visible.

Cardiac Magnetic Resonance

In recent years, there has been an increasing utilization of CMR, particularly in the assessment of cardiomyopathies. CMR, with its high spatial resolution and intrinsic contrast, offers the opportunity to distinguish between blood and myocardium, particularly beneficial in patients with limited echocardiographic apical views. Moreover, the capability of CMR to simultaneously evaluate intrathoracic structures and potential accompanying congenital anomalies enhances its diagnostic utility. Therefore, CMR is recommended to confirm the diagnosis of LVHT.

There are five distinct CMR criteria for diagnosing LVHT (Table 41). The first criterion, defined by Peterson et al.,⁷⁹⁴ involves measuring NC/C > 2.3 at end-diastole in any long-axis view (2-,

3-, 4-chamber) (Figure 126). However, despite the authors' claim of a sensitivity of 86% and specificity of 99% in diagnosis, the MESA study indicates that 43% of healthy individuals meet this criterion.⁷⁹⁵

The second criterion, proposed by Jacquier et al.,⁷⁹⁶ entails measuring NC mass exceeding 20% of the total LV mass from short-axis stack images at end-diastole. While this criterion may seem more reliable as it assesses LVHT globally rather than regionally, the analysis requires a longer period of time. Consequently, the Peterson criterion has become the most widely used criterion in routine clinical practice.⁷⁹⁷

Stacey et al.⁷⁹⁸ elucidated that an NC/C ratio of ≥ 2 on short-axis cine images at end-systole suggests LVHT (Figure 127).

Grothoff et al.⁷⁹⁹ proposed a criterion comprising four parameters in short-axis stack images at end-diastole as follows: 1. NC mass / total LV myocardial mass > 25%; 2. NC mass > 15 g/m²; 3. NC/C

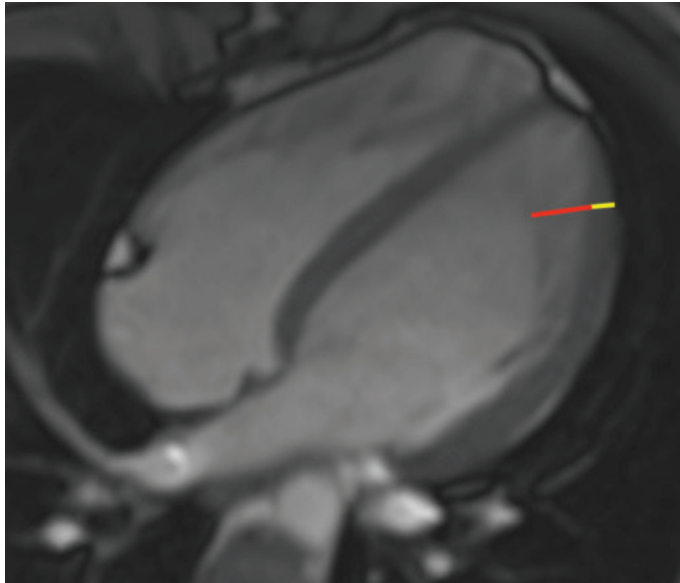


Figure 126. CMR Petersen Criterion: Noncompacted layer (red line) / compacted layer (yellow line) in the long-axis (4 chamber) cine image at end-diastole > 2.3 .

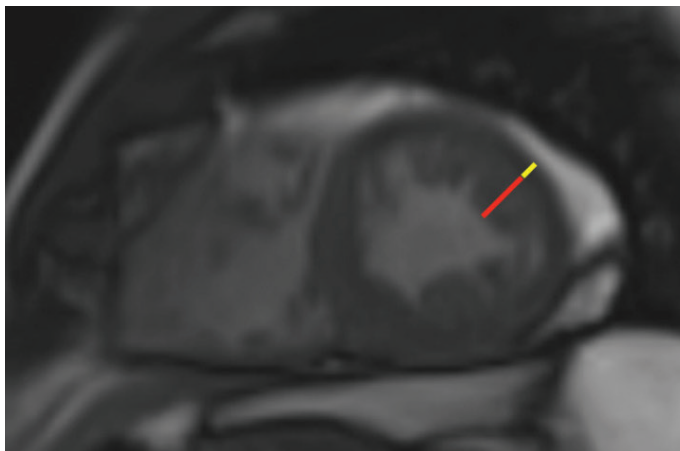


Figure 127. CMR Stacey Criterion: Noncompacted layer (red line) / compacted layer (yellow line) ≥ 2 in the short-axis cine image at end-systole.

≥ 2 in basal and septal segments 4–6; and 4. NC/C ≥ 3 in at least one of the other segments (1–3, 7–16) except the apical segment.

Lastly, Captur et al.⁸⁰⁰ introduced an unitless measurement value, the fractal dimension, determined by fractal analysis of all short-axis LV slices at end-diastole, assessing how thoroughly this intricate structure fills the space. The range of possible fractal dimensions for the endocardial border spans from a non-integer value of 1 (representing a solid line) to 2 (indicating complete filling of the 2-dimensional space contained by ventricular trabeculation). A maximum apical fractal dimension ≥ 1.30 serves as a diagnostic criterion for LVHT. According to the MESA study, patients with hypertension, left ventricular hypertrophy, high LV mass, and African Americans tend to exhibit higher fractal dimension values.⁸⁰¹

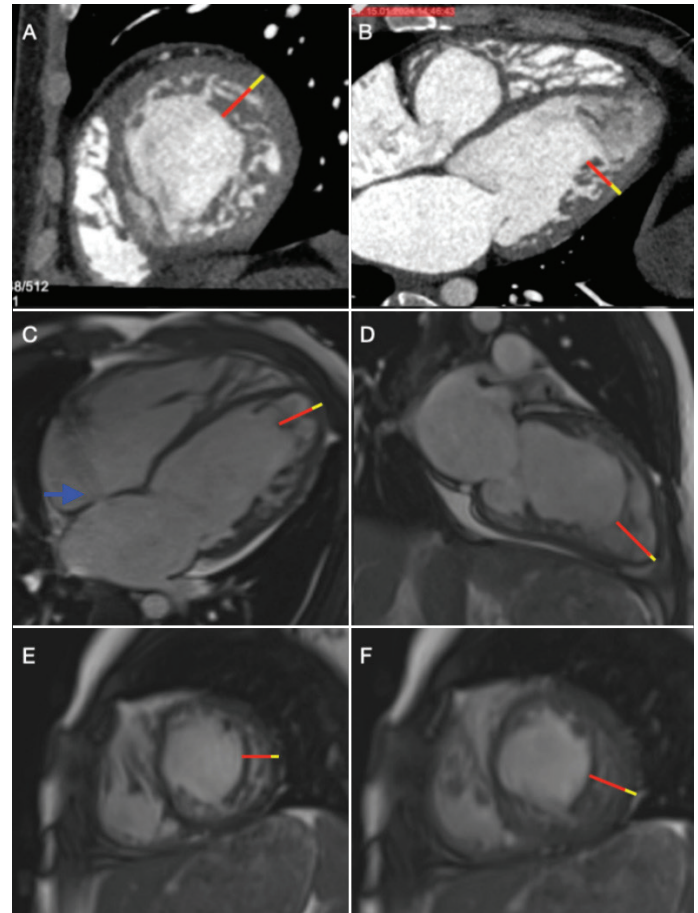


Figure 128. Detection of left ventricular hypertrabeculation by cardiac CT performed for coronary artery evaluation in a newly diagnosed dilated cardiomyopathy patient and confirmation of the diagnosis of hypertrabeculation with CMR. (A) Cardiac CT short-axis image. (B) Cardiac CT long-axis 4-chamber view. (C) CMR NC/C > 2.3 (Petersen criterion) at end-diastole on the long-axis (4-chamber) view. The blue arrow indicates a left-to-right shunt over a small atrial septal defect. (D) CMR NC/C > 2.3 (Petersen criterion) at end-diastole on the long-axis (2-chamber) view. (E) CMR NC/C ≥ 2 (Grothoff criterion parameter) on the short-axis view at end-diastole. (F) CMR NC/C ≥ 2 (Stacey criterion) on the short-axis view at end-systole. The yellow line represents the compacted layer, and the red line represents the noncompacted layer.

Late gadolinium enhancement (LGE), which plays a significant role in the differential diagnosis of cardiomyopathies, does not serve as a reliable guide in the diagnosis of hypertrabeculation.

Cardiac Computed Tomography

CT, while not the preferred imaging modality due to concerns regarding radiation exposure and contrast agent use, can be utilized to assess HT in patients with limited echocardiographic windows and undergoing CT examination for other indications, such as coronary artery evaluation (Figure 128).

According to the study by Melendez-Ramirez et al.,⁸⁰² NC/C > 2.2 in at least two segments from the short axis at end-diastole confirms the diagnosis of HT.

Sidhu et al.⁸⁰³ found that an NC/C value > 2.3 measured from the long axis at end-diastole is diagnostic in patients previously diagnosed with LVHT by echocardiography and CMR.

Fuch et al.⁸⁰⁴ established a threshold value of NC/C > 1.8 at end-diastole in the short axis basal, mid, and apical segments for the early stages of hypertrabeculation and in patients with a small LV cavity. However, despite the publication of these criteria, the role of cardiac CT in the diagnosis of LVHT remains unclear.

Many publications investigating diagnostic criteria for LVHT indicate that while the sensitivity of these criteria is very high, the specificity is very low, particularly in patients with a low pre-test probability and in African American individuals.^{805–807} Consequently, more healthy individuals may be misdiagnosed with LVHT.

Clinical Presentation

While asymptomatic patients are often diagnosed during routine cardiac imaging, the most common presenting symptoms of LVHT include heart failure, thromboembolism, arrhythmias, and sudden cardiac death. Thromboembolism is believed to occur due to reduced blood flow in the recesses between noncompacted trabeculae. Severe systolic dysfunction and atrial fibrillation are also contributing factors to thromboembolism.⁸⁰⁸ Notably, thromboembolism has not been reported in individuals with asymptomatic LVHT phenotype with preserved ventricular function.⁸⁰⁹

Differential Diagnoses of Left Ventricular Hypertrabeculation

During the evaluation with echocardiography, which serves as the first line imaging modality, other conditions affecting the LV apical region may be mistaken for LVHT, particularly in patients with limited echocardiographic windows. These conditions may include apical hypertrophic cardiomyopathy, endomyocardial fibrosis, and thrombus. However, when the apical region of the ventricle is examined more clearly with CMR, which offers superior resolution, the potential differential diagnoses expand to include true LVHT, HT secondary to pathological remodeling due to loading conditions such as dilated cardiomyopathy, or HT secondary to physiological remodeling observed in situations such as athletes and pregnancy.⁸¹⁰

Etiology

Genetic

LVHT frequently exhibits a familial pattern and is often associated with variants of genes, including those encoding sarcomere, Z-disk, cytoskeleton, and nuclear envelope proteins.¹

Exercise

LVHT observed in athletes represents a reversible phenotype resulting from the increased cardiac preload demand associated with intense exercise.⁸¹¹ The manifestation of LVHT varies depending on the specific sports discipline and the ethnicity of the athlete.⁸¹² The prevalence of LVHT meeting echocardiography criteria among athletes ranges from 1% to 10%.^{785,812}

In athletes meeting LVHT criteria, suspicion of cardiomyopathy arises only in the presence of LV dysfunction (EF <50%),

a family history, and cardiac symptoms.⁸¹⁵ Additional echocardiographic criteria supporting cardiomyopathy diagnosis in athletes include a very thin compacted layer (<5 mm in end-diastole or <8 mm in end-systole by CMR) and impaired myocardial relaxation ($E' < 9$ cm/s).^{813,814} To ascertain whether LVHT in athletes signifies cardiomyopathy phenotype or physiological adaptation, an algorithm incorporating EF assessment, CMR imaging, presence of LGE, and family history is recommended.

Patients with EF <50%, positive LGE, and/or a positive genetic test are more likely to be diagnosed with cardiomyopathy and should be advised to restrict sports participation. For patients with EF >50% and a positive family history, ECG abnormalities, and/or ventricular tachyarrhythmia, evaluation with CMR and genetic tests is recommended before clearing them for sports participation.⁸¹²

When forensic data were scrutinized, none of the cases of sudden death in athletes were directly attributed to LVHT.⁸¹⁵ Moreover, there is no data indicating routine restriction of athletes with isolated HT and normal LV function from engaging in high-intensity exercise and competitive sports.⁷⁸⁴ Although definitive data are lacking, the American Heart Association (AHA) and the American College of Cardiology (ACC) do not restrict asymptomatic athletes with normal ventricular systolic function, without any history of syncope or significant atrial or ventricular tachycardia, from participating in competitive sports.⁸¹⁶

Furthermore, a dose-response relationship was not discovered between activity intensity and LVHT in physical activity performed by non-athletes.⁸¹⁷

Pregnancy

Hypertrabeculation, believed to arise secondary to increased afterload during pregnancy in patients without pre-existing cardiac problem, represents a reversible phenotype that frequently resolves within approximately 12 weeks after pregnancy.⁷⁸⁶ This phenomenon is more prevalent among African American women, indicating that myocardial response to afterload may be influenced by genetic predisposition.⁸¹⁸

Neuromuscular Diseases

Hypertrabeculation has been identified in various neuromuscular disorders, encompassing Barth syndrome, mitochondrial disorders, nuclear envelopeopathies, dystrobrevinopathy, myotonic dystrophy, zaspopathy, and myoadenylate deaminase deficiency, along with genetically determined diseases such as Duchenne and Becker muscular dystrophies.⁷⁸⁴ Research has indicated that the co-occurrence of the LVHT phenotype and neuromuscular disease may carry clinical and prognostic implications.⁸¹⁹

Renal Diseases

LVHT has been documented in cases of polycystic kidney disease. Various hypotheses suggest that this occurrence may stem from either a shared genetic basis for the two conditions⁸²⁰ or an increase in preload resulting from chronic renal failure.⁸²¹

Hematological Diseases

Hypertrabeculation has been found to be associated with β thalassemia⁸²², sickle cell anemia⁸²³, hemoglobinopathies, and

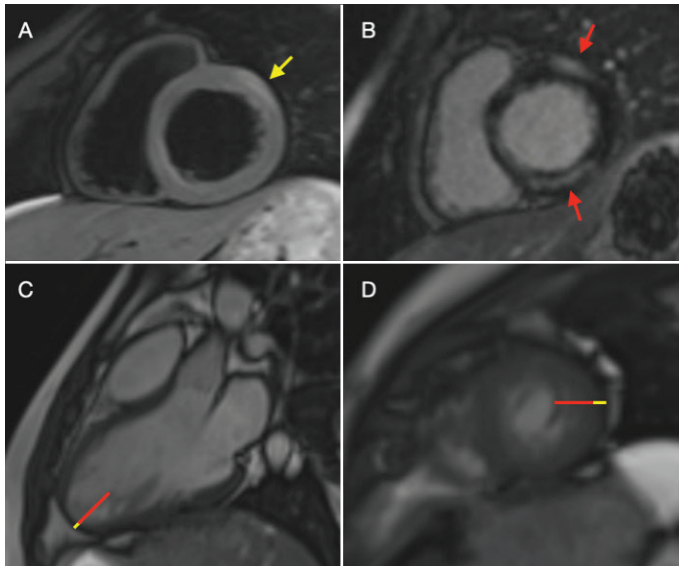


Figure 129. CMR in a 23-year-old male patient with a preliminary diagnosis of myocarditis due to chest pain, elevated troponin levels, and ventricular dysfunction following viral infection. The Updated Lake Louise criteria confirmed acute myocarditis. (A) T2-weighted image showing edema (yellow arrow) in the basal anterolateral wall. (B) T1-weighted image revealing nonischemic late gadolinium enhancement (red arrow) in the basal anterolateral, inferior, and inferolateral walls, consistent with myocarditis. (C) Cine images on long-axis 4-chamber view at end-diastole, demonstrating NC/C > 2.3 (Petersen criterion), (D) Cine images on short-axis view at end-systole, indicating NC/C ≥ 2 (Stacey criterion) hypertrabeculation. The yellow line represents the compacted layer, and the red line represents the noncompact layer.

chronic hematological diseases.⁸²⁴ As ventricular functions are preserved in the majority of patients with LVHT, it is believed that LVHT does not necessarily indicate an underlying myopathy.⁷⁸⁴

Cardiac Diseases

LVHT has been identified as a reversible phenomenon secondary to changing preload and afterload in myocarditis (Figure 129), coronary artery disease⁸²⁵, and heart failure with reduced EF.⁸²⁶ Additionally, LVHT has been observed in congenital heart diseases, most commonly associated with LVOT anomalies (46%), Ebstein anomaly (25%) (Figure 130), and tetralogy of Fallot (8%).⁸²⁷

Prognosis

Upon examining the entire cohort and subgroups of the EuroCMR registry, LVHT was not found to be associated with an increased risk of all-cause mortality, morbidity, or CMR LV indices. Consequently, it is believed that isolated LVHT does not serve as a predictor of poor prognosis.⁸²⁸ Furthermore, a study involving patients with dilated cardiomyopathy revealed that clinical outcomes were linked to right and left ventricular remodeling and LGE, but not

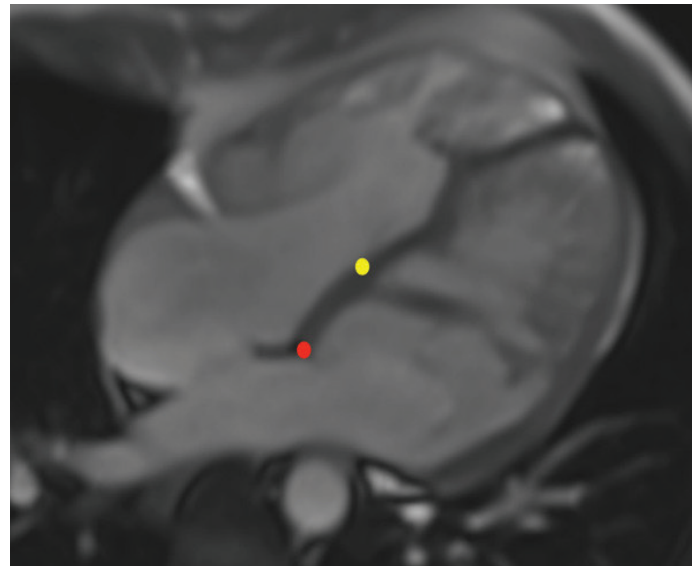


Figure 130. CMR 4-chamber cine image of a 27-year-old male patient with coexistence of biventricular hypertrabeculation and Ebstein anomaly. The red dot indicates the attachment site of the mitral valve anterior leaflet, while the yellow dot highlights the attachment site of the tricuspid valve septal leaflet, which is located more apically and is compatible with Ebstein anomaly.

to hypertrabeculation.⁸²⁹ Research has demonstrated that isolated LVHT is not correlated with long-term LV remodeling⁸⁰⁵ or poor clinical outcomes.^{830,831} Therefore, based on this data, isolated LVHT with normal ventricular functions does not necessitate close follow-up concerning poor clinical outcomes.

Conclusion

Hypertrabeculation of the left ventricle represents a dynamic entity that has been the subject of numerous research studies, with ongoing updates regarding its definition. While there are accepted echocardiography and CMR criteria for diagnosis, one of the limitations of these criteria is the exclusion of functional evaluation. LVHT may have a genetic basis or may manifest as a variant of normal anatomy. Additionally, remodeling secondary to increased preload and afterload can be considered among the causes of reversible LVHT. Studies have consistently demonstrated that isolated LVHT with normal left ventricular functions is not associated with poor clinical outcomes.

The primary approach in patients with LVHT should involve comprehensive evaluation, including assessment of not only the NC/C ratios on echocardiography or CMR images, but also ventricular functions, family history, genetic testing, and clinical presentation. This holistic approach ensures a thorough understanding of the condition and guides appropriate management strategies.

Imaging in Viral and Autoimmune Myocarditis

Myocarditis is an inflammatory disease of the heart defined by histological, immunological, and immunohistochemical criteria. It is a rare yet potentially fatal condition characterized by the infiltration of inflammatory cells and subsequent myocardial damage, occurring independently of ischemic cardiomyopathy (CMP), which results from the obstruction of the coronary arteries.⁸³² In 2013, an estimated 1.5 million cases of myocarditis were reported globally.⁸³³ Between 0.5% and 4.0% of patients with acute myocarditis are hospitalized with heart failure (HF), and when a biopsy is performed on patients with chronic HF, inflammation is detected in up to 30% of cases.⁸³⁴ Myocarditis is the primary cause of HF in individuals under 40 years of age and may lead to dilated CMP, with 10–20% of affected individuals developing HF, even in the absence of clinical symptoms.^{835,836}

Diagnosing myocarditis is challenging due to the variety of clinical presentations. The main pathophysiological feature is myocardial inflammation, which may arise from viral agents or as a result of the systemic effects of autoimmune diseases. While the pathophysiological steps of viral myocarditis are better understood through mouse models, the mechanisms in autoimmune diseases and other causes remain less clear. Non-infectious factors are believed to account for about 70% of myocarditis cases, half of which are autoimmune in nature.⁸³⁷ Evidence suggests that a virus-induced myocardial inflammatory process may lead to chronic activation of the immune system against self-antigens, complicating the physiological distinction between different disease subgroups.⁸³⁸

The underlying mechanisms of autoimmunity-induced myocarditis include genetic susceptibility linked to the major tissue compatibility complex, detection of heart-specific autoantibodies, association with autoimmune diseases, and the beneficial effects of immunosuppressive therapy on some types of myocarditis.^{839–841} These factors related to autoimmune myocarditis are detailed in Table 42.

Despite numerous potential causes of myocarditis, viral infection remains the most prevalent etiology, associated with myocardial inflammation. Cardiotropic viruses include Coxsackie B virus, non-Coxsackie enteroviruses, some types of adenovirus, parvovirus B19, and Epstein-Barr virus.⁸⁴² Following an acute viral infection, immune activation occurs, involving the activation of T and B cells, antibody production, cytokine release, and complement activation. However, our understanding of viral myocarditis is limited because the mechanisms of viral infection, the details of the viral life cycle, and the nature of the immune response are well elucidated only in certain species.

Table 42. Autoimmune Myocarditis	
Giant Cell Myocarditis	Inflammatory Myocarditis
Eosinophilic Granulomatous Non-Infectious Myocarditis	Systemic Lupus Erythematosus
Sarcoidosis	Rheumatoid Arthritis
Celiac Disease	Primary Biliary Cirrhosis
Myasthenia Gravis	Crohn's Disease
Colitis Ulcerosa	Polymyositis/Dermatomyositis
Reactive Arthritis	Pemphigus Pemphigoid

The etiological diagnosis of myocarditis is critical for guiding treatment strategies, which may vary from immunosuppressive treatments to antiviral therapy and immunomodulators, depending on the patient's clinical context and histological evidence. However, detecting myocardial inflammation is challenging due to its heterogeneous and non-specific clinical presentation and the absence of specific traditional invasive and non-invasive diagnostic methods. Although endomyocardial biopsy (EMB) is considered the gold standard for diagnosis, its routine use is limited due to potential risks associated with the procedure and the lack of a universally accepted histopathological standard. Furthermore, its sensitivity is low as myocardial inflammation can be focal and located in areas that are easily missed.⁸⁴³ The advent of sensitive, non-invasive cardiac imaging techniques, especially cardiac magnetic resonance imaging (CMR), has enhanced our ability to detect subclinical myocardial inflammation and identify patients who might benefit early from treatment.⁸⁴⁴⁻⁸⁴⁶

Echocardiography

The primary echocardiographic indications of myocarditis include non-specific left ventricular (LV) regional or global dysfunction and LV dilatation. In a study of cases with histologically confirmed myocarditis, the most frequent findings were regional abnormalities in wall motion—such as hypokinesia, akinesia, and dyskinesia—that can resemble LV dysfunction seen in global or acute myocardial infarction.⁸⁴⁷ Diastolic dysfunction is also common, typically exhibiting a restrictive pattern. Additionally, echocardiography is useful for identifying LV thrombus, transient LV aneurysms, right ventricular involvement, and pericardial effusion.^{847,848} Notably, right ventricular dysfunction serves as an independent predictor of adverse outcomes, potentially leading to death or the necessity for heart transplantation in myocarditis cases.⁸⁴⁹

Temporary increases in LV wall thickness have been noted in some case series during the acute phase of myocarditis.⁸⁵⁰ Hiramitsu et al.⁸⁵⁰ studied 25 patients with histologically confirmed myocarditis and observed significant regression in the thickness of the interventricular septum and LV wall between the acute and recovery phases. In some instances, myocarditis can mimic symmetric or asymmetric hypertrophic cardiomyopathy.⁸⁵⁰⁻⁸⁵³

The acoustic characteristics of the myocardium, based on the hypothesis that myocardial density and elasticity are influenced by edema size and cellular infiltration, have been explored using ultrasonic backscattering. This technique assesses the physical condition of the heart muscle, thereby aiding in the evaluation of myocardial acoustic properties and potentially facilitating the diagnosis of myocarditis. Lieback et al.⁸⁵⁴ investigated the acoustic properties of the myocardium in 106 patients with suspected myocarditis. They found that, in histologically confirmed cases, the average gray value (a measure of brightness) of myocardial echogenicity was significantly higher compared to control subjects. However, the study did not report diagnostic accuracy, and it was unable to differentiate between idiopathic dilated cardiomyopathy and acute myocarditis using ultrasonic tissue characterization. Nevertheless, several case reports indicate that an increase in brightness, heterogeneity, and contrast might be helpful markers for confirming acute myocarditis.^{855,856}

Although echocardiography is not specifically tailored for imaging myocarditis, it is useful in ruling out other known causes of heart failure. When differentiating between ischemic and non-ischemic CMP upon encountering a dilated ventricle, it is important to consider the following: ischemic CMP typically presents with more regional wall motion defects along with scarred or aneurysmatic areas, and is generally characterized by reduced global function. In contrast, non-ischemic CMP usually shows a uniform reduction in wall motion. However, in cases of myocarditis with focal involvement, segmental wall motion defects can occur. Many instances of dilated CMP may follow an episode of acute myocarditis that was not clinically diagnosed. If an echocardiographic examination is performed early in the course of the disease, global systolic dysfunction is often observed while LV wall thickness and cavity diameter remain relatively preserved. Mild acute myocarditis usually shows slight LV dilatation and normal wall thickness, whereas fulminant myocarditis may present with increased LV wall thickness, yet the heart cavities remain within normal limits. If the myocardium does not fully recover, LV dilation typically progresses, accompanied by wall thinning and increased systolic dysfunction. Once myocarditis is clinically diagnosed, serial echocardiographic monitoring is essential, as improvements in LV systolic function can vary widely.

In cases of myocarditis, acute non-fulminant myocarditis, often due to viral infections or other infectious agents, is the most common form and usually follows a mild clinical course that resolves spontaneously. In contrast, giant cell myocarditis (GCM) and cardiac sarcoidosis (CS) are rare and severe forms of myocarditis with pathogeneses that are not yet fully understood.^{857,858} Although these conditions exhibit significant clinical and histopathological similarities, GCM is considered distinct due to its exclusive cardiac symptoms, rapid clinical progression, and poorer prognosis. In contrast, CS is primarily a systemic disease characterized by slower progression and a better prognosis.

GCM is an aggressive, autoimmune myocarditis that predominantly affects young and middle-aged adults and is often fatal. It typically presents with subacute-onset heart failure (1–3 months) that worsens despite medical intervention, frequently accompanied by high-grade atrioventricular block and malignant ventricular arrhythmias.⁸⁵⁹ In 20% of cases, an autoimmune disorder such as inflammatory bowel disease, thymoma, myasthenia gravis, Hashimoto's thyroiditis, or rheumatoid arthritis is present. GCM should be considered when acute heart failure does not respond to standard treatments or in the presence of resistant electrical storms, despite aggressive anti-arrhythmic therapy. A rapid decline in LV systolic function over a few days is a critical indicator for suspecting this condition. Lymphocytic and GCM may also present with involvement of the anterior wall and right ventricle.

Cardiac sarcoidosis is a multi-system inflammatory disease characterized by the formation of non-caseating granulomas in many organs, with cardiac involvement in up to 40% of cases. Cardiac manifestations may affect the pericardial and myocardial systems. Despite the clinical and histological similarities between GCM and CS, the two can be distinguished by the progression and severity of symptoms. CS tends to have a slower progression,



Figure 131. Monitoring the recovery process of a patient who had acute viral myocarditis using global longitudinal strain values in strain examination performed one month apart.

and its impact is often more significant in the basal posterior, lateral wall, and septum, coupled with systemic signs and diagnostic imaging findings, contrasting with the rapid and severe progression of GCM.

In the evaluation of autoimmune and viral myocarditis, two- and three-dimensional strain echocardiography serves as a valuable advanced technique for both the diagnosis and ongoing monitoring of myocarditis. Strain imaging plays several crucial roles in the management of myocarditis:

1. Early Diagnosis and Differential Diagnosis: Strain imaging is critical for the early detection of myocarditis and for differentiating it from other cardiac conditions. Even when traditional echocardiographic measurements appear normal or show minimal changes, strain imaging can identify myocardial dysfunction specific to myocarditis at an early stage. This capability provides a significant advantage over conventional methods, enhancing early diagnosis and informing treatment strategies.

2. Evaluation of Treatment Response: Following the initiation of treatment for myocarditis, it is essential to monitor the reversal of myocardial function in patients (Figure 131). Strain imaging provides a more sensitive method for tracking the regression of myocardial damage. Unlike traditional echocardiographic methods that might show myocardial function within the normal range, strain imaging can detect subtle improvements or deteriorations in myocardial function, thereby offering a more accurate assessment of how the heart is responding to treatment.

3. Determination of Complications: As myocarditis progresses, complications such as heart failure, myocardial fibrosis, and arrhythmias can develop. Early detection of these changes is beneficial for managing patient outcomes. During strain imaging, a permanent decrease in strain values may indicate the development of myocardial fibrosis, providing critical insights into the extent of myocardial damage.

4. Determination of Prognosis: The degree and pattern of myocardial deformation assessed through strain imaging serve

as important markers for predicting the long-term clinical outcomes of patients with myocarditis. This information can guide clinicians in making informed decisions about ongoing management and potential interventions, aiming to improve patient prognosis based on the severity and progression of myocardial deformation.

In a study aimed at distinguishing acute viral myocarditis from inflammatory myocarditis conditions such as dermatomyositis (DM)/polymyositis (PM), it was found that strain analysis/global longitudinal strain (GLS) values were lower in the basal segments than in the apex for PM myocarditis patients. For DM/PM patients with proximal muscle involvement, late gadolinium (LGE) enhancement was significantly more pronounced in the basal regions than in the apical regions, similar to findings in CMR.⁸⁶⁰

In another study comparing the GLS assessments of patients with acute myocarditis-diagnosed through laboratory and conventional echocardiographic data-with results from CMRI, ejection fractions calculated by speckle tracking follow-up were found to be lower than those determined by CMRI.^{860,861} In centers where CMRI is unavailable, strain imaging provides a valuable alternative for the detailed evaluation of myocarditis patients.

Nuclear Imaging

Gallium-67, an imaging agent known for its ability to depict chronic inflammation, has been utilized in diagnosing various autoimmune and chronic inflammatory conditions. Clinical and experimental studies have confirmed that gallium-67 citrate scintigraphy is effective in detecting myocarditis.⁸⁶² Matsura et al.⁸⁶³ highlighted the utility of gallium-67 imaging in a study involving 46 consecutive children during the acute phase of Kawasaki disease, specifically to identify myocarditis. However, its lack of specificity has led to a gradual decline in the use of gallium imaging over time.

Indium-111, an antimyosine antibody, was utilized by Khaw et al.⁸⁶⁴ in a non-invasive imaging technique to detect myocyte

necrosis through a monoclonal antibody targeting human cardiac myosin. Antimyosine (AM) antibodies labeled with indium-111 have been shown to indicate myocardial necrosis effectively in both animal models and human myocarditis cases.^{863,864} Yasuda et al.⁸⁶⁵ reported the first clinical use of indium-111 AM imaging in 28 patients suspected of having myocarditis. The AM scans were positive in 61% of the study group, with nine individuals showing evidence of myocarditis in EMB, and all patients without myocarditis on biopsy tested negative. Therefore, the sensitivity of AM imaging was 100%, while its specificity was 58%. However, the use of these nuclear techniques has declined due to significant limitations in administration, including limited access to mitigate blood pool effects, concerns over radiation exposure, and a required 48-hour delay in obtaining imaging results after injection.

Cardiac Magnetic Resonance Imaging

In myocarditis patients, it is crucial to conduct safe evaluations with CMR, while providing a clear assessment of anatomical structures without being overly open to interpretation. CMR is essential for assessing both regional and global functions, and for non-invasive tissue characterization. It can identify three main factors that develop from acute inflammation of the myocardium: edema, hyperemia, necrosis, or fibrosis, which are integral to the Lake Louise criteria established in 2009.⁸⁶⁶ The increased permeability of cell membranes during inflammation leads to cell dysfunction due to intracellular edema and the loss of large molecules as Na⁺ enters the cell. T2-weighted images, with their high signal intensity, are sensitive to tissue edema detection (Figure 132A,B). The "triple inversion recovery turbo spin echo" sequences, which suppress fat and blood imaging, offer enhanced views of edema. Regional edema is detected in 36% of patients diagnosed with active myocarditis using Dallas criteria and T2-weighted CMR sequences.⁸⁶⁷

Another significant change during inflammation is the development of regional vasodilation, which increases blood flow and consequently enhances contrast material retention early on. Since gadolinium-based contrasts displace quickly into the interstitial space, this phase occurs shortly after contrast media introduction.⁸⁶⁶ Thus, T1-weighted fast sequences are effective in capturing this phase. LGE specifically indicates irreversible myocardial damage such as fibrosis and necrosis. Early in the necrosis phase, gadolinium penetrates damaged cells, increasing the distribution volume, allowing for observation of myocarditis-related necrosis. Following the removal of inflammation in necrotic areas, an increase in gadolinium distribution volume is noted during the late washout period, facilitated by the activation of fibrocytes in the extracellular region (Figure 132C). This process helps delineate the sequelae of inflammation.

Damage distribution aids in differentiating between ischemic and non-ischemic etiologies.⁸⁶⁸ Typically, myocarditis involvement is more pronounced in the epicardial region, and this finding can fully resolve following complete recovery.⁸⁶⁹ CMR also reveals functional abnormalities, such as deterioration in LV and right ventricular function, concurrent pericardial effusions, and morphological changes in ventricular volumes, including alterations in LV mass.

Francone and colleagues categorized myocarditis into three distinct patterns in their CMR study, during which EMB was performed on all patients. In the infarct-like pattern, cardiac structures and dimensions are typically preserved, with a mild increase in troponin and clear signs of inflammation. Patients often experience frequent chest pain and ST-segment changes on electrocardiography, with the highest CMR sensitivities observed (T2wSTIR up to 81%, and EER up to 71% for LGE). Subepicardial/mid-basal involvement, typically observed in the lateral wall, is associated with potential cell necrosis density. In

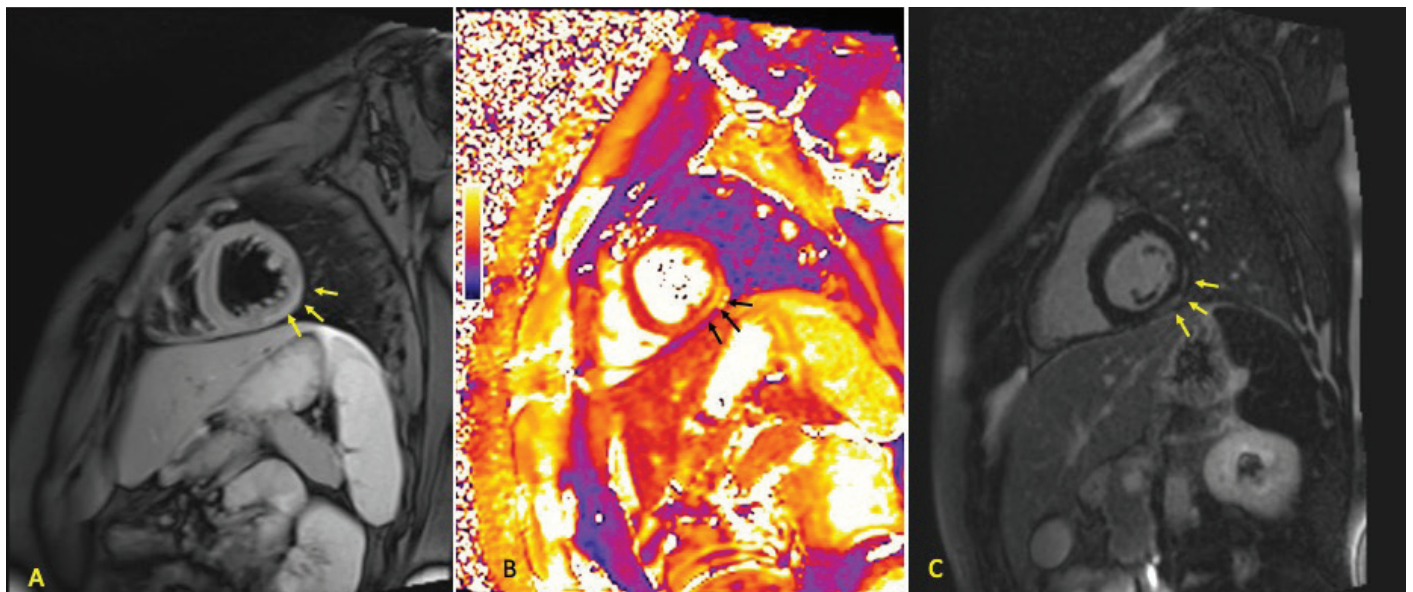


Figure 132. (A) T2-weighted images show a bright field marked with arrows in the inferolateral wall in the subepicardial region, revealing edema. (B) T2 mapping shows a bright-field area pointed with arrows marking edema in the inferolateral wall with in the subepicardial region. (C) Late gadolinium uptake in the area indicated by the arrow in the subepicardial area of the inferolateral wall.

the cardiomyopathic pattern, patients exhibit slowly developing heart failure symptoms, and widespread myocardial damage mediated by T-cells, usually in response to viral or myocardial antigens. In these cases, T2w-STIR sensitivity may decrease to 28%, making EER and LGE more indicative of midwall septal involvement. The arrhythmic pattern, described by Francione and colleagues, is seen in patients with pathologically acute myocarditis, with CMR positivity decreasing to 46%. Here,

involvement may be due to technical issues, such as focal lesions, or affect the conduction system.⁸⁷⁰ Table 43 displays different CMR features in various myocarditis scenarios.

Following histological or clinically controlled studies examining whether it is possible to diagnose all cases of myocarditis with CMR, the Lake Louise criteria were updated in 2018 (Table 44).⁸⁷¹

Table 43. Different CMR features for different myocarditis scenarios⁸⁶⁹

Diseases	Pathology	CMRI Findings	Considerations
Acute viral myocarditis	Edema Hyperemia ± Necrosis	Increased T2 Increased T1 LGE +/-	Differentiate from ischemia
Chronic viral myocarditis	± Edema ± Hyperemia ± Necrosis ± Regional fibrosis (scar) ± Diffuse fibrosis	Increased/No T2 Increased /No T1 LGE +/-	ECV may provide additional information
Acute autoimmune myocarditis	Edema Hyperemia ± Necrosis	Increased T2 Increased T1 LGE +/-	Differentiate from ischemia
Chronic autoimmune myocarditis	± Edema ± Hyperemia ± Necrosis ± Regional fibrosis (scar) ± Diffuse fibrosis	Increased/No T2 Increased /No T1 LGE +/-	ECV may provide additional information
Acute giant cell myocarditis	Edema Hyperemia ± Necrosis	Increased T2 Increased T1 LGE +/-	Differentiate from ischemia
Cardiac sarcoidosis	± Edema ± Hyperemia ± Necrosis ± Regional fibrosis (scar) ± Diffuse fibrosis	Increased/No T2 Increased /No T1 LGE +/-	ECV may provide additional information
Healed myocarditis	± Regional fibrosis ± Diffuse fibrosis	No/Decreased T2 No/Increased T1 LGE +/-	ECV may provide additional information

LGE, Late Gadolinium Enhancement; ECV, Extracellular Volume.

Table 44. The Lake Loise Criteria⁸⁶⁹

Diagnostic Targets	Lake Loise Criteria (2 out of 2)
	Main Criteria
Myocardial edema	T2-based imaging Regional high T2 SI or Global T2 SI ratio ≥ 2.0 in T2 Weighted CMR images or Regional or global increase of myocardial T2 relaxation time
↑ T1 – edema (intra/extracellular), hyperemia, capillary leak, necrosis, fibrosis EGE – hyperemia, capillary leak LGE – necrosis, fibrosis, (extracellular acute edema) ↑ ECV – edema (extracellular), hyperemia, capillary leak, necrosis, fibrosis	T1-based imaging Regional or global increase of native myocardial T1 relaxation time or ECV or Areas with high SI in a nonischemic distribution pattern in LGE images
	Supportive Criteria
Pericardial inflammation	Pericardial effusion in cine CMR images or High signal intensity of the pericardium in LGE images, T1-mapping or T2-mapping or T1 mapping or T2 mapping
Left ventricular dysfunction	Systolic LV wall motion abnormality in cine CMR images

EGE, Early Gadolinium Enhancement; ECV, Extracellular Volume; LGE, Late Gadolinium Enhancement; CMR, Cardiac Magnetic Resonance; LV, left ventricular.

In acute viral myocarditis, CMR may not be effective in distinguishing between viral and secondary causes, but T2 mapping proves more useful in cases of chronic viral myocarditis. Although no specific CMR protocols have been tailored for giant cell myocarditis, atypical subendocardial and myocardial involvement with high signal intensity in extensive areas may be observed. LGE images in eosinophilic myocarditis can differentiate high signal intensity in subendocardial regions from that seen in viral myocarditis.⁸⁶⁹

Myocarditis in autoimmune conditions often presents as a pattern of chronic myocarditis. In such cases, the sensitivity of CMR

significantly decreases. For instance, in patients with rheumatoid arthritis, areas of myocardial edema have been identified on focal LGE and T2-weighted images. A study involving patients with systemic sclerosis found increased focal LGE, elevated native T1 and extracellular volume, and heightened T2 signaling areas. These abnormalities are associated with abnormal systolic and diastolic strains, findings that are similarly observed in patients with lupus.

CMRI tissue characterization can detect subclinical myocarditis in patients with these chronic conditions, providing a valuable diagnostic tool in the management of chronic myocarditis.⁸⁷¹

Genetic Evaluation in Cardiomyopathies

Cardiomyopathies are structural and functional abnormalities of the heart muscles that are not due to a secondary cause. They are categorized based on the characteristics of heart muscle involvement, including hypertrophic cardiomyopathy, dilated cardiomyopathy, arrhythmogenic cardiomyopathy, left ventricular noncompaction, and restrictive cardiomyopathy. The genetic basis of these conditions varies by subtype but generally involves genes that encode components of the heart muscle.

The detection rate of causative genes in cardiomyopathy varies between 20% and 60%, depending on the subtype. Causal variants identified in genetic studies are typically associated with Mendelian inheritance inheritable diseases. Additionally, cardiomyopathies of digenic or oligogenic origin have been identified, where multiple influential variants are believed to cumulatively affect the disease's penetrance. This leads to more severe clinical manifestations and an earlier onset of the disease.⁸⁷² Further research is essential to better understand the impacts of modifier genes, environmental factors, and genetic architecture.

This review will discuss the effects of genetics on the diagnostic, prognostic, and therapeutic guidance of cardiomyopathies inherited through a single-gene pattern. The subject will be examined under two main headings. First, the fundamental steps in genetic studies for patients undergoing genetic investigation will be addressed. Under the second heading, genetic evaluations according to the types of cardiomyopathies will be explained.

Basic Stages of Genetic Study in Cardiomyopathies

The testing process for genetic studies in cardiomyopathies consists of a series of stages due to the nature of genetic tests. These stages are:

- a) Identification of the proband and clinical evaluation
- b) Collection of family information
- c) Pre-test genetic counseling
- d) Genetic testing
- e) Interpretation of variants
- f) Post-test genetic counseling
- g) Family screening

Identification of the proband and clinical evaluation

The initial stage of genetic testing for cardiomyopathy involves clinical assessment and family screening. Due to the significant individual variability in gene sequences, the probabilistic nature of genetic results, and the challenges in interpreting the effects of gene variants, the yield of genetic testing is higher in cases of cardiomyopathy with a clear clinical diagnosis that cannot be explained by secondary causes.

Following the clinical evaluation of the patient, first-degree relatives with more pronounced clinical symptoms may be identified during family screening. In such cases, conducting the initial genetic study on the other individual with more pronounced clinical symptoms may be more appropriate.

One of the most critical decisions following proband evaluation is selecting the genetic testing method. If findings suggest a chromosomal abnormality in the patient, chromosomal analysis or

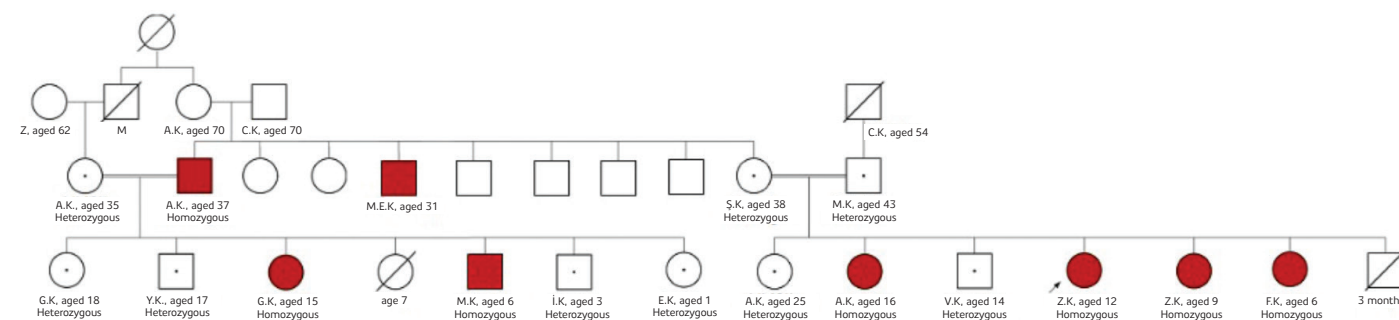


Figure 133. The completed pedigree following clinical and genetic screening of the family members of a patient referred to our center with hypertrophic cardiomyopathy revealed numerous affected individuals. Additionally, it showed that the variant detected in the patient follows an autosomal recessive inheritance pattern.

array-CGH should be preferred. When studying an arrhythmia panel, it is crucial to ensure that the panels cover the genes causing the disease. If necessary, broader panels or clinical exome sequencing (CES) methods should be considered.

Collection of family information

It is essential to inquire about similar disease symptoms among family members, keeping in mind that clinical findings can vary significantly from one individual to another. Additionally, it is crucial to ask about instances of sudden death under the age of 40 and the causes of early death in the family. A family pedigree of three generations is drawn up at this stage. This pedigree is invaluable for determining the inheritance pattern of the disease. Moreover, it serves as a visual roadmap for screening and examining other affected family members and for interpreting variations identified in the index case after testing (Figure 133).

Pre-test genetic counseling

This is a crucial stage in genetic studies. Given the probabilistic nature of how genetic tests are associated with disease, it is extremely critical to provide genetic counseling before conducting genetic studies. In pre-test genetic counseling, individuals should be given detailed information about the risks, benefits, and legal implications of genetic tests. Additionally, it is necessary to inform the family about potential test results to help manage their expectations for the future.

One of the key benefits of pre-test genetic counseling is the ability to make informed decisions about which tests to perform after evaluating the patient.

Genetic testing

The range of genetic testing options includes sequencing of a single gene, a focused group of genes associated with the specific phenotype under investigation, or exome sequencing in certain cases; genome sequencing is not commonly used in clinical settings. Sanger sequencing, which allows for a limited number of base pair scans in a single gene, is not typically used as an initial diagnostic test but may be preferred in clinically significant cases, such as TTR screening. Due to the numerous genes that can cause the same disease in cardiomyopathies, Next Generation Sequencing (NGS) is often the preferred initial diagnostic test. This technique includes all genes associated with the disease or related diseases, with panels usually containing between 30 to 120 genes. An evolving understanding of gene-

disease pairs has led to the formation of expert panels through the National Human Genome Research Institute-funded ClinGen Resource. These panels are systematically assessing the strength of evidence for associations between genes and cardiomyopathy phenotypes.⁸⁷³

The genes included in the NGS Cardiomyopathy panel are updated according to these recommendations. In this method, a sample of blood, saliva, or a buccal swab is taken from the patient. DNA is then extracted, purified, amplified, and fragmented from the sample, isolated, and attached to labeled sections short-read sequencing. Variants detected in the patient's sample are aligned against the "reference" human genome sequence. The probability of pathogenicity is determined by interpreting these variants thereafter.

Interpretation of variants

Interpreting genetic test results is challenging due to the high rate of genetic variation in the general population that does not lead to disease. To address the complexity of this process, the American College of Medical Genetics and Genomics (ACMG) and the Association for Molecular Pathology have developed a series of guidelines to standardize the interpretation of variants.⁸⁷⁴

Detected variants are interpreted based on various characteristics of the variation. Factors considered include the type of variant, such as mutations that may cause frameshifts or affect splice sites, which are highly likely to be pathogenic. Additionally, allele frequency in the general population and specific subgroups, using various databases, is assessed. Other considerations are the evolutionary conservation of the affected amino acid, prior demonstration of the variant's association with disease, and its detection in individuals without the disease. These features are fundamental criteria in variant interpretation.

Variants are classified into five categories based on ACMG criteria and the degree of pathogenicity: 1) pathogenic, 2) likely pathogenic, 3) variant of uncertain significance (VUS), 4) likely benign, and 5) benign. Variants identified as pathogenic or likely pathogenic indicate a positive test result, whereas those classified as likely benign or benign indicate a negative result.⁸⁷⁴

Post-test genetic counseling

After genetic testing results are available, it is crucial to provide counseling to the patient and/or their family regarding the implications of the results. The results should be thoroughly

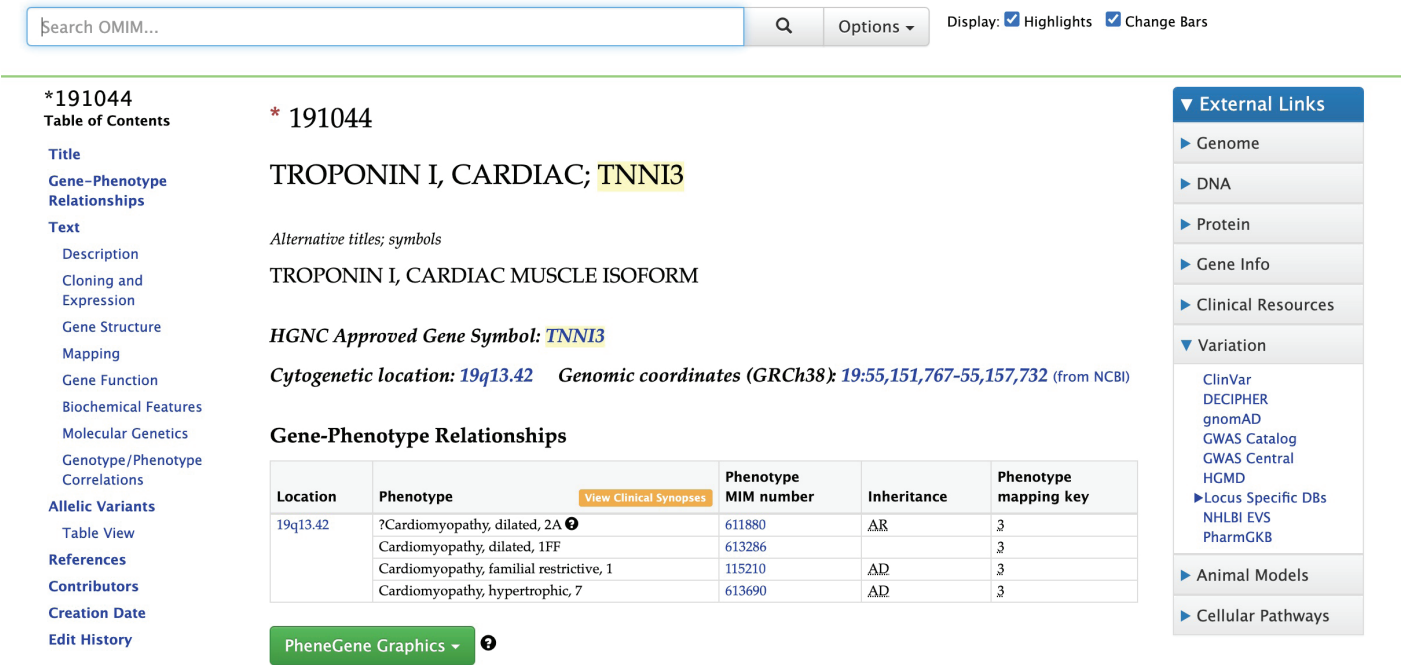


Figure 134. Example gene screening from the OMIM website. When examining the *TNNI3* gene, information regarding the gene's genomic location, associated diseases, and their inheritance patterns is provided.

explained and discussed in terms of their significance, and the effects on diagnosis, prognosis, and treatment of the disease should be elucidated.

When a pathogenic or likely pathogenic (P/LP) variant is detected in a patient, it is crucial to first verify on the OMIM site whether the gene associated with the variation is linked to the disease and its inheritance pattern (Figure 134). Additionally, it is necessary to confirm that the inheritance pattern in the patient's family pedigree matches the identified inheritance pattern of the gene (Figure 133). For example, if the gene's inheritance pattern is autosomal recessive and the zygosity of the detected variation in the patient is heterozygous, this result should not be considered causative of the disease, and the result should not be accepted as positive.

To properly evaluate the test, first ensure that the genetic panel includes all the genes associated with the disease. Additionally, verify whether the entire gene has been sequenced, identify any regions that may not have been read, and check if copy number analysis has been performed (Figure 135).

The test result can be presented in three ways: positive, negative, and a VUS. During counseling, it is crucial to emphasize that a negative genetic test result does not imply the absence of a genetic disease. Counselors should provide information about the next steps and discuss empirical risks with the patient and family.

One of the most challenging results to explain after genetic testing is the VUS. A VUS does not mean negative or positive; it simply means that the available data are insufficient to categorize the variant definitively as either. Often, a VUS arises from an incomplete evaluation of clinical findings or from insufficient

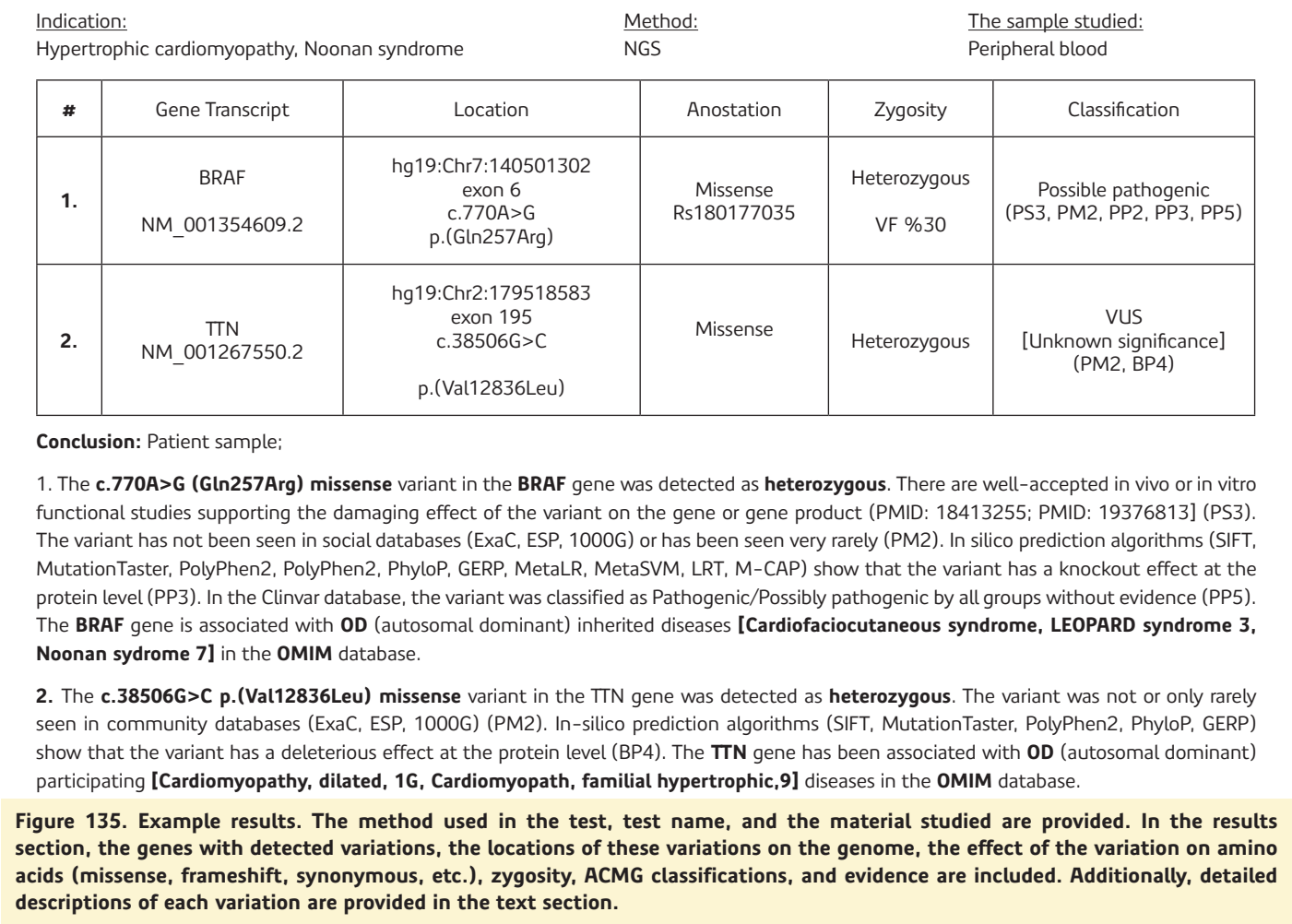
clinical and family information provided to the analyzing laboratory. Additionally, the presence of a large number of genes in genetic panels increases the likelihood of encountering a VUS in the test results.

Detecting a VUS in a patient can lead to a series of challenges, including psychological issues. Misinterpreting a VUS may result in removing the patient or potential disease candidates from necessary clinical supervision, the placement of unnecessary medical devices, additional tests that lack value, and a severe economic burden.

Some variants of uncertain significance can be reclassified as likely pathogenic or likely benign through thorough clinical surveys of the family and, where necessary, segregation analysis of the variation in family members. Results remain classified as VUS are not decisive for diagnosing or managing treatment for the patient. It is recommended that VUS be re-evaluated and potentially reclassified at regular intervals.

In the genetic counseling provided to the patient after the genetic result is obtained, the following topics should be addressed:

- Interpretation of negative, VUS, or positive results
- Implications of the result for diagnosis and prognosis
- Implications of the result for treatment management
- Identifying the need for psychological support and providing guidance if necessary
- Identifying individuals at risk and planning clinical and genetic screening for these individuals
- Explaining the risk of the disease occurring in the next generation
- Discussing possible precautions



Family screening

When a P/LP variant is identified in genetic test results, it is recommended to perform known variant screening on all first-degree family members (Class I indication). These screenings are crucial for identifying family members at risk and enabling necessary follow-ups to initiate early treatment. It is important to emphasize to family members that the clinical symptoms of cardiomyopathies may manifest late, making awareness and vigilance essential.

Family screening is conducted for segregation analysis for some individuals with VUS results. During this process, parents are typically the focus of clinical evaluations and screenings. The variant identified in the index case is examined in the parents to assess its presence and implications. Phenotype-genotype comparisons are made to determine whether the variant in the index case should be considered potentially pathogenic or potentially benign. This analysis helps clarify the significance of the variant and guides further medical decision-making.

Family screenings are typically conducted using the Sanger sequencing method. This approach is used to confirm variants detected by NGS and allows for necessary screenings to be conducted in family members at a lower cost. Sanger sequencing is particularly useful for targeted analysis of specific genetic

variations, making it an effective and economical option for confirming NGS findings in family studies.

It is important to recognize that in cardiomyopathies, both penetrance and expressivity can increase with age. These factors should be emphasized during the genetic counseling process. After family screening a detailed genetic counseling session is planned to discuss the results with the family. Recommendations are provided for at-risk individuals, and treatment is initiated where necessary. Measures such as preimplantation genetic diagnosis are discussed to support healthy childbearing. If the results remain classified as VUS even in family members who have undergoing segregation analysis, the importance of annually re-evaluating these results is emphasized to keep up with new insights and potential reclassifications.

Genetic Assessment in Cardiomyopathies

Cardiomyopathies often follow a single-gene inheritance pattern, with autosomal dominant being the most common. However, X-linked, autosomal recessive, or mitochondrial inheritance patterns can also occur. The manifestation and severity of the disease can vary significantly among individuals who carry the same genetic mutation. This variability is explained by characteristics known as penetrance and expressivity, which

describe how consistently and to what extent the genetic condition is expressed in individuals carrying the genotype.

Penetrance is the proportion of individuals carrying a specific gene who exhibit the related phenotype, compared to the total number of individuals who carry the gene and are expected to show the phenotype. For instance, if every individual with a particular genetic mutation clinically manifests the disease, the penetrance is considered to be 100%.

Expressivity refers to the degree to which a gene is expressed in individuals, or the severity of the phenotype. Variability in expressivity means that individuals carrying the same genotype may exhibit a range of symptoms, from mild to severe. This variability in how the phenotype is expressed is known as expressivity variability.

Genetic heterogeneity refers to the occurrence of the same or similar phenotypes resulting from different genes or alleles. This diversity means that various genetic mutations can lead to similar disease manifestations, complicating diagnosis and treatment strategies.

Allelic heterogeneity occurs when different mutations at a single gene locus lead to the same phenotypic features. This type of genetic variation means that multiple distinct mutations within the same gene can result in similar clinical manifestations.

Determining the genetic cause of cardiomyopathies can significantly impact the confirmation of the diagnosis and prognosis prediction of these conditions. It also aids in identifying at-risk family members and planning reproductive choices. Therefore, genetic evaluation is a crucial step in managing the disease.

Genetic assessment of hypertrophic cardiomyopathy

Hypertrophic Cardiomyopathy (HCM) is characterized by hypertrophy in the left ventricle, especially in the interventricular septum, which cannot be explained by other causes such as hypertension or valve diseases. Identified mutations are localized in proteins related to the structure and function of the heart's contractile unit, known as the sarcomere.⁸⁷⁵

There is genetic and allelic heterogeneity in hypertrophic cardiomyopathy. The visibility of the disease (penetrance) and its clinical manifestations (expressivity) increase with age. The inheritance pattern is generally autosomal dominant, although autosomal recessive inheritance rarely has been described.

Although numerous genes have been implicated in HCM, studies have identified eight sarcomeric genes with a strong gene-disease association. These sarcomeric genes include cardiac myosin-binding protein-C (*MYBPC3*), cardiac beta-myosin heavy chain (*MYH7*), myosin regulatory light chain (*MYL2*), myosin essential light chain (*MYL3*), cardiac troponin I (*TNNI3*), cardiac troponin T (*TNNT2*), alpha-cardiac actin (*ACTC1*), and tropomyosin 1 (*TPM1*). Positivity in these genes is detected in about 40–50% of hypertrophic cardiomyopathies.⁸⁷⁶ Additionally, it has been found that three different genes contribute to moderate HCM pathogenicity. These genes are cardiac troponin C (*TNNC1*), Junctophilin 2 (*JPH2*), and Cysteine-rich protein 3 (*CSRP3*). The most frequent variations in hypertrophic cardiomyopathy are found in the *MYBPC3* and *MYH7* genes.⁸⁷⁷

Genetic studies in hypertrophic cardiomyopathies offer three benefits: family screening, distinguishing phenocopies from patients with sarcomeric mutations, and ensuring healthy reproduction.⁸⁷⁸ Phenocopies include conditions such as lysosomal and glycogen storage diseases (e.g., Danon, Fabry, or Pompe diseases), RASopathies (e.g., Noonan syndrome or cardio-facio-cutaneous syndrome), and amyloidosis cases that mimic classic sarcomeric HCM. While the rate of phenocopies in adults is reported to be 1.45% in one study, it is expected to be much higher in children. Detecting phenocopies is important as they require different treatments and approaches compared to sarcomeric HCM.⁸⁷⁹ For instance, enzyme replacement therapy is given in Fabry disease, additional screening for conduction defects is required in cases with *PRKAG2* variation, and more aggressive treatment is necessary in Danon disease.^{880,881}

In the results of 140 patients who presented with a diagnosis of HCM and underwent genetic analysis at our center (publication in progress), it was found that 45% of the patients had a P/LP variant, most commonly in the *MYH7* and *MYBPC3* genes. The rate of VUS was 37.1%, and the rate of negative results was 17.8%. The rate of patients with identified phenocopies was 10.7%, with Noonan Syndrome being the most common.

In the 2022 EHRA (European Heart Rhythm Association) / HRS (Heart Rhythm Society) guidelines on genetic approaches in HCM, the following updated recommendations are provided:⁸⁸²

- Screening for genetic mutations in *MYH7*, *MYBPC3*, *TNNI3*, *TPM1*, *MYL2*, *MYL3*, *ACTC1*, and *TNNT2* genes, in addition to *CSRP3*, *TNNC1*, and *JPH2* genes, is recommended in genetic studies.
- Genetic testing is recommended to identify family members at risk of developing HCM.
- Genetic testing is recommended in cases of atypical clinical presentation or when there is suspicion of another genetic condition associated with unexplained hypertrophy (e.g., HCM phenocopies).
- Predictive genetic testing is recommended after the age of 10–12 years.
- The impact of screening for variant reclassification in phenotypically negative family members of patients with VUS is uncertain.
- Screening for variant reclassification is recommended in phenotypically positive family members.
- Genetic screening is not recommended in family members where no pathogenic/probable pathogenic variant is identified in the index case.

Regular clinical screening is recommended for family members who are found to carry the genetic variant causing the disease. Family members who have not undergone genetic testing or those with a negative variation in the index case should also be regularly monitored due to the heterogeneity in the age of onset and progression of the disease.

It has been observed that the prognosis is worse in patients with sarcomeric mutations compared to sarcomere-negative patients, with an earlier onset of symptoms and a higher incidence

of sudden cardiac death (SCD), atrial fibrillation, ventricular arrhythmias, and heart failure. However, it has been shown that this prognostic value varies significantly among families and within families.^{883,884}

Genetic assessment of dilated cardiomyopathy

Dilated Cardiomyopathy (DCM) is characterized by dilation and systolic dysfunction of the left ventricle, or both ventricles, without other causes such as abnormal loading conditions or coronary artery disease. The genes identified in dilated cardiomyopathy are associated with every structural and functional component of cardiomyocytes, including the sarcomere, desmosome, mitochondria, and ion channels. Although over 50 genes have been associated with dilated cardiomyopathy, a study found that 23 genes are responsible for over 97% of genetic DCM cases.⁸⁸⁵

Dilated cardiomyopathy also exhibits genetic and allelic heterogeneity. The inheritance pattern is generally autosomal dominant, but X-linked, autosomal recessive, or mitochondrial inheritance has also been reported. Penetrance in dilated cardiomyopathy increases with age. Therefore, the absence of phenotype in early electrocardiograms (ECG) and echocardiograms during family screening does not imply that the disease will not develop in later years.

It is classified into familial or sporadic groups based on whether it is detected in other family members. The genetic etiology is identified in approximately 50% of familial cases and 20-40% of sporadic cases.

EHRA/HRS 2022 Guidelines on Genetic Cardiac Diseases for Dilated Cardiomyopathy.⁸⁸²

- Initial genetic screening should include the *BAG3*, *DES*, *FLNC*, *LMNA*, *MYH7*, *PLN*, *RBM20*, *SCN5A*, *TNNC1*, *TNNT2*, *TTN*, and *DSP* genes.
- In the first screening, the *ACTC1*, *ACTN2*, *JPH2*, *NEXN*, *TNNI3*, *TPM1*, and *VCL* genes may also be included.
- Genetic testing is recommended in patients with dilated cardiomyopathy, whether familial, sporadic, or associated with an environmental cause.
- Genetic testing is useful for risk stratification and guiding treatment in patients with DCM.
- Following the identification of the variant causing the disease, variant-specific genetic testing is recommended for family members and appropriate relatives.
- Predictive genetic testing in relatives' children is recommended after 10-12 years.

NGS with the inclusion of target genes is the most cost-effective method for genetic studies. It is crucial to ensure that responsible core genes are included in the panel. In cases where the result is positive, proceed to family screening to identify genotype-carrying family members. If the variant is negative in the relatives of a patient with a detected variant as the cause of the disease, those relatives may be removed from follow-up. Even if relatives carrying the same variant do not exhibit a phenotype, they should be screened periodically with echocardiography and ECG.

One of the benefits of identifying the genetic cause is enabling the birth of healthy individuals through preimplantation genetic diagnosis. The prognostic impact of genetic tests is limited. Heart failure, arrhythmia, and impaired left ventricular remodeling are more prominently detected in individuals with a positive genotype.⁸⁸⁶ Additionally, due to the worse prognosis in patients carrying mutations in the *LMNA* gene, as well as in *FLNC*, *RBM20*, *PLN*, and *DES* genes, implantation of a prophylactic (primary) implantable cardioverter-defibrillator (ICD) may be considered at earlier stages in these patients.^{887,888}

Genetic assessment of arrhythmogenic cardiomyopathy (ACM)

Arrhythmogenic cardiomyopathy is primarily characterized by progressive global or regional ventricular dysfunction and a high burden of ventricular arrhythmias, often associated with fibro-fatty replacement or fibrosis of the myocardium. While it most commonly affects the right ventricle, it can also involve the left ventricle or both ventricles. Depending on the affected ventricle, it is referred to as arrhythmogenic right ventricular cardiomyopathy (ARVC), biventricular arrhythmogenic cardiomyopathy, or arrhythmogenic left ventricular cardiomyopathy (ALVC).

In contrast to other cardiomyopathies, the identification of pathogenic or likely pathogenic variants in ARVC is considered a major diagnostic criterion.⁴⁷⁵ The inheritance pattern is generally autosomal dominant, but in Naxos and Carvajal syndromes, it manifests with clinical autosomal recessive inheritance. The genetic yield in arrhythmogenic cardiomyopathy is generally reported to be around 50-60%.

ARVC primarily arises from mutations in desmosomal proteins. Since haploinsufficiency is the underlying pathological mechanism in genes causing ARVC, nonsense, frameshift, and splicing mutations lead to the disease.⁸⁸⁹ Mutations are detected in approximately 50% of patients, with mutations found in one or more genes, primarily the *PKP2* gene. Variants related to non-desmosomal proteins constitute a very small portion of patients.

In biventricular arrhythmogenic cardiomyopathy, the genetic etiology arises from variations in genes that encode desmosomal proteins. In ALVC with left ventricular involvement, variations in desmosomal genes *DSG2* and *DSC2* are associated. However, non-desmosomal variants in *FLNC*, *RBM20*, and *DES* are most commonly associated with ALVC.⁸⁹⁰

The detection of a LP or P variant in a patient is beneficial for confirming the diagnosis in borderline phenotypic cases. In patients with isolated left ventricular involvement, demonstrating a pathogenic genetic variant may be necessary to associate electrical and/or structural signs with the diagnosis of ACM.

It is crucial to confirm the presence of genes responsible for the disease in the panel being studied. Additionally, copy number variation analysis should be conducted. In cases of rarely detected variants in genes responsible for ACM, due to the high noise associated with them, it is recommended that genetic evaluation in these patients be carried out in centers experienced in cardiovascular molecular genetics to achieve the best results.⁸⁹¹

Summary of the current recommendations for genetic testing in ACM in the 2022 EHRA/HRS guidelines.⁸⁸²

- Comprehensive genetic testing is recommended for all patients with phenotypic features of ACM, regardless of familial context, including cases diagnosed post-mortem.
- The inclusion of disease-defining genes (*PKP2*, *DSP*, *DSG2*, *DSC2*, *JUP*, *TMEM43*, *PLN*, *FLNC*, *DES*, *LMNA*) is recommended in the first-stage genetic screening.
- In families with multiple affected individuals, the individual with more severe or earlier onset symptoms is considered the "genetic proband," and the initial test should be conducted on this individual.
- Comprehensive genetic testing may be considered in patients with borderline ACM phenotypes. Identifying an LP/P genetic variant can be useful in confirming the diagnosis.
- After identifying the variant responsible for the disease, specific genetic testing for family members and appropriate relatives is recommended.
- Predictive genetic testing for relatives should be performed after age of 10–12.

The role of genetic studies in predicting prognosis in ACM patients has not been established. In diseases associated with truncating mutations such as *FLNC*, *DSP*, *LMNA*, *DES*, and *PLN*, early consideration of ICD implantation may be warranted.⁸⁹¹ Additionally, in ACM patients with variants identified in the *CDH2* gene, it should be noted that there is a high burden of ventricular arrhythmias.

Genetic assessment of left ventricular noncompaction cardiomyopathy

Left ventricular noncompaction (LVNC) is a phenotype characterized by prominent left ventricular trabeculations with deep intertrabecular recesses and thinning of the compact epicardium, which can manifest as a cardiomyopathy. In children, LVNC presents with severe heart failure and life-threatening arrhythmias, whereas the clinical picture is milder in adults. Patients with LVNC can present with isolated LV trabeculations without LV dysfunction or in conjunction with other cardiomyopathies such as hypertrophic or dilated cardiomyopathy.⁸⁹² Additionally, it can manifest as a physiological change, such as during pregnancy or in athletes. Due to the heterogeneous nature of LVNC patients, genetic testing is guided by a comprehensive clinical evaluation of the patient and their family.

The inheritance pattern of LVNC is most commonly reported as autosomal dominant; however, autosomal recessive, X-linked, or mitochondrial inheritance patterns can also be observed. Variants identified in LVNC are reported in cardiomyopathy genes, primarily in sarcomeric genes such as *MYH7*, *MYBPC3*, and *TTN*. Although the effectiveness of genetic testing has been reported to be between 17–41%, it is much lower in isolated noncompaction cases without left ventricular dysfunction or concurrent cardiomyopathies.⁸⁹³

LVNC can be detected in numerous patients both in physiological conditions and in association with other cardiomyopathies, as well as in isolated cases through imaging modalities such as echocardiography and cardiac MRI. Therefore, genetic testing is

not recommended in isolated cases as it may cause more harm than benefit.

The current recommendations outlined in the EHRA/HRS guidelines are as follows.⁸⁸²

- Genetic testing for LVNC cardiomyopathy may be useful for patients diagnosed with LVNC based on a cardiologist's evaluation of the patient's clinical history, family history, and ECG/echocardiographic/MRI phenotype.
- Genetic testing may be beneficial for patients diagnosed with LVNC cardiomyopathy associated with other cardiac or non-cardiac syndromic features.
- Genetic testing should not be performed in isolated or sporadic LVNC cases without associated syndromic features or a family history of the condition.
- Following the identification of the disease-causing variant, variant-specific genetic testing for family members and appropriate relatives may be considered.

Genetic testing can be beneficial in confirming the diagnosis. In the case of detecting a LP/P variant, first-degree family members should be screened. However, genetic testing does not provide information about prognosis.

Genetic assessment of restrictive cardiomyopathy

Restrictive cardiomyopathy (RCM) is a rare cardiomyopathy characterized by impaired left ventricular filling and reduced diastolic volume, with normal or near-normal left ventricular wall thickness and ejection fraction and it can be caused by both genetic and non-genetic factors. RCM overlaps with HCM and DCM in adults, and patients often present with heart failure and life-threatening arrhythmias.

There are significant similarities in the genetic causes of RCM and HCM/DCM, particularly involving sarcomere and cellular cytoskeleton genes. These genes include *MYH7*, *TNNI3*, *TNNT2*, *ACTC1*, *FLNC*, and *TTN*.⁸⁹⁴ The genes included in the panel for RCM should encompass genes associated with HCM and DCM, as well as those related to amyloidosis and Fabry disease, such as *TTR* and *GLA*.

The current recommendations outlined in the EHRA/HRS genetic guidelines are summarized as follows:⁸⁸²

- Genetic testing may be considered for patients in whom a clinical diagnosis of RCM is established by a cardiologist based on the patient's clinical history, family history, and ECG-echocardiographic phenotype.
- Genetic testing, especially for *TTR*, is recommended for patients diagnosed with RCM and clinically confirmed cardiac *TTR* amyloidosis.
- Following the identification of the disease-causing variant, variant-specific genetic testing for family members and appropriate relatives may be considered.

In RCMs, the most significant benefit of genetic testing is enabling the screening of diagnosed variations within families. While the utility of genetic testing in determining prognosis has not been reported, identifying diseases that cause RCM, such as Fabry disease or amyloidosis, indirectly affects prognosis.⁸⁹⁵

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