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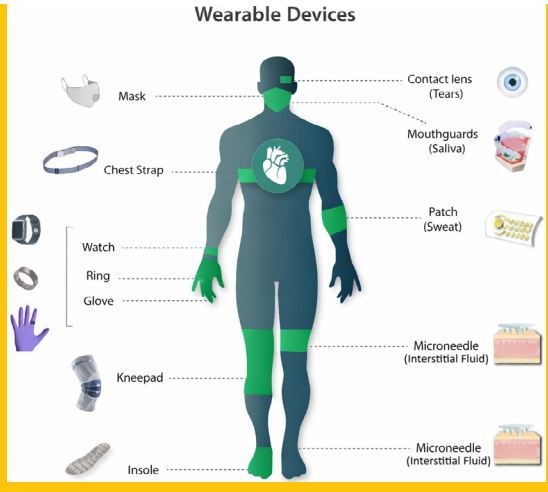

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ARCHIVES OF THE TURKISH SOCIETY OF CARDIOLOGY

Official journal of the TURKISH SOCIETY OF CARDIOLOGY

Prof. Eugene Braunwald: Passing of a Visionary in Cardiology

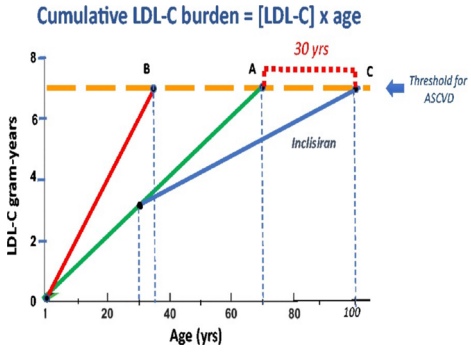
Prof. Eugene Braunwald: Kardiyolojinin Bir Vizyonerini Kaybettik

EDITORIAL
EDITORYAL

The cardiovascular community mourns the loss of a true visionary, Professor Eugene Braunwald, who has passed away at the age of 96. His monumental contributions to the study of heart failure, acute coronary syndromes, and hypertrophic cardiomyopathy did more than just advance the field; they fundamentally redefined the standard of care for patients globally. As the founder of the Thrombolysis in Myocardial Infarction (TIMI) Study Group, Professor Braunwald pioneered the architecture of the modern, large-scale international randomized controlled trial. Now entering its 80th landmark study, the TIMI Group remains a testament to his commitment to evidence-based medicine. Having had the privilege of serving on steering committees and as a National Lead Investigator for several TIMI trials, I was consistently struck by the exacting standards he maintained. His attention to detail and scientific rigor were unparalleled. Beyond his research, his legacy as the founding editor of Braunwald's Heart Disease has shaped the education of generations of physicians. To have contributed a chapter to this definitive text remains one of the most profound honors of my professional career.

He also had pioneering thoughts on preventive cardiology. He believed that lower LDL-C for longer was better and was one of the first to advocate the cumulative exposure to LDL-C hypothesis, highlighting the importance of early and rigorous LDL-C lowering, which he also practiced himself. He wrote in Braunwald's Corner in the European Heart Journal until his last day, where he shared his vision on different topics. One of these publications was a provocative paper, "How to live to 100 before developing clinical coronary artery disease: a suggestion".[1] He stated that the atherogenic effect of LDL-C is dependent on both the level of circulating LDL-C and the duration of this level. He hypothesized that administering early lipid lowering beginning at the age of 30 years would lead to a decline in the rate of progression of atherosclerotic burden, and the threshold for MACE would be reached 30 years later, when the subject reached the age of 100.

Professor Braunwald was the quintessential academician—an unparalleled mentor and educator whose intellectual vigor remained undiminished until his last day. Beyond his scientific brilliance, he modeled the virtues of humility and inclusivity. His legacy will continue through the generations of physicians he championed, his prolific body of work, and the paradigm-shifting therapies that continue to save lives across the cardiovascular spectrum.



Reference

1. Braunwald E. How to live to 100 before developing clinical coronary artery disease: a suggestion. *Eur Heart J*. 2022;43(4):249-250. [CrossRef]

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ARCHIVES OF THE TURKISH SOCIETY OF CARDIOLOGY

Official journal of the TURKISH SOCIETY OF CARDIOLOGY

Smart Sensors, Smarter Hearts: The Wearable Revolution in Cardiology

Akıllı Sensörler, Daha Akıllı Kalpler: Kardiyolojide Giyilebilir Teknoloji Devrimi

ABSTRACT

Cardiovascular disease (CVD) continues to claim more lives than any other condition worldwide. Traditional clinic visits capture only brief snapshots of health, leaving many opportunities for prevention and early intervention unmet. Wearable technologies now extend cardiovascular care into daily life, delivering continuous physiologic and behavioral data that could transform how we detect, treat, and ultimately prevent CVD. This review highlights how wearable devices, ranging from consumer-grade wristbands to advanced sensor-embedded textiles, are reshaping cardiovascular medicine. We discuss mechanical, optical, and electrochemical sensing modalities and their applications across the spectrum of care: risk assessment, arrhythmia and ischemia detection, heart failure monitoring, and cardiac rehabilitation. When paired with artificial intelligence, these devices generate predictive insights that anticipate clinical deterioration before symptoms appear. Landmark studies demonstrate real-world potential, but persistent challenges, including measurement accuracy, patient adherence, data overload, and limited integration into health systems, temper their current impact. Equally important, gaps in affordability and digital literacy risk widening disparities in cardiovascular outcomes if not urgently addressed. Wearables are moving cardiovascular medicine beyond the hospital and into the home, offering an unprecedented opportunity to shift from reactive treatment to proactive, personalized, and equitable care. Advances in multimodal sensing, artificial intelligence, and seamless health system integration could position wearables as cornerstone tools in the fight against CVD, provided that innovation is matched with rigorous validation, thoughtful regulation, and a commitment to health equity.

Keywords: Artificial intelligence, cardiovascular disease, smart sensors, wearable devices

ÖZET

Kardiyovasküler hastalık (KVH), dünya genelinde diğer tüm hastalıklardan daha fazla ölüme neden olmaya devam etmektedir. Geleneksel klinik ziyaretleri yalnızca sağlığın kısa süreli bir anlık görüntüsünü sunar ve bu durum, korunma ve erken müdahale için birçok fırsatın kaçırılmasına yol açar. Giyilebilir teknolojiler artık kardiyovasküler bakımı günlük yaşama taşıyarak sürekli fizyolojik ve davranışsal veri sağlamaktadır; bu da KVH'nin nasıl tespit edildiğini, tedavi edildiğini ve nihayetinde nasıl önlendiğini dönüştürme potansiyeline sahiptir. Bu derleme, tüketici sınıfı bilekliklerden gelişmiş sensör içeren akıllı tekstillere kadar uzanan giyilebilir cihazların kardiyovasküler tıbbı nasıl yeniden şekillendirdiğini ele almaktadır. Mekanik, optik ve elektrokimyasal algılama yöntemleri ile bunların bakım sürecinin farklı aşamalarındaki uygulamaları tartışılmaktadır: risk değerlendirmesi, aritmi ve iskemi tespiti, kalp yetersizliği izlem ve kardiyak rehabilitasyon. Yapay zekâ ile birleştirildiğinde bu cihazlar, semptomlar ortaya çıkmadan önce klinik kötüleşmeyi öngörebilen öngörüsel içgörüler üretmektedir. Öncü çalışmalar gerçek yaşamda önemli bir potansiyel ortaya koysa da ölçüm doğruluğu, hasta uyumu, veri fazlalığı ve sağlık sistemlerine sınırlı entegrasyon gibi süregelen zorluklar mevcut etkilerini sınırlandırmaktadır. Bunun yanı sıra, maliyet ve dijital okuryazarlık konularındaki eşitsizlikler acilen ele alınmazsa kardiyovasküler sonuçlardaki farklılıkların daha da artması riski bulunmaktadır. Giyilebilir teknolojiler, kardiyovasküler tıbbı hastane ortamının ötesine taşıyarak ev ortamına ulaştırmakta ve reaktif tedavi yaklaşımından proaktif, kişiselleştirilmiş ve eşitlikçi bir bakıma geçiş için benzersiz bir fırsat sunmaktadır. Çok modlu algılama teknolojileri, yapay zekâ ve sağlık sistemleriyle sorunsuz entegrasyon alanındaki ilerlemeler, gerekli bilimsel doğrulama, dikkatli düzenleme ve sağlık eşitliğine bağlılık sağlandığı takdirde giyilebilir cihazları KVH ile mücadelede temel araçlardan biri haline getirebilir.

Anahtar Kelimeler: Yapay zekâ, kardiyovasküler hastalık, akıllı sensörler, giyilebilir cihazlar

REVIEW
DERLEME

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Cardiovascular disease (CVD) remains the leading cause of morbidity and mortality worldwide, accounting for nearly 18 million deaths annually despite advances in prevention, diagnosis, and treatment.[1] Early detection of risk factors, continuous monitoring, and timely interventions are critical to reducing this burden. Wearable technologies have emerged as promising tools to complement traditional approaches by enabling the continuous, non-invasive acquisition of physiological and behavioral data outside of clinical settings.[2,3]

Modern wearables integrate mechanical, optical, and electrochemical sensors capable of monitoring heart rate, rhythm, blood pressure, physical activity, and biochemical markers in real time.[4–6] These devices not only provide patients and clinicians with immediate feedback but also generate large datasets that can be harnessed by artificial intelligence (AI) to support risk stratification, disease prediction, and personalized management.[7,8]

In cardiology, the potential applications of wearables span the spectrum of care, from primary prevention and lifestyle modification to the early detection of acute coronary syndromes, arrhythmia surveillance, heart failure management, and cardiac rehabilitation.[9–12] Consumer adoption continues to expand, particularly among younger and middle-aged adults, making these technologies well suited for preventive strategies. Meanwhile, ongoing validation studies are exploring their role in both acute and chronic disease management.[13,14]

Nevertheless, several challenges remain, including device accuracy, patient adherence, regulatory oversight, and integration into clinical workflows.[15,16] Addressing these limitations will be essential for translating wearable-derived insights into improved cardiovascular outcomes. This review summarizes the current landscape of wearable devices in cardiovascular medicine, discussing sensor modalities, preventive and therapeutic applications, and the barriers that must be overcome for widespread clinical adoption.

Methods

This article is a narrative review intended to provide a clinically focused overview of wearable technologies in cardiovascular medicine. The literature was identified through targeted searches of PubMed, MEDLINE, and Google Scholar, with emphasis on English-language studies published between 2010 and 2024. Priority was given to landmark randomized trials, large observational cohorts, meta-analyses, professional society guidelines, and pivotal validation studies evaluating wearable sensors, artificial intelligence–enabled analytics, and clinical outcomes. Additional references were selected based on relevance to emerging technologies, regulatory considerations, and real-world implementation across prevention, acute cardiovascular syndromes, arrhythmia management, heart failure, and cardiac rehabilitation. Given the rapidly evolving nature of the field, this review is not intended to be exhaustive but rather to synthesize foundational and practice-informing evidence to contextualize current capabilities, limitations, and future directions.

Sensors in Wearables

Wearable sensors are broadly categorized by their signal transduction modality, including mechanical, optical, electrical, electrochemical, and bioimpedance sensors. These sensors can be integrated into a variety of devices, either independently or in combination, generating continuous physiological data that can be leveraged by artificial intelligence for cardiovascular monitoring (Figure 1).

Mechanical and Optical Sensors

Mechanical sensors utilize capacitive, triboelectric, piezoelectric, piezoresistive, photoelectric, and optical technologies to convert physical forces into electrical signals. (1) Physical activity, blood pressure, heart rate, respiration, and aspects of the cardiac cycle

ABBREVIATIONS

AF	Atrial fibrillation
AI	Artificial intelligence
ASCVD	Atherosclerotic Cardiovascular Disease
BCG	Ballistocardiography
BEAT-HF	Better Effectiveness After Transition–Heart Failure
CR	Cardiac rehabilitation
CVD	Cardiovascular disease
ECG	Electrocardiography
GDMT	Guideline-directed medical therapy
HF	Heart failure
HRV	Heart rate variability
PA	Physical activity
PPG	Photoplethysmography
SCD	Sudden cardiac death
SCG	Seismocardiography
STEMI	ST-elevation myocardial infarction
SVT	Supraventricular tachycardias
TAVR	Transcatheter aortic valve replacement
TIM-HF2	Telemedical Interventional Management in Heart Failure II

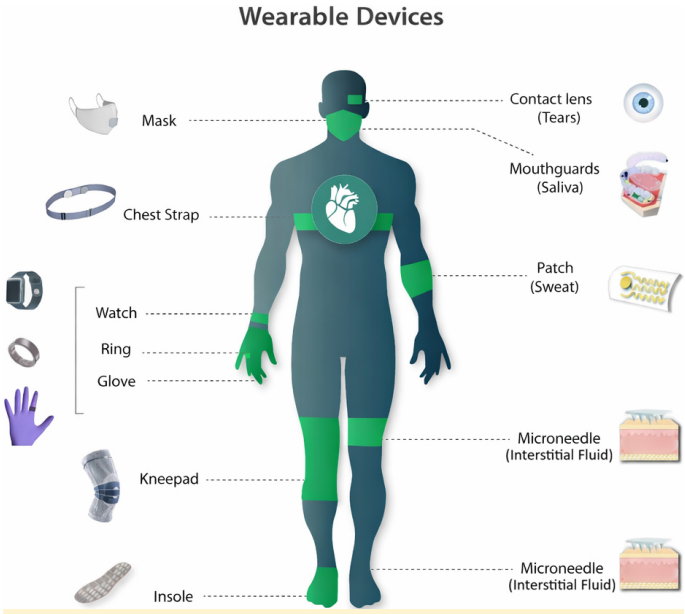

Figure 1. Wearable modalities for cardiovascular monitoring. Sensors can be integrated into multiple wearable devices, including wristbands, smartwatches, chest patches, rings, and smart textiles, enabling continuous physiologic and biochemical monitoring.

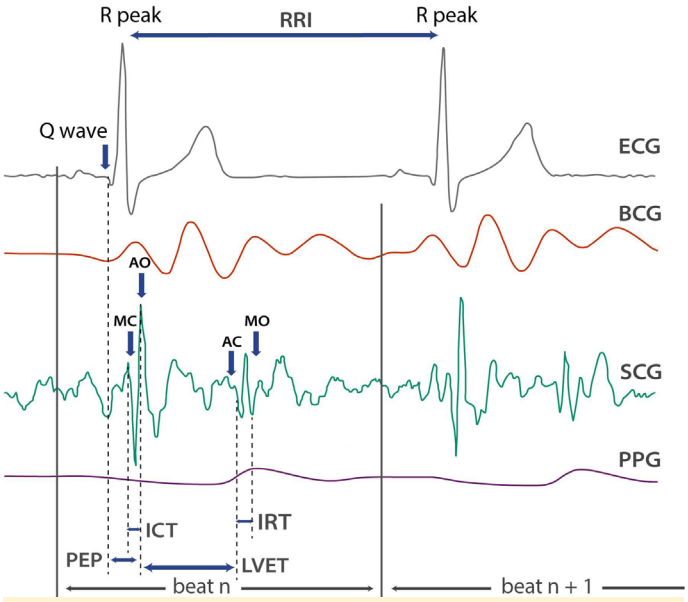

Figure 2. Representative cardiac waveforms and intervals derived from wearable sensors. Simultaneous recordings from electrocardiography (ECG), ballistocardiography (BCG), seismocardiography (SCG), and photoplethysmography (PPG) illustrate complementary mechanical and hemodynamic signatures of the cardiac cycle across consecutive beats. The R–R interval (RRI) is defined as the interval between successive ECG R peaks. Derived systolic and diastolic intervals are defined as follows: the pre-ejection period (PEP), from the ECG Q-wave to aortic valve opening (AO); isovolumetric contraction time (ICT), from mitral valve closure (MC) to AO; left ventricular ejection time (LVET), from AO to aortic valve closure (AC); and isovolumetric relaxation time (IRT), from AC to mitral valve opening (MO). Fiducial points (MC, AO, AC, and MO) are identified from characteristic features in SCG and BCG waveforms, as shown. These fiducials and intervals are presented as representative, recognizing that precise timing and morphology depend on sensor placement, signal processing, and algorithmic definitions.

can be tracked using these sensors (Figure 2). Accelerometry detects motion and physical activity. Chest placement yields optimal accuracy, although wrist placement remains popular for consumer devices.[3] Seismocardiography (SCG) records precordial vibrations to assess ventricular contraction, relaxation, and valvular events, with applications in heart failure monitoring.[17] Ballistocardiography (BCG) measures recoil forces generated by cardiac ejection, enabling estimates of cardiac output and blood pressure.[18] Photoplethysmography (PPG) uses optical sensors to track blood volume changes, providing information on heart rate, blood pressure, oxygen saturation, and cardiac rhythm. Limitations include variations in skin tone, sweat, and strap quality, although accuracy improves with chest-worn sensors.[4]

Electrical, Electrochemical, and Bioimpedance Sensors

Electrical and electrochemical sensors extend wearable utility to biochemical and electrophysiological measurements.[5] Consumer electrocardiography (ECG) devices typically record single-lead tracings and have been validated for atrial fibrillation (AF) detection, with emerging potential for ischemia detection and interval analysis.[6] Limitations include the need for manual activation, although integration with PPG or multi-lead reconstruction algorithms may expand utility. Amperometric sensors enable enzyme-based detection of glucose and other metabolites, and continuous glucose monitoring is already established for improving glycemic outcomes.[19] Potentiometric and voltammetric sensors allow detection of electrolytes, drugs, and pH, although translation into wearable formats remains in the early stages of development.[20] Bioimpedance sensors can estimate total body water and body composition, aiding fluid management in patients with heart failure.[21]

Clinical Applications of Wearable Technologies Across Cardiovascular Care

The clinical applications of wearable technologies in cardiovascular care continue to expand, spanning prevention, acute coronary syndromes, electrical disorders, heart failure management, and cardiac rehabilitation. However, the clinical maturity of these applications varies substantially (Table 1). Clinically validated outcome improvements have been demonstrated when wearables are embedded within structured care pathways, such as targeted atrial fibrillation screening, selected heart failure telemonitoring programs, wearable cardioverter-defibrillator therapy, and home-based cardiac rehabilitation, where continuous physiological data directly inform actionable clinical decisions. In contrast, the clinical utility of several emerging applications, including AF burden-guided management and post-procedural rhythm surveillance, remains under investigation. Other technologies, such as ischemia detection using smartwatch ECG surrogates and non-invasive biochemical sensing, remain in the early conceptualization phase.

Wearables in Prevention

Most smartwatch users are under 50 years old, making them an ideal population for preventive strategies.[9] Traditional cardiovascular risk calculators, such as the Atherosclerotic Cardiovascular Disease (ASCVD) 10-year score, do not capture dynamic lifestyle and physiological factors. Wearables can provide continuous data on sleep, resting heart rate, and heart rate variability, which are associated with cardiometabolic risk.[10,22]

Beyond monitoring, wearables can support behavior change. In the All of Us program, higher daily step counts tracked by wearables correlated with lower rates of hypertension, diabetes, and sleep apnea.[23] Randomized trials such as BE FIT (Behavioral Economics Framed Incentives Trial) and ENGAGE (Encouraging Goals And Gamified Exercise) demonstrated that gamification and goal-setting interventions increased physical activity, including among disadvantaged populations.[24] While activity levels consistently improve, translation into sustained reductions in blood pressure or glycemia remains limited, often due to short follow-up durations.[25]

Wearables also enable just-in-time adaptive interventions (JITAIs), in which real-time prompts encourage healthy behavioral choices. However, current systems remain limited, with delayed or non-personalized notifications.[26]

Pharmacologic prevention remains essential. Wearables may enhance hypertension screening and medication titration, while novel technologies such as smart contact lenses show promise for non-invasive cholesterol monitoring.[27]

Table 1. Clinical impact and evidence maturity of wearable technologies across cardiovascular scenarios

Clinical scenario	Primary wearable function	Evidence of outcome modification	Evidence maturity	Interpretation
Atrial fibrillation screening	Rhythm detection (PPG/ECG)	Yes (selected populations) – Increased AF diagnosis and anticoagulation initiation; stroke reduction suggested	Validated	Outcomes improve when targeted to high-risk populations within structured care pathways
AF burden monitoring/ post-cardioversion	Burden quantification, rhythm confirmation	Potential benefit – Improved rhythm-guided management; outcomes under investigation	Emerging	Decision-support tool with evolving outcome impact
Supraventricular tachycardia	Episodic rhythm documentation	No clear outcome benefit – Improves diagnostic yield and referral efficiency	Early conceptualization	Decision-support tool with evolving clinical impact
Bradyarrhythmias/ conduction disease	Event-triggered ECG capture	Limited – Case-based detection; no population-level outcome data	Early conceptualization	Primarily diagnostic or monitoring with indirect benefit
Acute coronary syndromes (STEMI)	Ischemia detection via ECG surrogates	Not yet – Feasibility demonstrated; no outcome trials	Early conceptualization	Primarily diagnostic/monitoring; not outcome-modifying
Heart failure remote monitoring	Volume status, activity, and physiologic trends	Yes (selected populations) – Reduced hospitalizations in structured trials	Validated	Monitoring/adjunctive strategy; outcome-modifying when embedded in structured programs
Post-TAVR rhythm surveillance	Detection of conduction abnormalities	Potential benefit – Earlier detection and facilitation of safe early discharge	Emerging	Outcome-modifying in procedural care
Cardiac rehabilitation	Activity tracking, feedback, adherence support	Yes – Comparable outcomes to center-based cardiac rehabilitation	Validated	Outcomes improved through expanded access and adherence
Primary prevention/ lifestyle modification	Activity, sleep, and HRV monitoring	Mixed – Behavioral change demonstrated; limited hard outcome data	Emerging	Indirect outcome benefit
Sudden cardiac death prevention (SCD)	Arrhythmia detection and therapy	Yes – Reduced arrhythmic mortality in selected populations	Validated	Outcome-modifying with a direct therapeutic role

Wearables in Acute Coronary Syndromes

The diagnosis of ST-elevation myocardial infarction (STEMI) conventionally requires ST-segment changes in at least two contiguous leads on a standard 12-lead electrocardiogram (ECG), a requirement that underscores the fundamental limitation of current wearable devices. These devices are not a substitute for a conventional 12-lead ECG and typically generate single-lead tracings.[28] A wrist-worn device producing an Einthoven lead I equivalent demonstrates excellent specificity (100%) but limited sensitivity (34%) for detecting ischemic changes.[29]

The diagnostic potential improves when sensors are repositioned to generate additional leads. Placement on the ankle or left lower abdominal wall can reproduce Einthoven leads II and III, while positioning across the chest wall can approximate precordial leads V1–V6.[30,31] While technically feasible, these approaches are less practical in routine use and are highly dependent on user technique, sensor positioning, and signal quality, all of which may introduce variability and error.

Clinical validation is emerging. In a study of 81 patients presenting with suspected acute coronary syndrome, sequential smartwatch-derived ECGs were compared with standard 12-lead recordings. Physicians correctly identified ST elevation with an accuracy of 95%.[11] Despite these promising findings, commercially available devices currently lack integrated artificial intelligence algorithms to automatically interpret ST-segment changes or baseline ECG abnormalities. As such, the current clinical utility of wearable ECGs in acute coronary syndromes is best confined to clinician-led pathways, such as remote triage, teleconsultation, or resource-limited settings, rather than self-diagnosis without clinician oversight.

Looking ahead, the development of wearable systems capable of generating true multi-lead ECGs, such as sensor-embedded garments, combined with advanced AI-driven algorithms for automated detection, could substantially enhance early recognition of STEMI and other acute coronary syndromes.

Wearables for Electrical Abnormalities

Electrocardiography and photoplethysmography form the foundation of wearable arrhythmia detection. Initially validated for atrial fibrillation, these technologies are increasingly being applied to other electrical abnormalities, including supraventricular tachycardias (SVT), bradyarrhythmias, sudden cardiac death (SCD) risk, and drug- or post-procedural monitoring. Current devices typically generate single-lead ECG tracings equivalent to lead I, which can reliably detect AF but may be less informative for other arrhythmias. Nonetheless, advancements in AI algorithms and multi-lead configurations are rapidly expanding their utility.[32–34]

Atrial Fibrillation

Atrial fibrillation is a major cause of stroke and heart failure, with many patients remaining asymptomatic.[35–37] Wearables enable large-scale screening, particularly among high-risk individuals

with elevated CHA_2DS_2-VASc scores (Congestive Heart Failure, Hypertension, Age ≥ 75 years, Diabetes Mellitus, Stroke/Transient Ischemic Attack/Systemic Embolism, Vascular Disease, Age 65–74 years, Sex Category). Compared with traditional Holter monitors, smartwatches and adhesive patches are less burdensome and allow longer monitoring periods.[37]

The Apple Heart Study, enrolling over 400,000 participants, demonstrated that a PPG-based irregular pulse notification had an 84% positive predictive value for atrial fibrillation,[12] while the mSToPS trial (mHealth Screening to Prevent Strokes) showed that continuous patch monitoring increased AF diagnosis and anticoagulation at one year, with an associated reduction in stroke risk at three years.[38,39] Despite these findings, the clinical implications of widespread AF screening remain controversial, as device accuracy varies across real-world settings and increased AF detection has not consistently translated into reductions in adverse clinical outcomes.[40,41] Accordingly, effective AF screening with wearables requires a clearly defined clinical implementation pathway in which device-generated alerts prompt structured triage and confirmatory clinician-interpreted ECG testing rather than automatic diagnosis or treatment. Without standardized workflows for documentation, escalation, and management of inconclusive or low-quality recordings, false positives, incidental findings, and increased clinician workload may offset potential benefits. In this context, the ongoing HEARTLINE trial (Heart Health Study Using Apple Watch to Investigate Effects of Notifications and Engagement) will evaluate whether systematic AF screening using combined PPG and ECG features on a wearable device paired with an iPhone application can accelerate AF diagnosis and improve cardiovascular outcomes, including stroke and treatment adherence, in older adults.[42]

Beyond detection, wearables offer the ability to quantify AF burden, highlighting an important tension between guideline-based management and wearable-derived evidence. Current guidelines recommend anticoagulation based on stroke risk scores irrespective of AF burden, prioritizing stroke prevention and reflecting concerns regarding undertreatment. However, growing evidence suggests that AF burden is biologically and clinically relevant, with lower AF burden associated with substantially reduced thromboembolic risk, challenging the traditional binary framework of AF as simply present or absent.[43] The REACT.COM pilot trial (Rhythm Evaluation for Anticoagulation with Continuous Monitoring) demonstrated that implantable monitor-guided intermittent anticoagulation reduced therapy duration by 94% without increasing thromboembolic events.[44] The iCARE-AF pilot trial (Intermittent vs. Continuous Anticoagulation Therapy in Patients with Atrial Fibrillation) further demonstrated that daily smartphone ECG-guided intermittent anticoagulation in patients with paroxysmal AF was feasible and may reduce bleeding compared with continuous therapy without increasing thromboembolic events.[45] Attempts to translate burden-guided strategies to consumer wearables have been limited by adherence and data continuity, although larger trials such as REACT-AF (Rhythm Evaluation for AntiCoagulaTion for Atrnoial Fibrillation) are ongoing. Wearables may also assist with rate-control strategies and with confirming AF persistence prior to cardioversion.[46,47]

Supraventricular Tachyarrhythmias

Several reports describe smartwatch detection of SVT, with patients capturing tracings during symptomatic episodes.[48,49] However, current devices often underestimate brief arrhythmias (< 60 seconds), and PPG frequently underreports peak rates.[50] In a prospective study of 47 patients with induced atrioventricular nodal reentrant tachycardia (AVNRT), atrioventricular reentrant tachycardia (AVRT), or atrial tachyarrhythmia, single-lead smartwatch tracings yielded sensitivities between 66% and 77% depending on the interpreter.[51] While diagnostic accuracy remains below that of standard ECG, the demographic most prone to SVT—patients under 50 years of age—is also the most receptive to wearable adoption, suggesting a growing role for these devices as algorithms improve.[50]

Bradyarrhythmias

Wearables have more limited application in bradyarrhythmia detection, as recordings usually require patient initiation. This limitation hinders use in presyncope or syncope, where continuous monitoring is preferable. Nevertheless, case reports describe smartwatch detection of complete heart block and medication-induced bradycardia.[52,53] In one study, physicians identified all bradycardia cases among 216 participants using smartwatch tracings, although differentiation between sinus rhythm and atrioventricular (AV) block was less reliable (81%). Accuracy improved to 95% when alternative sensor positions were used to generate pseudo-precordial leads.[6] Algorithms capable of automatically triggering ECG recording based on bradycardic PPG signals are in development but remain unvalidated.

Sudden Cardiac Death

Wearable cardioverter-defibrillators (WCDs) are established as a bridge to implantable defibrillators, reducing SCD risk by detecting and treating ventricular tachycardia or fibrillation, although inappropriate shocks remain a concern.[54,55] Beyond therapy, consumer wearables may help screen for conditions predisposing to SCD. In young adults, repositioning a smartwatch to chest-lead equivalents increased detection of Brugada syndrome, hypertrophic cardiomyopathy, long-QT, and pre-excitation from 64% to 89% compared with 12-lead ECGs, although cardiologist interpretation was required.[56]

For out-of-hospital cardiac arrest, early recognition remains the weakest link in survival. The HEART-SAFE project (Heart Attack Early Recognition Technology for Sudden Arrest and Fatal Events) is developing AI algorithms to detect cardiac arrest from smartwatch PPG and motion data and automatically alert emergency services, although clinical validation is pending.[57]

Drug and Post-Procedural Monitoring

Many antiarrhythmic agents prolong the QT interval, necessitating monitoring. During the coronavirus disease 2019 (COVID-19) pandemic, remote QT assessment using devices such as the Apple Watch and KardiaMobile was explored, with studies showing good concordance with 12-lead ECGs when multi-position recordings were used.[34,58] Further trials are required before routine clinical integration.

After transcatheter aortic valve replacement (TAVR), wearables have shown promise in detecting conduction abnormalities. In one study, smartwatch monitoring detected 76% of conduction

disturbances, while the SMART TAVR trial (Smartwatch Monitoring for Arrhythmias after Transcatheter Aortic Valve Replacement) demonstrated the feasibility of early discharge with ongoing remote rhythm surveillance.[59,60] These findings highlight the potential for wearables to streamline post-procedural care, although larger safety studies are needed.

Wearables in Heart Failure

Heart failure (HF) remains a leading cause of hospitalization and healthcare utilization worldwide. Remote monitoring through wearables offers opportunities to reduce readmissions, guide therapy, and improve quality of life, although the lack of standardization and limited randomized trial evidence have slowed widespread adoption.[13,61–63]

Monitoring Volume Status

Conventional approaches to heart failure volume assessment rely on weight, blood pressure, and oxygen saturation, which are burdensome and inconsistently predictive of decompensation.[64] Large randomized trials such as TIM-HF2 (Telemedical Interventional Management in Heart Failure II) and BEAT-HF (Better Effectiveness After Transition–Heart Failure) assessed comprehensive telemonitoring care models that combined wearable-based ECG, blood pressure, and pulse oximetry with predefined monitoring schedules and structured clinical response protocols. In TIM-HF2, this integrated telemedical strategy reduced hospitalization days and improved survival compared with usual care, whereas BEAT-HF highlighted the critical importance of adherence, with only 61% of elderly participants maintaining sustained engagement.[61,62] These findings underscore that wearable devices can yield clinical improvements when integrated into structured care pathways that enable timely and actionable clinical responses.

Implantable hemodynamic monitoring provides an important benchmark for congestion-guided management. Devices such as CardioMEMS have demonstrated that pulmonary artery pressure–guided therapy can reduce heart failure hospitalizations by nearly 40%, establishing a high evidentiary standard for physiologic monitoring.[63] Non-invasive wearable approaches aim to approximate this paradigm but currently lack comparable outcome-level validation. Wearable bioimpedance-based systems, such as the U.S. Food and Drug Administration (FDA)-cleared ReDS (Remote Dielectric Sensing) vest, show promise for monitoring pulmonary congestion, with early studies reporting fewer 30-day readmissions and improved self-care following hospitalization.[65,66] Emerging technologies such as seismocardiography and multisensor patches analyzed with AI have further demonstrated the ability to predict decompensation several days before clinical presentation.[17,67]

Disease Stratification

Accelerometer-based measures of physical activity (PA) are reliable prognostic markers in HF. Multiple studies show that reduced PA and greater variability are associated with worse outcomes, including mortality and rehospitalization.[68–70] Accelerometry may also objectively approximate the New York Heart Association (NYHA) functional class, providing a more reproducible measure of disease severity than traditional clinician assessment.[71,72] In addition, wearables themselves can act as behavioral interventions: structured PA programs delivered through these devices have improved exercise adherence and functional status in patients with HF.[73,74]

Titration of Guideline-Directed Therapy

Optimal use of guideline-directed medical therapy (GDMT) improves outcomes in heart failure with reduced ejection fraction (HFrEF), but real-world titration is often suboptimal. Wearables can provide continuous heart rate and blood pressure measurements to aid clinicians in dynamic therapy adjustment.[75] The Zoll LifeVest has been investigated not only for arrhythmic protection but also as a remote monitoring tool for GDMT titration and treatment response.[76]

Non-invasive potassium monitoring remains experimental, but proof-of-concept studies using PPG-based sensors have demonstrated clinically meaningful precision in detecting hyperkalemia.[77] Finally, heart rate variability (HRV) derived from wearable ECG and PPG signals may identify patients most likely to respond to cardiac resynchronization therapy (CRT), supporting a more personalized approach to device therapy.[78]

Wearables in Cardiac Rehabilitation

Cardiac rehabilitation (CR) integrates exercise training, education, and lifestyle modification to promote secondary prevention, thereby reducing morbidity and mortality. The American Heart Association (AHA) recommends CR as a class I intervention for patients following myocardial infarction, revascularization, or a new diagnosis of heart failure.[79,80] Yet, traditional CR remains underutilized due to cost, travel requirements, and limited access, driving interest in home-based programs with wearable-enabled remote monitoring.

Evidence supports this approach. A Cochrane review found home-based CR to be as effective as center-based programs for class I indications.[81] The REMOTE-CR trial (Remotely Monitored Exercise-Based Cardiac Telerehabilitation) demonstrated that chest-worn wearables providing individualized feedback on heart rate, physical activity, and respiration produced outcomes equivalent to those of in-center rehabilitation, but at lower cost.[82] Similarly, the SmartCare-CAD study (SmartCare for Coronary Artery Disease) showed that continuous data sharing from wearables, even without specialist feedback, reduced relapse into sedentary behavior.[83]

Consumer-grade wearables are increasingly being studied in CR. A pilot program using Fitbit devices for patients with heart failure combined exercise and nutrition guidance with app-based messaging. At three months, patients demonstrated greater improvements in 6-minute walk distance and muscle strength compared with usual care, although adherence was modest (73%) and the trial was limited to 30 participants.[84]

Overall, wearables have the potential to expand access to CR, promote adherence, and improve outcomes. Future work should determine which populations benefit most, how to optimize engagement, and whether consumer devices can be standardized to meet clinical quality benchmarks.

Limitations of Wearable Devices in Cardiology

Although wearable technologies show great promise in cardiovascular medicine, several challenges limit their routine

clinical application. These include concerns about accuracy, data interpretation, patient adherence, regulatory oversight, privacy, system integration, and equitable access. Addressing these barriers will be critical for safe and effective adoption.

Accuracy and Reliability of Data

Most consumer wearables are not designed as medical-grade devices, and variability in measurement accuracy remains a major concern. Heart rate and rhythm detection, in particular, can differ substantially across devices, use conditions, and patient populations, occasionally resulting in clinically meaningful misclassification or false reassurance. Such variability limits confidence in wearable-derived data for diagnostic or therapeutic decision making.[15]

Data Overload and Interpretation

Continuous physiologic monitoring generates large volumes of data that may overwhelm both clinicians and patients. Although artificial intelligence and machine learning algorithms offer potential solutions for signal filtering and pattern recognition, these tools remain vulnerable to algorithmic bias, limited training datasets, and context-specific errors. These limitations can lead to false alerts or missed diagnoses, particularly in underrepresented populations. The absence of standardized analytic frameworks further restricts clinical interpretability and adoption.[7]

Limited Validation for Clinical Decision-Making

While select wearable technologies have received regulatory clearance for defined indications, such as single-lead ECG rhythm analysis, many devices lack rigorous validation for guiding therapy in complex cardiovascular conditions, including heart failure. Clinical trials evaluating wearable-guided management strategies remain limited, and long-term outcome data are sparse. As a result, wearable-derived information currently serves primarily as an adjunct rather than a replacement for established clinical assessment and monitoring strategies.[8]

Patient Adherence and Engagement

Long-term adherence to wearable use is inconsistent. Factors such as device discomfort, limited battery life, technical complexity, and frequent maintenance requirements contribute to declining engagement over time. These challenges are particularly pronounced among older adults and patients with multiple comorbidities. In addition, disparities in digital literacy and access further limit sustained use, highlighting the need for user-centered design, simplified interfaces, and structured onboarding and support strategies.[16]

Privacy

Wearables collect sensitive cardiovascular data that must be securely transmitted and stored. Regulatory frameworks such as the Health Insurance Portability and Accountability Act (HIPAA) do not fully address these risks, and patient concerns about third-party access persist. Clear frameworks are needed to govern data ownership, informed consent, and third-party access. Patients should retain transparency and control over how wearable-derived data are stored, shared, and monetized. Core safeguards include encryption, role-based access, audit trails, and explicit opt-in consent for secondary data use beyond clinical care. Existing regulatory standards will need to evolve to address these emerging risks.[14,85]

Interoperability

Limited interoperability with electronic health records can hinder seamless workflow integration, underscoring the need for standardized data formats and integration pathways. Similarly, AI-generated clinician-facing outputs should prioritize concise, actionable summaries and trend-based alerts rather than continuous raw data streams to reduce cognitive burden. Aligning wearable outputs with existing clinical decision-support frameworks will be critical for sustainable use.[85]

Accessibility and Equality

Without measured implementation strategies, wearable technologies risk exacerbating existing disparities in cardiovascular care.[86] To mitigate cost and digital literacy barriers, implementation strategies may include reimbursement pathways through public and private payers, institutional loaner or prescription-based wearable programs, and multilingual onboarding supported by accessible technical assistance. Validation studies must also deliberately include diverse populations, accounting for differences in age, sex, comorbidity burden, and skin tone–related variability in optical sensors such as photoplethysmography, to minimize performance disparities and algorithmic bias.

Future Directions

Wearable technologies are poised to transform cardiovascular care from reactive treatment to proactive, preventive medicine. Next-generation devices capable of simultaneously capturing electrophysiologic, hemodynamic, and biochemical signals, combined with artificial intelligence, may enable early detection of arrhythmias, ischemia, and heart failure decompensation while delivering personalized risk insights. To realize this promise, large outcomes trials must demonstrate meaningful reductions in morbidity, mortality, and healthcare costs across diverse populations. Seamless integration with electronic health records will be essential to translate continuous data into actionable clinical decisions, while equity in access and digital literacy must be prioritized to prevent widening disparities. Regulatory frameworks that ensure accuracy, security, and privacy will provide the foundation for safe adoption. Ultimately, success will depend on designing systems that sustain engagement, positioning wearables as active partners in cardiovascular care and as cornerstones of the future of heart health.

Conclusion

Wearable technologies are reshaping the landscape of cardiovascular medicine by bridging the gap between continuous physiological monitoring and real-world patient care. With capabilities spanning mechanical, optical, and electrochemical sensing, these devices provide unprecedented access to dynamic data on heart rate, rhythm, blood pressure, physical activity, fluid status, and even biochemical markers. When combined with advances in artificial intelligence and machine learning, wearable-derived datasets offer powerful opportunities for early disease detection, risk stratification, and personalized management that extend beyond the scope of conventional clinic-based assessments.

In prevention, wearables can complement traditional risk calculators by capturing lifestyle and physiological trends in real time, supporting just-in-time interventions and long-term behavior change. In acute care, emerging systems capable of multi-lead ECG acquisition and automated interpretation may enhance early recognition of ischemia and arrhythmias, potentially narrowing the time to reperfusion and reducing sudden cardiac death. For patients with heart failure, multisensor approaches integrating accelerometry, bioimpedance, and seismocardiography, analyzed through predictive algorithms, may enable preemptive interventions before decompensation occurs. Similarly, in cardiac rehabilitation, remote wearable-enabled programs can expand access, improve adherence, and reduce disparities in secondary prevention.

Despite these advances, key challenges remain. Device accuracy and reliability vary across settings, and sustained adherence is often poor, particularly among older patients. Integration with electronic health records is limited, regulatory frameworks remain underdeveloped, and large-scale trials demonstrating improved long-term outcomes are scarce. Moreover, equitable access and affordability must be prioritized to ensure that the benefits of these technologies are not confined to select populations.

Looking forward, the convergence of sensor miniaturization, multimodal integration, and next-generation AI will likely yield wearables capable of comprehensive cardiovascular surveillance and real-time therapeutic guidance. Future devices may continuously monitor ischemia, arrhythmia, hemodynamics, and metabolic status in parallel, enabling a shift from reactive treatment to proactive, individualized care. Advances in remote diagnostics, digital therapeutics, and closed-loop management systems could further embed wearables into the continuum of cardiovascular care, reducing hospitalizations and improving survival.

If these scientific, technical, and policy challenges are successfully addressed, wearable devices stand poised to become indispensable components of cardiovascular medicine. By extending care beyond clinic walls and empowering both patients and providers with actionable insights, wearables have the potential to transform cardiovascular disease from the leading global cause of death into a condition managed more effectively, equitably, and preventively in the decades to come.

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In Vitro Effects of Liquid Cardiac Drugs on Human Catalase Enzyme

Sıvı Kalp İlaçlarının İnsan Katalaz Enzimi Üzerindeki *İn Vitro* Etkileri

ABSTRACT

Objective: When liquid medications are administered intravenously, the first cellular defense encountered by the drug is erythrocytes. Catalase is the main antioxidant system in erythrocytes. Drug-related catalase inhibition can cause adverse effects. Although catalase is a well-known enzyme, studies investigating drug-catalase interactions are scarce in the literature. Therefore, we investigated the impact of liquid cardiac drugs on human erythrocyte catalase activity *in vitro*.

Method: Catalase activity was determined by a spectrophotometric method using a procedure developed by Aebi. Liquid cardiac drugs were incubated with human blood *in vitro*. IC50 values were compared among the drugs.

Results: The most potent inhibitors were noradrenaline (IC_{50}: 4.61 μM), adrenaline (IC_{50}: 32.58 μM), and amiodarone hydrochloride (IC_{50}: 41.86). Dopamine hydrochloride (IC_{50}: 429.15 μM) and lidocaine hydrochloride (IC_{50}: 453.1 μM) showed less inhibitory effects on catalase activity compared with adenosine (IC_{50}: 58.49 μM), atropine sulfate (IC_{50}: 68.75 μM), dobutamine hydrochloride (IC_{50}: 80.79 μM), glyceryl trinitrate (IC_{50}: 86.66 μM), and heparin sodium (IC_{50}: 92.4 μM).

Conclusion: Noradrenaline, adrenaline, and amiodarone hydrochloride have strong inhibitory effects on catalase activity. Catalase inhibition may be responsible for the side effects of these drugs. Therefore, when these drugs are used in treatment, their dosages and duration of administration should be carefully controlled to prevent adverse effects due to catalase enzyme inhibition.

Keywords: Catalase, inhibition, *in vitro*

ÖZET

Amaç: İntravenöz ilaçlar damara uygulandığında, ilaçla ilk karşılaşan savunma mekanizması eritrositlerdir. Katalaz, eritrositlerde bulunan temel antioksidan enzimdir. İlaca bağlı katalaz inhibisyonu, ilaç yan etkilerine yol açabilir. Katalaz iyi bilinen bir enzim olmasına karşın, literatürde ilaç–katalaz etkileşimini araştıran çalışma sayısı sınırlıdır. Bu nedenle bu çalışmada, sıvı kardiyak ilaçların katalaz aktivitesi üzerindeki etkileri *in vitro* olarak araştırıldı.

Yöntem: Katalaz aktivitesi, Aebi tarafından geliştirilen ve spektrofotometrik temele dayanan yöntem kullanılarak değerlendirildi. İlaçlar *in vitro* koşullarda insan kanı ile etkileşime tabi tutuldu. Elde edilen IC_{50} değerleri karşılaştırıldı.

Bulgular: En güçlü katalaz inhibitörleri noradrenalin (IC_{50}: 4,61 μM), adrenalin (IC_{50}: 32,58 μM) ve amiodaron hidroklorür (IC_{50}: 41,86 μM) olarak belirlendi. Dopamin hidroklorürün (IC_{50}: 429,15 μM) ve lidokain hidroklorürün (IC_{50}: 453,1 μM) katalaz inhibisyonu üzerindeki etkilerinin oldukça düşük olduğu saptandı. Diğer ilaçların IC_{50} değerleri ise adenozin için 58,49 μM, atropin sülfat için 68,75 μM, dobutamin hidroklorür için 80,79 μM, gliseril trinitrat için 86,66 μM ve heparin sodyum için 92,4 μM olarak bulundu.

Sonuç: Noradrenalin, adrenalin ve amiodaron hidroklorür, katalaz enzimi üzerinde güçlü inhibitör etkiye sahiptir. Katalaz inhibisyonu, bu ilaçların yan etkilerinden sorumlu olabilecek mekanizmalardan biri olabilir. Bu nedenle söz konusu ilaçlar tedavide kullanılırken, katalaz inhibisyonu ile ilişkili olası yan etkilerin önlenmesi amacıyla ilaç dozları ve uygulama süreleri dikkatle kontrol edilmelidir.

Anahtar Kelimeler: Katalaz, inhibisyon, *in vitro*

ORIGINAL ARTICLE
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Catalase is a tetrameric enzyme containing four polypeptide chains, each consisting of more than 500 amino acids. It contains four heme (porphyrin) groups that enable the enzyme to react with hydrogen peroxide (H_2O_2).[1] Catalase catalyzes the decomposition of H_2O_2 into water and molecular oxygen without the formation of free radicals.[2] Catalase is a ubiquitous enzyme found in almost all organisms exposed to oxygen.[3]

Oxidative stress causes the production of hydrogen peroxide and free radicals. Reactive oxygen species, such as the hydroxyl radical, superoxide radical, and hydrogen peroxide, are produced during metabolism. These radicals attack and damage DNA, lipid membranes, and proteins. These oxidant products affect membrane lipids and make the cell membrane more fragile.[4] The toxic effects of oxidative agents are eliminated by enzymatic and non-enzymatic antioxidant defense systems. Enzymatic defense systems include catalase, superoxide dismutase, glutathione reductase, glutathione peroxidase, and glutathione S-transferase.[5,6] Gaetani et al.[7] reported that dependence on glutathione reductase and glutathione peroxidase mechanisms did not increase until more than 98% of catalase was inactivated. Catalase is the primary regulatory mechanism protecting the body from the toxic effects of hydrogen peroxide and reactive oxygen species.[8] As an antioxidant, catalase removes toxic free radicals and hydrogen peroxide that may contribute to oxidative stress–related diseases at the cellular level. Furthermore, Tarnai et al.[9] showed that erythrocyte catalase activity is the main regulator of free radical and hydrogen peroxide metabolism, and that any deficiency in catalase may lead to the accumulation of hydrogen peroxide derivatives with toxic effects.

Erythrocytes are the first tissues to interact with foreign substances entering the body or with intravenously administered drugs. Therefore, erythrocyte catalase comes into direct contact with drugs. Any inherited or drug-related deficiencies in catalase may increase the toxic effects of oxygen radicals and hydrogen peroxide.[9]

In recent years, interest in drug–enzyme interaction studies has increased. Some drugs have toxic side effects, and understanding the mechanisms underlying these effects is important for diagnosis and treatment. Although catalase is a well-known enzyme, catalase inhibition related to cardiac drugs has not been sufficiently investigated. Therefore, this study aimed to investigate and compare the effects of cardiac drugs on catalase activity.

Materials and Methods

Potassium dihydrogen phosphate, dimethyl sulfoxide (DMSO), and hydrochloric acid used in the study were obtained as analytical-grade reagents from Sigma-Aldrich Co.

This study was conducted *in vitro* using blood samples obtained from five female and five male participants aged between 20 and 40 years who presented to the cardiology outpatient clinic and were found to be healthy after clinical examination. Participants who smoked cigarettes, consumed alcohol, or used any medications were excluded from the study. Samples were centrifuged at 1000 × g for 20 minutes at 4°C, and the supernatant was removed. The packed erythrocytes were washed three times with 0.9% NaCl and then hemolyzed in cold water. The pH of the hemolysate was adjusted to 8.5 with a solid Tris base.

ABBREVIATIONS

BSA	Bovine serum albumin
DMSO	Dimethyl sulfoxide
H_2O_2	Hydrogen peroxide

The detailed optimization of the purification method was described in the study by Çıkrıkcı et al.[10] As a result of affinity gel optimization studies, it was determined that the most appropriate equilibration buffer was 25 mM Tris base/0.05 M NaCl (pH: 8.5), while the most appropriate washing buffer was 25 mM Tris base/26 mM NaCl (pH: 9.5).

Subsequently, purification was performed using Na_2HPO_4 (pH: 5) buffers prepared at different concentrations (0.05 M, 0.1 M, 0.15 M, and 0.2 M). The highest activity for the elution buffer was obtained with 0.2 M Na_2HPO_4 (pH: 5). Purification was carried out using all prepared optimum buffer solutions. The 25 mL hemolysate was applied to an affinity column containing ω-aminohexyl agarose-1,2,3-triazole-5-carboxylic acid, pre-equilibrated with 25 mM Tris base/0.05M NaCl (pH: 8.5). The affinity gel was washed with 25 mM Tris base/26 mM NaCl (pH: 9.5) buffer, and catalase was eluted with 0.2 M Na_2HPO_4 (pH: 5).

Catalase activity was determined by a spectrophotometric method using a procedure developed by Aebi.[11] According to this method, the H_2O_2 substrate added to the experimental environment is converted into water and oxygen by catalase.

One unit of catalase activity (enzyme units, EU) was defined as the amount of enzyme that catalyzed the decomposition of 1 μmol H_2O_2 (30 mM) at 25°C in phosphate buffer (50 mM, pH 7.0) in 60 seconds. Enzyme activity was determined by measuring the decrease in H_2O_2 absorbance at 240 nm. Activity was calculated as the amount of enzyme (EU) that consumes 1 μmol H_2O_2 per minute, using an extinction coefficient of $\varepsilon = 0.04\ mmol^{-1} \times cm^{-1}$ at 240 nm. The inhibitory effects of the drugs on catalase activity were tested *in vitro*. All measurements were repeated at least three times for each sample. Quantitative protein determination was performed at 595 nm using the Bradford method. Bovine serum albumin (BSA) was used as a standard, and a purification table was prepared. To assess the purity of the purified catalase and determine its molecular weight, SDS-PAGE (sodium dodecyl sulfate–polyacrylamide gel electrophoresis) was performed according to the Laemmli method.

In this study, the H_2O_2 substrate was used to determine the IC_{50} values of the drugs. The inhibitor concentration required to reduce catalase activity by 50% (IC_{50}) was calculated from plots of activity (%) versus inhibitor level. All drugs used in this study inhibited the catalase enzyme at micromolar levels. Catalase activity was measured in the presence of different drug concentrations, and percentage activities were calculated. Control activity in the absence of drugs was accepted as 100%.

For most of the tested cardiovascular drugs, dose-specific Cmax values are not reported in official product information because of continuous intravenous infusion and rapid pharmacokinetics. Therefore, only approximate steady-state plasma concentrations reported in clinical pharmacokinetic studies can be used for comparison. These concentrations are generally several orders

Table 1. Summary of the purification procedure for human erythrocyte catalase using ω-aminohexyl agarose-3-amino-1,2,4-trizole-5-carboxylic acid affinity column chromatography

Purification step	Total colume (mL)	Activity (EU/mL)	Total activity (EU)	Protein (mg/mL)	Total protein (mg)	Specific activity (EU/mg)	Yield (%)	Purification (Fold)
Hemolysate	10	120.5	1205	1570.20	15702	0.077	100	–
Catalase	3	146.7	440	4.02	12.06	36.484	2.72	473.8

EU, Enzyme units.

Table 2. IC_{50} values of cardiac drugs for catalase inhibition

Drug	IC_{50} (μM)	Cmax (μM)
Noradrenaline	4.61	0.6
Adrenaline	32.58	0.3
Amiodarone hydrochloride	41.86	3.70
Adenosine	58.49	0.80
Atropine sulfate	68.75	0.07
Dobutamine hydrochloride	80.79	3.0
Glyceryl trinitrate	86.66	0.022
Heparin sodium	92.4	0.70
Dopamine hydrochloride	429.15	3.0
Lidocaine hydrochloride	453.1	18

IC50 values are presented as the mean ± standard error of the mean of three parallel measurements ($P < 0.05$).

of magnitude lower than the IC_{50} values obtained *in vitro*. Therapeutic plasma concentrations of the tested cardiac drugs were obtained from established pharmacological references and clinical pharmacokinetic studies.[12] Concentration ranges were converted to micromolar units using molecular weight values to allow comparison with IC_{50} values.

Enzyme activity (%) values at different concentrations of each drug were determined by statistical analysis using Microsoft Office 2010 Excel. Enzyme activity in the absence of drugs was accepted as 100% activity. IC50 values (50% inhibition of enzyme activity) were determined using activity (%)-drug concentration graphs. Statistical analyses were performed using one-way analysis of variance (ANOVA).

The study was approved by Balıkesir University University of Health Sciences Non-Interventional Research Ethics Committee (Approval Number: 17.12.2024, Date: 2024/234), and conducted in accordance with the Declaration of Helsinki. Informed consent was obtained from all participants. Authors declare they did not use artificial intelligence (AI)–assisted technologies (such as large language models [LLMs], chatbots, or image creators) in the production of this study.

Results

Quantitative protein determination was performed using the Bradford method for catalase purified from human erythrocytes by affinity chromatography. Catalase was purified from human erythrocytes with a specific activity of 39.801 EU/mg, a 473.8-fold purification, and a yield of 2.72% (Table 1). To determine enzyme purity and molecular mass, SDS-PAGE was performed, and a single band was observed at an approximate molecular weight of 60 kDa

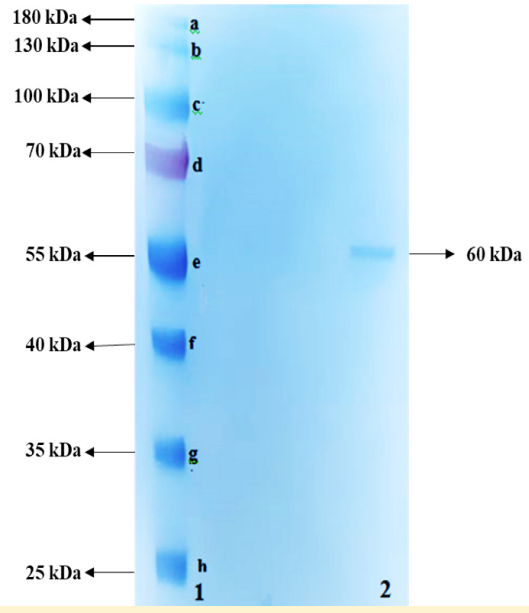

Figure 1. Sodium dodecyl sulfate–polyacrylamide gel electrophoresis (SDS-PAGE) of human erythrocyte catalase (CAT) purified using an affinity gel. Line 1: Protein standards (a: 180 kDa, b: 130 kDa, c: 100 kDa, d: 70 kDa, e: 55 kDa, f: 40 kDa, g: 35 kDa, h: 25 kDa). Line 2: Human erythrocyte CAT.

(Figure 1). The activity of purified catalase was assayed at different temperatures (10, 20, 30, 40, 50, and 60°C), and the optimum reaction temperature was determined to be 30°C.

The inhibitory effects of liquid cardiac drugs commonly used in the treatment of cardiac diseases on catalase activity were evaluated in this study. The most potent inhibitors were noradrenaline (IC_{50}: 4.61 μM), adrenaline (IC_{50}: 32.58 μM), and amiodarone hydrochloride (IC_{50}: 41.86 μM). Dopamine hydrochloride (IC_{50}: 429.15 μM) and lidocaine hydrochloride (IC_{50}: 453.1 μM) showed less inhibitory effects on catalase activity compared with adenosine (IC_{50}: 58.49 μM), atropine sulfate (IC_{50}: 68.75 μM), dobutamine hydrochloride (IC_{50}: 80.79 μM), glyceryl trinitrate (IC_{50}: 86.66 μM), and heparin sodium (IC_{50}: 92.4 μM). Activity (%)-inhibitor level graphs were plotted for all drugs, and IC_{50} values were calculated from these graphs (Figure 2, Table 2).

Discussion

In this study, the *in vitro* effects of liquid formulations of frequently used cardiac drugs on erythrocyte catalase activity were investigated.

Noradrenaline (IC_{50}: 4.61 μM), adrenaline (IC_{50}: 32.58 μM), and amiodarone hydrochloride (IC_{50}: 41.86 μM) were identified

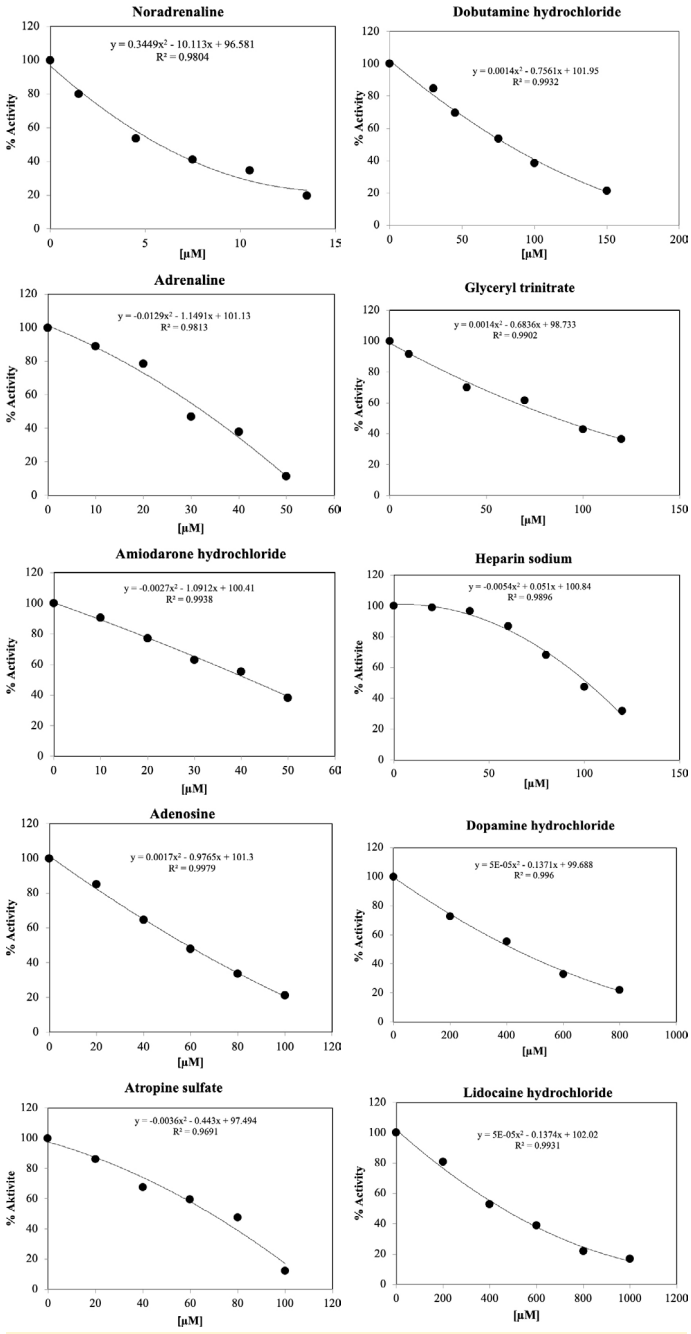

Figure 2. Inhibition curves of drugs on catalase activity (noradrenaline, adrenaline, amiodarone hydrochloride, adenosine, atropine sulfate, dobutamine hydrochloride, glyceryl trinitrate, heparin sodium, dopamine hydrochloride, and lidocaine hydrochloride).

as the most potent catalase inhibitors in our study. Dopamine hydrochloride (IC_{50}: 429.15 µM) and lidocaine hydrochloride (IC_{50}: 453.1 µM) showed minimal effects on catalase activity.

Many diseases are associated with malfunction, deficiency, or inhibition of the catalase enzyme. These diseases can be classified into neurological, metabolic, and other categories. Parkinson's disease, Alzheimer's disease, bipolar disorder, and schizophrenia are neurological disorders; type 1 and type 2 diabetes mellitus, osteoporosis, and hypertension are metabolic diseases; and Crohn's disease, gastric and colorectal cancer, asthma, acatalasemia, anemia, Wilson's disease, *Helicobacter pylori*–infected gastritis, and vitiligo are other disease groups associated with catalase enzyme dysfunction.[13-16]

The importance of catalase has been well recognized for many years. Although a large amount of data is available on catalase, there are few reports in the literature addressing enzyme-related drug side effects and drug–catalase interactions. Drugs reported to interact with catalase include piroxicam, ketoprofen, diclofenac sodium, sulfamethoxazole, nidazole,[2] sodium nitroprusside,[17] efavirenz, lamivudine, nevirapine, abacavir,[3] oxytetracycline,[18] 4-aminoantipyrine,[19] acetylsalicylic acid, ampicillin sodium, paracetamol, potassium penicillin, amoxicillin, and gentamicin sulphate.[20]

As mentioned above, catalase dysfunction, deficiency, or inhibition causes a wide variety of diseases and symptoms. Because of this broad spectrum of diseases and symptoms, it is difficult to directly attribute the side effects of drugs that potently inhibit catalase solely to catalase inhibition. Catalase may also be indirectly or partially involved in the side effects of these drugs. In the present study, noradrenaline, adrenaline, and amiodarone hydrochloride were identified as the most potent catalase inhibitors.

Amiodarone is a class III antiarrhythmic drug commonly used to treat atrial and ventricular arrhythmias.[21] It affects all phases of the cardiac action potential. Amiodarone causes serious dose- and duration-related side effects and toxicity[22] in many organs, including the lungs, thyroid, heart, liver, gastrointestinal tract, skin, and eyes, during and after treatment. These adverse effects include hyperthyroidism, hypothyroidism, pulmonary fibrosis, corneal microdeposits, liver dysfunction, and myopathy.[23,24]

Oxidative stress is thought to be the main factor in amiodarone-induced damage. Amiodarone has been shown to cause oxidative damage through a decrease in antioxidants and an increase in reactive oxygen species.[25]

Silva Santos et al.[26] showed that amiodarone causes oxidative damage to proteins and lipids and decreases catalase and superoxide dismutase activities. In our study, amiodarone was also found to be a potent catalase inhibitor, consistent with the findings of Silva Santos et al.[26] We suggest that one of the reasons for the common side effects observed with amiodarone may be related to catalase inhibition. Given the significant role of oxidative stress in amiodarone-related toxic effects, antioxidant therapies may represent promising strategies to reduce these toxic effects in the future.

Adrenaline is widely used worldwide in cardiopulmonary resuscitation and the treatment of shock. Adrenaline acts through alpha- and beta-adrenergic receptors, leading to vasoconstriction, increased heart rate, and enhanced myocardial contractility.[27] Similarly, noradrenaline is commonly used as a vasoactive drug in treatment.

Although adrenaline and noradrenaline are frequently used as inotropes in the treatment of cardiogenic shock in intensive care units, evidence supporting their effectiveness and safety is limited. They have not been shown to have a positive effect on

mortality and are reported to have numerous side effects in many studies.[28,29] Harmful effects of inotropes include progressive cardiac remodeling and arrhythmias, which may lead to adverse outcomes.[30-32] These effects become more pronounced with prolonged treatment. Adrenaline can undergo auto-oxidation to generate H_2O_2 and other free radicals.[33] Free radical species can disrupt the polyunsaturated phospholipids of cell membranes through lipid peroxidation.[34] Loss of membrane integrity results in cell death. Louis et al.[35] reported that noradrenaline toxicity caused widespread cell death via noradrenaline-mediated auto-oxidation products. Similarly, adrenaline induces genotoxic effects on DNA mainly through the generation of reactive oxygen species.

Another factor affecting catalase activity is glucose. Both adrenaline and noradrenaline stimulate β-adrenergic receptors in pancreatic tissue and increase glucagon secretion, resulting in elevated blood glucose levels. It has been suggested that increased blood glucose inhibits catalase activity.[36,37] This mechanism may help explain catalase inhibition by inotropic agents.

In our study, adrenaline and noradrenaline were identified as potent catalase inhibitors. Catalase inhibition may therefore represent one of the mechanisms responsible for the side effects of these drugs.

A common feature of adrenaline, noradrenaline, and amiodarone is that they are associated with numerous side effects and toxicities, the incidence of which increases with prolonged treatment. Long-term treatment with these drugs may induce chronic oxidative stress. We conclude that catalase inhibition may be one of the mechanisms contributing to the adverse effects of these drugs.

In our study, lidocaine was the drug that inhibited catalase activity the least. Cano-Europa et al.[38] showed that lidocaine enhances catalase activity in the amygdala in a rat model. In that study, lidocaine may have stimulated antioxidant defense responses by altering reactive oxygen species production. Similarly, Lee et al.[39] demonstrated that lidocaine dose-dependently protects endothelium-dependent vasorelaxation against reactive oxygen species-induced damage via hydrogen peroxide scavenging in a rabbit abdominal aorta model. These studies indicate that lidocaine does not inhibit catalase activity in oxidative stress models; on the contrary, it has been associated with increased catalase activity in response to oxidative stress.

Limitations

First, the results of this *in vitro* study need to be supported by human and animal studies. Second, liquid medications are often used during hospitalization and are typically discontinued or switched to tablet (oral) formulation upon discharge. Therefore, the duration of patient exposure to liquid medications is shorter than that of tablet formulations. The metabolism of the tablet formulations in the body may differ from that of intravenous forms. After oral administration, tablets are absorbed from the intestines and subsequently enter the bloodstream. During this process, these drugs are exposed to stomach acid, interact with intestinal microbiota and other intestinal enzymes, and are rapidly metabolized by the liver. In contrast, liquid medications administered intravenously come into direct contact with the blood and interact with erythrocyte catalase. Therefore, investigating the interaction of catalase with tablet formulations may also be beneficial. Third, this study investigated only catalase-drug interactions. Studies including other oxidative stress markers would be valuable for further evaluation of drug-related side effects. Additional oxidative stress biomarkers were not assessed, which limited the comprehensiveness of the oxidative status evaluation. Fourth, sex-specific analyses were not performed, which may limit the generalizability of the findings across sexes. Fifth, the IC_{50} values obtained in our experiments were higher than typical plasma concentrations, which may reduce the direct clinical relevance of the results. Sixth, the absence of positive controls (known catalase inhibitors) limits the contextual interpretation of the magnitude of inhibition observed. Seventh, although our data suggest that catalase inhibition may play a role in the underlying mechanism of the observed side effects, a direct causal clinical relationship cannot be established. Further studies are needed to confirm this potential association.

Conclusion

Our study demonstrated that adrenaline, noradrenaline, and amiodarone have strong inhibitory effects on catalase activity. A common feature of these drugs is their association with numerous side effects and toxicities. We conclude that catalase inhibition may be one of the mechanisms responsible for the adverse effects of these drugs. Therefore, when these drugs are used in clinical treatment, their dosages and duration of administration should be carefully controlled to prevent side effects related to catalase enzyme inhibition. These results are of interest for further research on catalase-drug interactions. Our data suggest that catalase inhibition may be involved in the mechanisms underlying the observed adverse effects; however, direct clinical causality cannot be established. Additional studies are needed to validate this potential association.

Ethics Committee Approval: Ethics committee approval was obtained from Balıkesir University University of Health Sciences Non-Interventional Research Ethics Committee (Approval Number: 17.12.2024, Date: 2024/234).

Informed Consent: Informed consent was obtained from all participants.

Conflict of Interest: The authors have no conflicts of interest to declare.

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T-786C Polymorphism of the *NOS3* Gene and Its Role in the Development of Renal Dysfunction in Patients of the Uzbek Population with Chronic Heart Failure

Kronik Kalp Yetersizliği Olan Özbek Hastalarda Böbrek Disfonksiyonu Gelişiminde *NOS3* Geninin T-786C Polimorfizminin Rolü

ABSTRACT

Objective: The aim of this study was to investigate the impact of the T-786C polymorphism of the *NOS3* gene on the onset and progression of renal dysfunction in patients of the Uzbek population with chronic heart failure (CHF).

Method: The study included 200 patients of Uzbek nationality diagnosed with CHF. Among them, 110 patients had a glomerular filtration rate (eGFR) ≥ 60 mL/min/1.73 m², while in 90 patients this indicator was lower. The control group consisted of 120 conditionally healthy donors of Uzbek nationality. Analysis of the *NOS3* T-786C polymorphism was performed using commercially available test kits developed by NPF Litex LLC (Moscow, Russia) in accordance with the manufacturer's standard protocol. Amplification of the polymorphic region of the *NOS3* promoter was carried out using a Rotor-Gene Q thermal cycler (QIAGEN, Hilden, Germany). Polymerase chain reaction (PCR) was performed in a total volume of 25 µL under the following cycling conditions: initial denaturation at 95°C for 5 minutes; 35 cycles of denaturation at 95°C for 30 seconds, primer annealing at 60°C for 30 seconds, and DNA extension at 72°C for 1 minute; followed by a final extension at 72°C for 10 minutes. The resulting data were analyzed using the SPSS statistical package (IBM Corp., Armonk, NY, USA) and OpenEpi v9.2 (OpenEpi, Emory University, Atlanta, GA, USA).

Results: Differences were observed in the distribution of genotypic and allelic variations. In the main group, the frequency of the C allele was 35.5%, compared to 28.3% in the control group. Patients with eGFR < 60 mL/min/1.73 m² were more likely to have the C/C genotype (15.6% versus 10.8% in the control group). The T-786C polymorphism may exacerbate renal impairment by reducing *NOS3* activity and lowering nitric oxide (NO) production.

Conclusion: The genetic variant C of the T-786C *NOS3* polymorphism is associated with impaired renal function in patients with CHF.

Keywords: Chronic heart failure, clinical and humoral aspects, genetic aspects, renal dysfunction

ÖZET

Amaç: *NOS3* geninin T-786C polimorfizminin, kronik kalp yetersizliği (KKY) olan Özbek hastalarda böbrek yetersizliğinin başlangıcı ve ilerlemesi üzerindeki etkisini araştırmak amaçlanmıştır.

Yöntem: Çalışmaya, KKY tanılı 200 Özbek hasta dâhil edildi. Glomerüler filtrasyon hızı (eGFR) 110 hastada 60 ml/dak/1,73 m²'nin üzerinde, 90 hastada ise bu değerin altındaydı. Kontrol grubu, 120 sağlıklı Özbek bireyden oluşturuldu. *NOS3* T-786C polimorfizminin analizi için, üreticinin standart protokolüne uygun olarak NPF Litex LLC (Moskova, Rusya) tarafından geliştirilen ticari test kitleri kullanıldı. *NOS3* promotör bölgesindeki polimorfik alanın amplifikasyonu, Rotor-Gene Q termal döngü cihazı (QIAGEN, Hilden, Almanya) kullanılarak gerçekleştirildi. Polimeraz zincir reaksiyonu (PCR), toplam 25 µL hacimde ve şu döngü koşullarında uygulandı: 95 °C'de 5 dakika süren başlangıç denatürasyonu; ardından 95 °C'de 30 saniye denatürasyon, 60 °C'de 30 saniye primer bağlanması ve 72 °C'de 1 dakika DNA uzaması olmak üzere 35 döngü; son olarak 72 °C'de 10 dakika süreyle son uzatma aşaması gerçekleştirildi. Elde edilen veriler, SPSS istatistik paket programı (IBM Corp., Armonk, NY, ABD) ve OpenEpi v9.2 (OpenEpi, Emory University, Atlanta, GA, ABD) kullanılarak analiz edildi.

Bulgular: Genotip ve allelik varyasyonların dağılımında farklılık eğilimi olduğu saptandı. Ana grupta C alelinin sıklığı %35,5 iken kontrol grubunda bu oran %28,3 olarak bulundu. eGFR değeri < 60 ml/dak/1,73 m² olan hastalarda C/C genotipine sahip olma olasılığı daha yüksekti (%15,6;

ORIGINAL ARTICLE
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kontrol grubunda %10,8). T-786C polimorfizminin, *NOS3* aktivitesini bozarak nitrik oksit (NO) üretimini azalttığı ve bu durumun böbrek fonksiyon bozukluğunu ağırlaştırdığı gözlendi.

Sonuç: *NOS3* geninin T-786C polimorfizmine ait C genetik varyantı, kronik kalp yetersizliği olan hastalarda bozulmuş böbrek fonksiyonu ile ilişkilidir.

Anahtar Kelimeler: Kronik kalp yetersizliği, klinik ve humoral yönler, genetik yönler, böbrek fonksiyon bozukluğu

Chronic heart failure (CHF) remains one of the leading causes of morbidity, hospitalization, and mortality worldwide. These concerns are also supported by national data collected in 2022 (Figure 1).

As CHF progresses, cardiorenal syndrome frequently develops—a bidirectional pathological interaction between the heart and kidneys in which dysfunction of one organ contributes to the deterioration of the other.[1] The pathogenesis of cardiorenal syndrome is multifactorial and involves neuroendocrine, humoral, and molecular genetic mechanisms. In recent years, increasing attention has been focused on the role of endothelial dysfunction, which represents a key pathogenic link in both cardiovascular and renal diseases. One of the main mediators of endothelial function is nitric oxide (NO), the production of which is directly dependent on the activity of endothelial nitric oxide synthase (eNOS). Impaired NO synthesis leads to vasoconstriction, reduced tissue perfusion, inflammation, and vascular remodeling, thereby aggravating the course of CHF and contributing to the progression of renal dysfunction.[2] Genetic variations, particularly the T-786C polymorphism located in the promoter region of the *NOS3* gene encoding eNOS, influence the level of gene expression and, consequently, nitric oxide synthesis. According to several studies, carriage of the C allele is associated with an increased risk of cardiovascular diseases, including coronary heart disease and CHF, and may also be linked to the severity of renal dysfunction.[3]

In the context of a polymorphic background, the application of pharmacogenetic approaches in clinical practice is becoming increasingly relevant. The investigation of genetic biomarkers, such as variants in the *NOS3*, ACE, and ET-1 genes, provides opportunities for patient risk stratification, prediction of therapeutic response, and selection of personalized treatment strategies.[4–6]

Considering the above, the study of clinical, humoral, and genetic aspects of endothelial dysfunction in patients with CHF complicated by renal dysfunction represents a relevant and promising direction in modern medicine. Effective management of chronic heart failure requires a multidisciplinary approach, emphasizing the importance of collaboration between primary care physicians and cardiology specialists in optimizing patient outcomes.[7] The results of such studies may contribute to a deeper understanding of the pathogenesis of cardiorenal syndrome and to the optimization of therapeutic strategies.

Purpose of the Study

The purpose of this study was to determine the significance of the T-786C polymorphism of the *NOS3* gene in the development and clinical course of renal dysfunction in patients with CHF.

ABBREVIATIONS

ACE	Angiotensin-converting enzyme
CHF	Chronic heart failure
eGFR	Glomerular filtration rate
eNOS	Endothelial nitric oxide synthase
NO	Nitric oxide
NYHA	New York Heart Association
PCR	Polymerase chain reaction

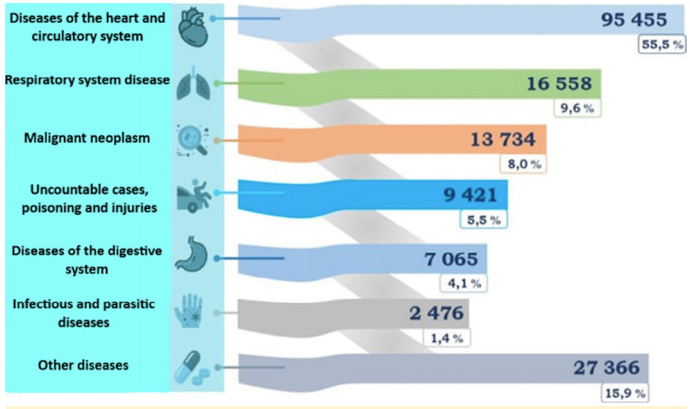

Figure 1. Main factors influencing mortality in January-February 2022 (number of cases).

Ethical Consideration

Ethics committee approval was obtained from The Ministry of Health of The Republic of Uzbekistan the Republican Specialized Scientific Practical Medical Center of Therapy and Medical Rehabilitation (Approval Number: 15, Date: 27.12.2024). The authors certify that all appropriate patient consent forms were obtained. In these forms, patients provided consent for their clinical information to be reported in the journal. Patients understand that their names and initials will not be published and all reasonable efforts will be made to protect their anonymity.

Study Materials

The study included 200 patients of Uzbek nationality diagnosed with CHF. Only patients aged 35-65 years, in a stable clinical condition, and receiving standard therapy in accordance with current clinicl guidelines were enrolled. As part of the clinical and laboratory assessment, the following parameters were recorded and analyzed: blood pressure, heart rate, glomerular filtration rate (GFR), creatinine level, proteinuria, glycemia, left ventricular ejection fraction, and the medications used, including angiotensin-converting enzyme (ACE) inhibitors and β-blockers. Patients were

also stratified according to the presence of arterial hypertension, metabolic syndrome, coronary heart disease, and other comorbid conditions. Detecting moderate or weak genetic associations in a population requires substantial statistical power, particularly in multifactorial diseases such as chronic heart failure complicated by renal dysfunction. Nevertheless, the sample size of the present study—200 patients with CHF and 120 individuals in the control group—is adequate and consistent with that of previously published studies addressing similar research questions. Moreover, all patients were carefully phenotyped and stratified according to CHF functional class and the degree of renal dysfunction, which increased group homogeneity and reduced variability, thereby improving the ability to detect even moderate effects.

Among the patients with CHF, 110 individuals had a glomerular filtration rate > 60 mL/min/1.73 m², whereas 90 patients had a < GFR 60 mL/min/1.73 m². The control group comprised genomic DNA samples obtained from 120 conditionally healthy donors of Uzbek nationality without evidence of cardiovascular or renal disease. The average age of control participants was 54 ± 6 years, with a male-to-female ratio of 1:1. All participants had normal blood pressure (mean value 120/80 mmHg), creatinine levels (mean 82 ± 11 μmol/L), and glomerular filtration rates (GFR > 90 mL/min/1.73 m²). Exclusion criteria included no presence of cardiovascular or renal pathology according to medical examination; no use of medications within the previous three months; a history of arterial hypertension, diabetes, coronary heart disease, chronic kidney disease, or other chronic illnesses; acute infectious diseases at the time of inclusion; intake of any regular medications; age younger than 40 years or older than 65 years; and refusal to participate in the study.

The analysis showed that the genotype distribution of the T-786C polymorphism of the *NOS3* gene in both the main group (patients with CHF) and the control group conformed to the Hardy–Weinberg equilibrium. These calculations were performed using the OpenEpi v9.2 statistical software package. The exact p-values for the Hardy–Weinberg test were P = 0.37 for the main group and P = 0.43 for the control group. The study included patients with clinically confirmed chronic heart failure of New York Heart Association (NYHA) functional classes II–IV, with preserved or reduced glomerular filtration rate, defined as ≥ 60 or < 60 mL/min/1.73 m², and aged 40–75 years. Patients were excluded from the study if they had acute infectious diseases, malignant neoplasms, acute coronary syndrome within the previous three months, or severe liver failure; were receiving immunosuppressive therapy; or had chronic kidney disease of non-cardiac etiology, including diabetic nephropathy or polycystic kidney disease.

Biochemical studies were conducted to assess the activity of the NO synthase system. Forty healthy volunteers matched to the main group by age, sex, and basic clinical parameters were selected as the control group.

To determine nitric oxide levels, 3–5 mL of venous blood was collected from the cubital vein after an overnight fast. The obtained samples remained stable at room temperature for several hours. Serum was obtained by centrifugation at 3000 rpm for 10 minutes. The serum samples were stored at –20°C; under these conditions, they remained stable for up to six months and tolerated up to five freeze-thaw cycles.

The concentration of nitric oxide was determined spectrophotometrically using the Griess reagent at a wavelength of 540 nm. Nitrites were used as metabolites of NO.

Analysis of the T-786C polymorphism of the *NOS3* gene was performed using test systems developed by NPF Litex LLC (Russia), in accordance with the manufacturer's standard protocol. Amplification of the polymorphic region of the *NOS3* promoter was carried out using a Rotor Gene Q thermal cycler (QIAGEN, Germany). Polymerase chain reaction (PCR, 25 μL) was performed under the following conditions: denaturation at 95°C for 5 minutes; 35 cycles of denaturation at 95°C for 30 seconds, primer annealing at 60°C for 30 seconds, and DNA synthesis at 72°C for 1 minute; followed by a final extension at 72°C for 10 minutes. The resulting data were analyzed using the SPSS statistical software package (IBM Corp., Armonk, NY, USA) and OpenEpi version 9.2 (OpenEpi, Emory University, Atlanta, GA, USA). Numerous epidemiological and statistical tools for summarizing medical data are available through OpenEpi (www.OpenEpi.com), a free, open-source, operating system-independent, web-based platform designed for use in public health and medical research, education and practice.

Therefore, the results should be interpreted with caution, considering the higher risk of false-positive findings due to the absence of multiple testing correction. In this study, the main focus was on the primary comparative analysis of allele and genotype frequencies, as well as the assessment of relative risks, including odds ratios (ORs) and relative risks (RRs), without the use of multivariate methods. This limitation was related to both the sample size and the nature of the study.

OpenEpi is compatible with browsers that support JavaScript and Hypertext Markup Language (HTML), which were used in its development. OpenEpi: A Web-based Public Health Epidemiologic and Statistical Calculator (PDF) is available at https://www.researchgate.net/publication/24430413_OpenEpi_A (retrieved May 5, 2025).

This study used observational and hypothesis-generating methods with the primary objective of identifying potential clinical-genetic associations. The study controlled for key clinical and demographic factors, such as age, blood pressure, comorbidities, and treatment, to minimize the influence of confounding factors.

Results

The study presents the results of an analysis of the clinical course in patients with chronic heart failure, taking into account indices of endothelial dysfunction, humoral factors, and the NO synthase system, stratified by the presence or absence of renal dysfunction. According to the obtained data, compared with the control group, patients with CHF, regardless of renal function status, demonstrated statistically significant differences in nitric oxide concentrations in both studied subgroups (P < 0.01) (Figure 2).

In patients with chronic heart failure and reduced glomerular filtration rate (≤ 60 mL/min/1.73 m²), serum NO concentrations were decreased by 35.8%, measuring 80.6 ± 10.7 nmol/mL compared to 109.6 ± 9.7 nmol/mL in the reference group (P < 0.01).

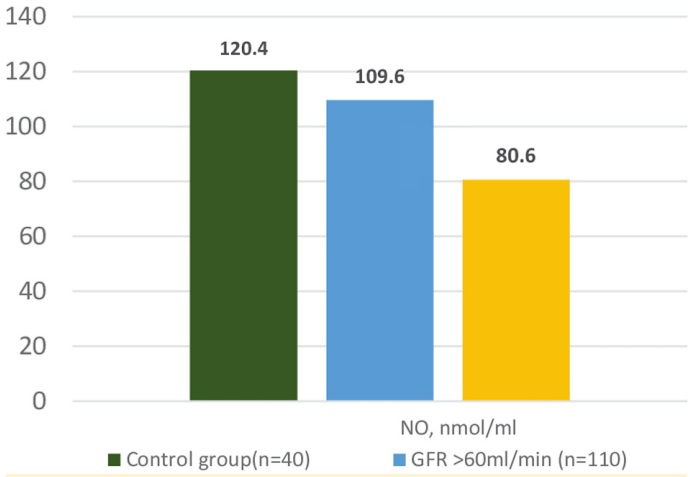

Figure 2. Endothelial function indicators in patients with chronic heart failure according to the presence of renal dysfunction (M ± SD).

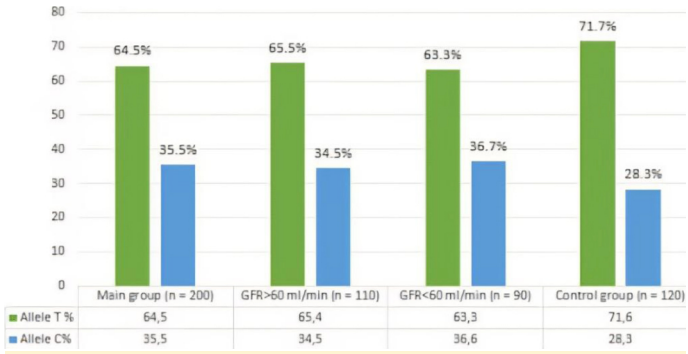

Figure 3. Distribution of T and C alleles of the *NOS3* T-786C polymorphism in patients with chronic heart failure (CHF) and in the control group (%).

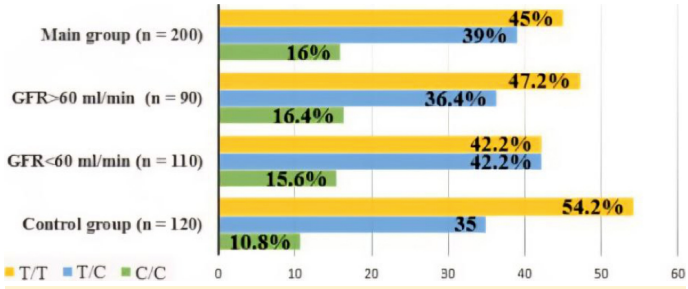

Figure 4. Distribution of T/T, T/C, and C/C genotypes of the *NOS3* T-786C polymorphism in the main group, subgroups stratified by eGFR level, and the control group (%).

The distribution of genotypes for the *NOS3* T-786C polymorphism in both patient and control groups was consistent with Hardy-Weinberg equilibrium. Analysis of allelic and genotypic frequencies revealed trends toward variation between the main group, subgroups stratified by estimated glomerular filtration rate, and the control group.

In the main group, the frequencies of the T and C alleles were 64.5% and 35.5%, respectively, whereas in the control group they were 71.7% and 28.3% (χ^2 = 3.5; P = 0.1). Comparison of allele distributions indicated a trend toward a higher frequency of the mutant C allele among patients with chronic heart failure. The calculated odds ratio for carriage of the C allele was 1.4 (95% confidence interval [CI]: 0.98–1.97), suggesting a potential increase in the risk of renal impairment among CHF patients harboring the C allele of the *NOS3* T-786C polymorphism (Figures 3 and 4).

Multiple regression analysis revealed that eGFR was significantly influenced by age (β = –0.41; P < 0.05), blood pressure (β = –0.18; P < 0.05), and the presence of the C allele of the *NOS3* T-786C polymorphism (β = –8.4; P < 0.01).

Regarding genotype distribution, the frequencies of the T/T, T/C, and C/C genotypes in the patient group were 45.0%, 39.0%, and 16.0%, respectively. In the control group, the corresponding frequencies were 54.2%, 35.0%, and 10.8%, respectively.

The prevalence of the unfavorable C/C genotype was marginally higher among patients with preserved renal function (eGFR > 60 mL/min/1.73 m²) compared to those with impaired renal function (16.4% vs. 15.6%; P = 0.4). Similarly, the T/T genotype was more frequently observed in patients with higher eGFR values (47.3% vs. 42.2%), although this difference did not reach statistical significance (χ^2 = 1.1; P = 0.3). The heterozygous T/C genotype was detected in 42.2% of patients with eGFR > 60 mL/min/1.73 m² and in 36.4% of those with eGFR < 60 mL/min/1.73 m² (χ^2 = 1.1; P = 0.3) (Tables 1 and 2).

Although most of the observed differences, including the frequency of the C allele (P = 0.1) and genotype distributions (P = 0.3–0.4), did not reach the conventional threshold for statistical significance (P < 0.05), the findings indicate a certain trend that merits attention. The higher frequency of the unfavorable C allele and the homozygous C/C genotype in patients with reduced glomerular filtration rate compared to the control group suggests a potential role of the *NOS3* T-786C polymorphism in the pathogenesis of renal dysfunction in the context of chronic heart failure.

The estimated odds ratio (OR = 1.4; 95% CI: 0.98–1.97) reflects a trend rather than a statistically confirmed association. The confidence interval crosses one, indicating the absence of strict statistical significance. Nevertheless, this finding may be considered indicative of potential biological and clinical relevance rather than a confirmed effect, and it requires validation in studies with larger sample sizes. This emphasizes the need for studies with larger sample sizes to clarify the role of the *NOS3* T-786C polymorphism in the development of renal dysfunction.

The results suggest that, in patients with renal failure, the T-786C polymorphism may have a deleterious impact on *NOS3* gene activity. Renal dysfunction may be exacerbated by the ability of the C allele to reduce NO production. Investigation of this polymorphism may contribute to a better understanding of the genetic factors influencing kidney function and may support the development of individualized treatment approaches for patients with chronic renal disease. The study did not achieve statistical significance (T allele: OR = 1.4; 95% CI: 0.98–1.97; P = 0.1). However, the observed values, which are close to the significance threshold and demonstrate a consistent trend, indicate a possible underlying association.

Table 1. Comparative analysis of the distribution of T and C alleles of the *NOS3* T–786C polymorphism in patients with chronic heart failure according to eGFR level and in comparison with the control group

Groups	Allele	Results
Main group	T	χ^2 = 3.5; P = 0.1; OR = 0.7; 95% CI: 0.51–1.02
Control group	C	χ^2 = 3.5; P = 0.1; OR = 1.4; 95% CI: 0.98–1.97
CHF GFR > 60 mL/min	T	χ^2 = 2.1; P = 0.2; OR = 0.7; 95% CI: 0.5–1.11
Control group	C	χ^2 = 2.1; P = 0.2; OR = 1.3; 95% CI: 0.9–1.98
CHF GFR < 60 mL/min	T	χ^2 = 3.3; P = 0.1; OR = 0.7; 95% CI: 0.45–1.03
Control group	C	χ^2 = 3.3; P = 0.1; OR = 1.5; 95% CI: 0.97–2.21
GFR > 60 mL/min	T	χ^2 = 0.2; P = 0.7; OR = 1.1; 95% CI: 0.73–1.65
GFR < 60 mL/min	C	χ^2=0.2; P = 0.7; OR = 0.9; 95% CI: 0.6–1.38

CHF, Chronic heart failure; GFR, Glomerular filtration rate.

Table 2. Comparative analysis of the distribution of T/T, T/C, and C/C genotypes of the *NOS3* T–786C polymorphism in patients with chronic heart failure according to eGFR level and in comparison with the control group

Groups	Allele	Results
Main group	T/T	χ^2 = 2.5; P = 0.2; OR = 0.7; 95% CI: 0.44–1.09
	T/C	χ^2 = 0.5; P = 0.5; OR = 1.2; 95% CI: 0.74–1.9
Control group	C/C	χ^2 = 1.7; P = 0.2; OR = 1.6; 95% CI: 0.79–3.11
CHF GFR > 60 mL/min	T/T	χ^2 = 1.1; P = 0.3; OR = 0.8; 95% CI: 0.45–1.27
	T/C	χ^2 > 3.84; P = 0.9; OR = 1.1; 95% CI: 0.62–1.82
Control group	C/C	χ^2 = 1.5; P = 0.3; OR = 1.6; 95% CI: 0.75–3.45
CHF GFR < 60 mL/min	T/T	χ^2 = 2.9; P = 0.1; OR = 0.6; 95% CI: 0.36–1.07
	T/C	χ^2 = 1.1; P = 0.3; OR = 1.4; 95% CI: 0.77–2.38
Control group	C/C	χ^2 = 1.0; P = 0.4; OR = 1.5; 95% CI: 0.68–3.4
GFR > 60 mL/min	T/T	χ^2 = 0.5; P = 0.5; OR = 1.2; 95% CI: 0.7–2.15
	T/C	χ^2 = 0.4; P = 0.4; OR = 0.8; 95% CI: 0.44–1.38
GFR < 60 mL/min	C/C	χ^2 = 0.9; P = 0.9; OR = 1.1; 95% CI: 0.5–2.27

CHF, Chronic heart failure; GFR, Glomerular filtration rate.

Discussion

This article presents the results of an analysis of the clinical course in patients with chronic heart failure, taking into account indices of endothelial dysfunction, humoral factors, and the NO synthase system, stratified by the presence or absence of renal dysfunction. According to the obtained data, compared with the control group, patients with CHF, regardless of renal function status, demonstrated statistically significant differences in nitric oxide concentrations in both studied subgroups (P < 0.01).

The clinical heterogeneity observed among patients with CHF underscores the necessity of comprehensive phenotyping that extends beyond single biomarkers. Recent evidence from heart failure populations suggests that integrated assessments combining multiple diagnostic parameters provide superior prognostic stratification compared to individual markers.[8] In the present study, this multiparametric approach, which included stratification by eGFR alongside genetic analysis, enabled a more precise characterization of the relationship between the *NOS3* T–786C polymorphism and deterioration of renal function.

Carriage of the C allele of the *NOS3* T–786C polymorphism was associated with impaired renal function, likely reflecting endothelial dysfunction and reduced nitric oxide synthesis. These findings support a potential role for genetic factors in the pathogenesis of cardiorenal syndrome in patients with chronic heart failure.

Despite the lack of statistical significance, the observed associations may indicate a potential role of genetic factors in the pathogenesis of renal dysfunction, indicating the need for further investigation in the fields of medical genetics and nephrology.

In patients with signs of renal dysfunction, the T–786C polymorphism is presumed to be associated with reduced expression of the *NOS3* gene, which may lead to decreased nitric oxide production and, consequently, impaired vascular regulation. Although further studies with larger sample sizes are required to confirm the nature and strength of this relationship, the present findings allow consideration of using genetic testing as a tool for early risk stratification and individualization of therapy in patients with chronic kidney disease.

Conclusion

Based on the obtained data, comparison of patients with different levels of glomerular filtration rate (eGFR above and below 60 mL/min/1.73 m^2) revealed a tendency toward variation in renal function among carriers of the unfavorable C allele of the *NOS3*

T-786C polymorphism. Although the identified associations did not reach statistical significance, the obtained findings suggest a possible relationship between genetic factors and the development of renal dysfunction, which is of interest for further research in medical genetics and nephrology.

In patients with renal impairment, the T-786C polymorphism may be associated with reduced *NOS3* gene expression, potentially resulting in decreased nitric oxide production and impaired vascular regulation. Although further studies with larger samples are required to confirm the nature and strength of this association, the obtained data allow consideration of genetic testing as a tool for early risk stratification and individualization of therapy in patients with chronic kidney disease.

In the present analysis, only univariate comparisons were performed; multivariate regression modeling incorporating key clinical variables is planned for subsequent stages. In particular, evaluation of the combined effects of the *NOS3* T-786C C allele with conditions such as arterial hypertension or diabetes mellitus may reveal synergistic interactions and clarify their contribution to reductions in glomerular filtration rate. This approach may improve the accuracy of risk stratification in patients with chronic heart failure and provide a foundation for more personalized prognostic models.

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The Hidden Toll of On-Call Shifts: Reduced Heart Rate Variability and Increased Physiological Stress in Residents

Nöbet Vardiyalarının Gizli Bedeli: Asistanlarda Azalmış Kalp Hızı Değişkenliği ve Artan Fizyolojik Stres

ABSTRACT

Objective: The aim of this study was to assess autonomic dysfunction via heart rate variability (HRV) in residents with on-call shifts.

Method: A cross-sectional study of 140 residents (104 on-call, 36 non-on-call) was conducted. HRV parameters, stress indices, and physical activity (International Physical Activity Questionnaire, IPAQ) were compared using parametric and non-parametric tests.

Results: On-call residents showed elevated heart rates (84 vs. 79 bpm, P = 0.006), higher stress indices (12.1 vs. 9.96, P = 0.003), and reduced parasympathetic markers (root mean square of successive differences [RMSSD], standard deviation of normal-to-normal intervals [SDNN], parasympathetic nervous system index [PNS index]; all P ≤ 0.006). Physical activity did not differ between groups.

Conclusion: An association between on-call shifts and altered autonomic balance was observed, suggesting a potential increase in cardiovascular risk independent of lifestyle factors. These findings may be considered by policymakers when planning resident physician workloads.

Keywords: Autonomic nervous system, exercise, heart rate, internship and residency, physiological, shift work schedule, stress, work schedule tolerance

ÖZET

Amaç: Nöbet görevi olan asistanlarda otonomik disfonksiyonun kalp hızı değişkenliği (HRV) ile değerlendirilmesi amaçlandı.

Yöntem: Toplam 140 asistanın (104'ü nöbet tutan, 36'sı nöbet tutmayan) katıldığı kesitsel bir çalışma yapıldı. HRV parametreleri, stres indeksleri ve fiziksel aktivite düzeyi (IPAQ skoru) parametrik ve non-parametrik testler kullanılarak karşılaştırıldı.

Bulgular: Nöbet tutan asistanlarda daha yüksek kalp hızı (84'e karşı 79 vuru/dakika, P = 0.006), daha yüksek stres indeksleri (12.1'e karşı 9.96, P = 0.003) ve daha düşük parasempatik belirteçler (RMSSD, SDNN, PNS indeksi; tümü için P ≤ 0.006) saptandı. Fiziksel aktivite düzeyleri açısından gruplar arasında anlamlı fark bulunmadı.

Sonuç: Gece nöbetleri, yaşam tarzı faktörlerinden bağımsız olarak otonomik dengeyi bozmakta ve kardiyovasküler riski artırmaktadır.

Anahtar Kelimeler: Otonom sinir sistemi, egzersiz, kalp hızı, intörnlük ve asistanlık, psikolojik, vardiyalı çalışma, stress, iş çizelgesi toleransı

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Occupational stress is an increasingly recognized determinant of health, particularly among healthcare professionals. Medical residents, often at the frontline of healthcare systems, experience extended work hours, sleep deprivation, and irregular schedules—all of which can disrupt physiological homeostasis.[1,2] Among physiological indicators of stress, heart rate variability (HRV) has emerged as a robust, noninvasive measure of autonomic nervous system (ANS) function.[3]

Heart rate variability reflects the balance between sympathetic and parasympathetic activity, with reduced variability linked to heightened cardiovascular risk, impaired stress adaptation, and all-cause mortality.[4–6] Time-domain parameters (e.g., standard

deviation of normal-to-normal intervals [SDNN], root mean square of successive RR interval differences [RMSSD]), frequency-domain indices (e.g., low-frequency [LF] and high-frequency [HF] power), and non-linear measures (e.g., Poincaré plots) offer complementary perspectives on autonomic modulation.[7,8]

Longitudinal studies have demonstrated correlations between diminished HRV and increased incidence of hypertension, diabetes, and metabolic syndrome.[9] Furthermore, the relationship between autonomic imbalance and mental health outcomes, including depression, anxiety, and burnout, suggests that HRV may serve as a useful biomarker in occupational health surveillance.[10]

The demanding nature of medical training, combined with sleep deprivation and circadian disruption from shift work, creates a potentially hazardous physiological environment.[11] Previous studies have documented decreased HRV in shift workers across various industries, but the specific impact of medical residents' on-call schedules—characterized by prolonged wakefulness followed by insufficient recovery time—warrants focused investigation.[12]

Despite the ubiquity of on-call shifts in residency programs, their specific physiological consequences have not been sufficiently quantified. This study investigates whether on-call shifts are associated with autonomic imbalance, as evidenced by HRV parameters, and whether lifestyle factors such as physical activity mediate this relationship.

Materials and Methods

Study Design and Participants

This cross-sectional study included 140 consenting residents from two university-affiliated tertiary hospitals. Cohen's test with d = 0.735 yielded a required sample size of 35 participants per group. The study protocol received approval from the Health Sciences University Hamidiye Scientific Research Ethics Committee (Approval Number 24/557, Date: 20.09.2024), and the study was conducted in accordance with the Declaration of Helsinki. Participants were divided into two groups: those with regular 24-hour on-call shifts (n = 104) and those without any on-call shifts (n = 36). Although a sample size of 35 per group was initially targeted based on power calculations, the final distribution (n = 104 on-call vs. n = 36 non-on-call) reflects the higher prevalence of on-call duties among the available resident population at the participating tertiary hospitals. Efforts were made to include all available non-on-call residents to maximize the comparison group's statistical power. Inclusion criteria were full-time residency status and the absence of chronic illnesses, psychiatric disorders, or medications known to affect HRV. Individuals were excluded if they did not provide informed consent.

Data Collection and Instruments

R–R intervals were measured using a Polar H10 chest strap (sampling rate: 1000 Hz) during 30 minutes of supine relaxation in a quiet environment. Heart rate variability was analyzed offline using HRV analysis software (Kubios HRV, version 1.6.6; Kubios Oy, Kuopio, Finland). This device provides HRV measurements consistent with those obtained from laboratory-grade electrocardiography (ECG) devices.[13] All values are presented as medians with interquartile ranges. Time-domain measures included heart rate, RMSSD, SDNN, and mean RR interval. Frequency-domain measures included HF and LF power, as well as the LF/HF ratio. Non-linear measures included Poincaré indices SD1 and SD2. Additional autonomic indices (parasympathetic nervous system [PNS], sympathetic nervous system [SNS] index, and stress index) were derived using integrated algorithms.

All recordings were performed between 9:00 AM and 12:00 PM to minimize circadian variations in autonomic function. For residents in the on-call group, measurements were taken at least 48 hours after their most recent on-call duty to evaluate persistent rather than acute effects. Standardized conditions were maintained during recordings, with participants in a seated position following a 10-minute rest period in a quiet room at a comfortable temperature.

Physical activity was assessed using the International Physical Activity Questionnaire (IPAQ) short form, which estimates weekly energy expenditure in metabolic equivalent–minutes per week (MET-min/week; MET: metabolic equivalent of task) across walking, moderate, and vigorous activities, as well as sedentary time. IPAQ data were categorized according to standard protocols into three activity levels: inactive, minimally active, and health-enhancing physical activity (HEPA) active.

Demographic characteristics, duration of training, monthly number of shifts, sleep duration during shifts, and alcohol, tobacco, and caffeine consumption were recorded using a standardized questionnaire. Participants were asked not to consume coffee or alcohol on the day of recording. Body mass index was calculated from measured height and weight.

Statistical Analysis

Data were tested for normality using the Shapiro-Wilk test. Between-group comparisons were performed using the Mann-Whitney U test or the independent-samples t test, and chi-square tests were used for categorical variables. Receiver operating characteristic (ROC) curve analysis was used to assess the predictive capacity of HRV parameters for identifying residents with on-call shifts. Statistical significance was set at $P < 0.05$. All analyses were performed using SPSS version 27.0. (IBM Corp., released 2020; IBM SPSS Statistics for Windows, Version 27.0; Armonk, NY: IBM Corp.).

This observational study was reported in accordance with the STROBE guidelines (Strengthening the Reporting of Observational Studies in Epidemiology).

ABBREVIATIONS

ANS	Autonomic nervous system
BMI	Body mass index
COVID-19	Coronavirus Disease 2019
ECG	Electrocardiography
HEPA	Health-enhancing physical activity
HRV	Heart rate variability
IPAQ	International Physical Activity Questionnaire
MET	Metabolic equivalent value
PNS	Parasympathetic nervous system
RMSSD	Root mean square of successive differences
SNS	Sympathetic nervous system

Table 1. Baseline characteristics of the study population [median (interquartile range)]

	Without on-call shifts (n = 36)	With on-call shifts (n = 104)	*P*
Age (years)	28.5 ± 3.6	29.7 ± 3.4	0.937
Sex (% male)	16 (44.4%)	51 (49%)	0.634
BMI (kg/m^2)	22.8 ± 3.6	24 ± 3.6	0.083
Training duration (months)	24 (18-31)	24 (21-26)	0.829
Monthly number of on-call shifts	0	5 (4-8)	**<0.001**
Sleep time during shifts (hours)		4 (3-6)	
Smoking (packs/day)	0 (0-0.25)	0 (0-0.5)	0.530
Alcohol consumption (units/week)	2 (0-7)	2 (0-5)	0.840
Coffee consumption (cups/day)	2 (1-3)	2 (1-3)	0.273

BMI, Body mass index.

Table 2. Heart rate variability (HRV) parameters

Heart rate variability parameter	Without on-call shifts (n = 36)	With on-call shifts (n = 104)	*P*
Heart rate	79 (72-88)	84 (79-92)	**0.006**
RMSSD	34.5 (26-49.8)	27 (18-37.7)	**0.002**
PNS	-0.86 (-1.44-0.31)	-1.42 (-1.96-0.86)	**0.002**
SNS	1.07 (0.36-1.75)	1.78 (0.96-2.71)	**0.002**
Mean RR	758 (686-841)	712 (650-755)	**0.006**
SDNN	47.2 (36.6-55.2)	38.8 (28.4-50.1)	**0.006**
Poincaré SD1	24.4 (18.4-35.3)	19.3 (12.7-26.6)	**0.002**
Poincaré SD2	61.4 (48.7-72.2)	51.6 (38.6-66.9)	**0.012**
Stress index	9.96 (7.96-12.33)	12.1 (9.47-66.92)	**0.003**
RR	13.3 (11.9-16.3)	13.3 (11.3-15.5)	0.600
LF power	1183.1 (925.6-1952.2)	1061.3 (567.6-1596.1)	0.074
HF power	395.2 (301.1-998.7)	335.7 (125.4-613.8)	**0.014**
LF (%)	71.6 (62.3-81.7)	76.4 (67.3-82.6)	0.092
HF (%)	28.3 (18.4-37.7)	23.5 (17.4-32.6)	0.089
LF/HF ratio	2.52 (1.65-4.44)	3.25 (2.07-4.74)	0.093

Values are presented as median (interquartile range). HF, High frequency; LF, Low frequency; PNS, Parasympathetic nervous system; RMSSD, Root mean square of successive differences; RR, R-wave to R-wave interval; SD, Standard deviation; SDNN, Standard deviation of normal-to-normal (NN) R-R intervals; SNS, Sympathetic nervous system.

Results

Baseline Characteristics

Table 1 summarizes the demographic and lifestyle characteristics of the study population. Demographic and lifestyle factors were comparable between groups, including age, sex, body mass index (BMI), training duration, and smoking, alcohol, and coffee consumption (P > 0.05 for all). The mean age was 28.5 ± 3.6 years for non–on-call residents and 29.7 ± 3.4 years for residents with on-call shifts. Males constituted 44.4% of the non–on-call group and 49% of the on-call group. The mean number of monthly on-call shifts was 5 (range: 4-8) in the on-call group. Median sleep duration during shifts was 4 hours (range: 3-6 hours).

HRV Differences

Table 2 presents a comprehensive comparison of HRV parameters between groups. On-call residents exhibited significantly elevated heart rates (84 vs. 79 bpm, P = 0.006) and higher stress indices (12.1 vs. 9.96, P = 0.003). RMSSD (27 vs. 34.5, P = 0.002), SDNN (38.8 vs. 47.2, P = 0.006), PNS index (-1.42 vs. -0.86, P = 0.002), and Poincaré indices SD1 (19.3 vs. 24.4, P = 0.002) and SD2 (51.6 vs. 61.4, P = 0.012) were all significantly lower in the on-call group, indicating reduced autonomic modulation. The SNS index was elevated in the on-call group (1.78 vs. 1.07, P = 0.002), demonstrating heightened sympathetic tone. HF power was significantly lower among on-call residents (335.7 vs. 395.2, P = 0.014), while the LF/HF ratio trended higher (3.25 vs. 2.52, P = 0.093) but did not reach statistical significance. Figure 1 presents a boxplot illustrating differences in key HRV variables between groups.

The mean RR interval, representing the average time between consecutive heartbeats, was significantly shorter in residents with on-call shifts (712 vs. 758 ms, P = 0.006), consistent with their higher resting heart rates. This pattern of elevated heart rate, reduced time-domain HRV parameters, and altered frequency-domain components suggests a shift toward sympathetic predominance and reduced autonomic modulation in residents exposed to on-call shifts.

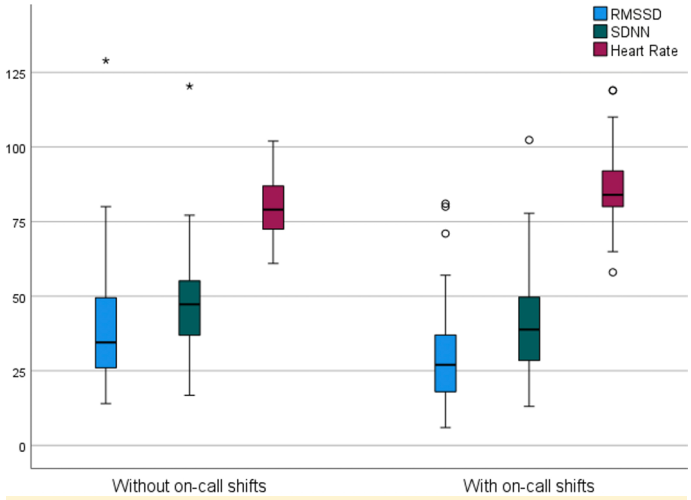
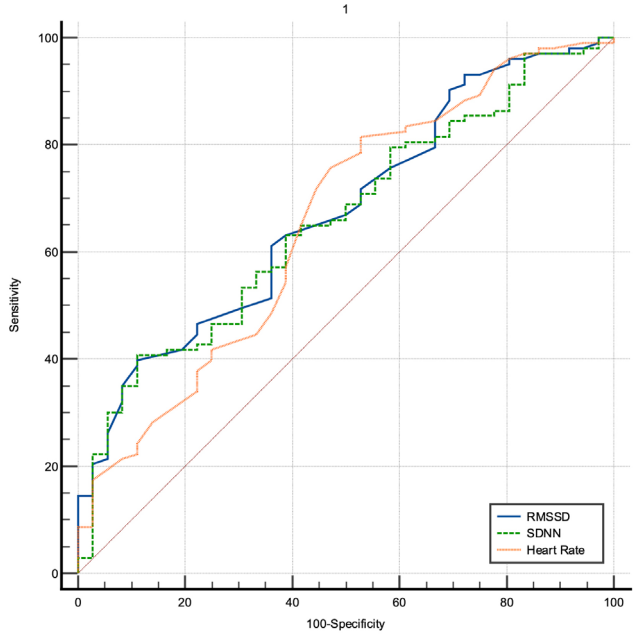


Figure 1. Boxplot illustrating differences in heart rate variability parameters between groups.

RMSSD, Root mean square of successive differences; SDNN, Standard deviation of normal-to-normal (NN) R-R intervals.



	Threshold	Specificity	Sensitivity	AUC (Confidence Interval)
Heart rate (beats/min)	> 80	56	72	0.656 (0.550–0.762)
RMSSD	≤ 32	61	63	0.674 (0.576–0.771)
SDNN	≤ 35.44	47	75	0.659 (0.561–0.757)

Figure 2. Receiver operating characteristic (ROC) analysis of heart rate variability parameters.

RMSSD, Root mean square of successive differences; SDNN, Standard deviation of normal-to-normal (NN) R-R intervals.

Physical Activity

Table 3 details the physical activity profiles of both groups as assessed by the IPAQ. Total weekly metabolic equivalent values (METs) and IPAQ classifications did not differ significantly between groups. Median total physical activity was 2290 MET-min/week for residents without on-call shifts and 1896 MET-min/week for those with on-call shifts (P = 0.148). Sedentary time was similar between groups, with both reporting a median of 480 minutes of sitting per day.

The distribution across activity categories showed that 2.8% of non–on-call residents and 7.8% of on-call residents were classified as inactive, 61.1% and 64.7% as minimally active, and 36.1% and 27.5% as HEPA active, respectively (P = 0.412). The absence of significant differences in physical activity patterns suggests that the observed HRV alterations are more likely attributable to the occupational stress associated with on-call shifts rather than differences in activity levels.

ROC Analysis

Figure 2 presents the results of ROC curve analyses for selected HRV parameters. An RMSSD value ≤ 32 demonstrated a sensitivity of 63% and a specificity of 61% (area under the curve [AUC] = 0.674) for identifying residents with on-call shifts. A heart rate > 80 bpm yielded an AUC of 0.656, with a sensitivity of 72% and a specificity of 56%, indicating modest predictive value. An SDNN value ≤ 35.44 showed a sensitivity of 75% but a lower specificity of 47% (AUC = 0.659).

Table 3. Physical activity profiles

	Without on-call shifts (n = 36)	With on-call shifts (n = 104)	*P*
Physical activity levels (IPAQ)			
Total MET-min/week	2290 (1416-3198)	1896 (1039-3082)	0.148
Vigorous MET-min/week	480 (0-960)	0 (0-960)	0.297
Moderate MET-min/week	60 (0-450)	0 (0-240)	0.279
Walking MET-min/week	1386 (717-2079)	1386 (693-2079)	0.480
Time spent sitting (min/day)	480 (315-540)	480 (300-600)	0.710
IPAQ categorical classification			0.412
Inactive	1 (2.8%)	8 (7.8%)	
Minimally active	22 (61.1%)	66 (64.7%)	
HEPA active	13 (36.1%)	28 (27.5%)	

Values are presented as median (interquartile range). HEPA, Health-enhancing physical activity; IPAQ, International Physical Activity Questionnaire; MET, Metabolic equivalent of task.

Discussion

Our study demonstrates that medical residents with on-call responsibilities exhibit significant reductions in HRV and increased markers of sympathetic activity compared to their non-on-call counterparts. These findings are consistent with existing literature on occupational stress and autonomic dysfunction.[14]

Heart rate variability is a well-established predictor of cardiovascular health and stress resilience.[15,16] The significantly reduced RMSSD and SDNN values observed in on-call residents indicate compromised autonomic modulation of cardiac function. RMSSD, which primarily reflects autonomic modulation of the sinoatrial node, showed a median reduction of approximately 22% in the on-call group. Similarly, SDNN, representing overall HRV, was reduced by approximately 18%. According to established clinical thresholds, reductions of this magnitude may have prognostic significance for long-term cardiovascular outcomes.[17]

Heart rate variability can also be influenced by disruptions in other homeostatic mechanisms. For example, infections may have lasting effects on cardiac autonomic balance. A study by Asarcıklı et al.[18] demonstrated deterioration in HRV during the period following Coronavirus Disease 2019 (COVID-19) infection.

Non-linear HRV parameters provide complementary insights into autonomic regulation. The reduced Poincaré SD1 values observed in on-call residents further support the presence of diminished short-term variability, which is traditionally associated with parasympathetic activity. The concurrent reduction in SD2 suggests that longer-term variability, reflecting both sympathetic and parasympathetic influences, is also compromised. These findings are consistent with an overall pattern of autonomic imbalance characterized by parasympathetic withdrawal and sympathetic predominance.[19]

Frequency-domain analysis revealed a significant reduction in HF power among on-call residents, which is traditionally interpreted as decreased parasympathetic activity. Although the difference in the LF/HF ratio did not reach statistical significance (P = 0.093), the trend toward higher values in the on-call group (3.25 vs. 2.52) aligns with the overall pattern of sympathovagal imbalance. Direct measures of autonomic indices corroborated these findings, with a significantly lower PNS index and a higher SNS index observed in residents with on-call shifts.

Importantly, the absence of differences in physical activity levels suggests that autonomic dysfunction is more likely attributable to occupational stress rather than behavioral factors. Chronic activation of the sympathetic nervous system, compounded by inadequate sleep during on-call shifts, may explain the observed autonomic imbalance.[20] Additionally, cortisol levels have been reported to increase in individuals exposed to night shift work.[21]

The stress index, which quantifies the degree of sympathetic activation based on heart rate patterns, was significantly elevated in residents with on-call shifts (12.1 vs. 9.96, P = 0.003). This finding is particularly noteworthy, as elevated stress index values have been associated with increased allostatic load and greater vulnerability to stress-related disorders.[22] The physiological interpretation of these results suggests that on-call shifts may induce a state of chronic sympathetic activation without adequate parasympathetic counterbalance, potentially compromising cardiovascular adaptability and stress resilience.

Our ROC curve analysis identified potential threshold values for HRV parameters that may serve as early indicators of autonomic dysfunction in residents. An RMSSD value ≤ 32 and a heart rate > 80 bpm demonstrated moderate sensitivity and specificity for identifying residents with on-call shifts. Although these values should not be interpreted as diagnostic thresholds, they provide preliminary guidance for occupational health monitoring in residency programs. Furthermore, the modest discriminatory performance (AUC range: 0.65–0.67) indicates that these values have limited clinical applicability for population-level screening and should be interpreted with caution.

These findings raise concerns regarding the long-term health implications for medical residents. Reduced HRV has been associated with hypertension, metabolic syndrome, depression, and even sudden cardiac death.[7,9,23,24] The cumulative effect of repeated 24-hour shifts over the course of residency training, typically spanning 3-5 years, may further amplify these risks.

Policy changes should acknowledge the physiological burden of night shifts, potentially incorporating these considerations into compensation models, scheduling practices, and retirement planning. This is particularly relevant given growing evidence linking shift work with increased allostatic load and chronic disease risk.[25] Implementation of countermeasures, such as strategic napping protocols,[26] chronobiologically optimized shift schedules,[27] and stress management interventions,[28] may help mitigate the autonomic consequences of on-call duties.

The clear physiological stress associated with on-call shifts also raises broader questions about the sustainability of traditional residency training structures and their potential conflict with the medical principle of "*first, do no harm*" when applied to physicians themselves.

Limitations

This study is cross-sectional and therefore cannot establish causality. Given the cross-sectional nature of this study, the findings should be considered hypothesis-generating with respect to the long-term cardiovascular impact of on-call shifts. HRV was assessed during daytime rest and may not capture nocturnal variations. Although the sample size was adequate to detect significant differences in primary outcomes, it may have limited statistical power for subgroup analyses. Additionally, specialty-specific variations in on-call intensity and potential chronobiological adaptations over time were not evaluated. Previous research suggests that adverse effects of HRV may persist for up to three nights after sleep deprivation; however, the intensive on-call schedules of residents in Türkiye made it difficult to recruit participants with three full days of recovery between on-call shifts. Consequently, a recovery period of 48 hours was used.[29] As the IPAQ is a self-reported instrument, the possibility of recall bias exists. Longitudinal studies are needed to evaluate chronic outcomes and potential compensatory mechanisms. Despite these limitations, the consistency of our findings across multiple HRV domains strengthens the evidence for autonomic dysfunction associated with on-call shifts.

Furthermore, although our sample size was sufficient to identify primary differences in HRV, it was not large enough to permit robust subgroup analyses by medical specialty. This represents a significant limitation, as specialty-specific workloads and the intensity of on-call duties (e.g., surgical vs. non-surgical disciplines) vary considerably and may impose different levels of physiological stress. Consequently, it was not possible to determine whether certain specialties are more vulnerable to autonomic dysfunction than others.

Conclusion

This study demonstrated an association between on-call shifts and significant reductions in HRV, independent of lifestyle-related factors. The observed pattern of decreased parasympathetic activity and elevated sympathetic tone indicates a state of autonomic imbalance that may predispose residents to adverse health outcomes. Structural interventions are urgently needed to mitigate the health impact of these occupational demands on young physicians. Future research should examine longitudinal changes in autonomic function throughout residency training using larger, equally sized cohorts. Additionally, forthcoming studies should prioritize the assessment of specialty-specific workload intensity to evaluate the effectiveness of targeted interventions aimed at preserving cardiovascular health in this vulnerable population.

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Personalized Prediction of Left Ventricular Ejection Fraction in the Follow-Up of Patients with ST-Segment Elevation Myocardial Infarction: Development of a Practical Nomogram Model

ST-Segment Elevasyonlu Miyokard Enfarktüsü Hastalarının Takibinde Sol Ventrikül Ejeksiyon Fraksiyonunun Kişiselleştirilmiş Öngörüsü: Pratik Bir Nomogram Modelinin Geliştirilmesi

ORIGINAL ARTICLE
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ABSTRACT

Objective: Accurate estimation of left ventricular ejection fraction (LVEF) after ST-segment elevation myocardial infarction (STEMI) is essential for optimizing long-term management and cardiovascular risk stratification. This study aimed to identify predictors of LVEF at six months after STEMI and to develop a clinically applicable nomogram for individualized prognostic assessment.

Method: This prospective, single-center cohort study included consecutive patients admitted with STEMI between July 2018 and October 2018. Baseline clinical, laboratory, and angiographic variables were collected. LVEF was assessed by transthoracic echocardiography during the index hospitalization and at six-month follow-up. Patients were categorized into four groups according to follow-up LVEF. Predictors of six-month LVEF were identified using proportional odds logistic regression, and a nomogram was constructed based on the final multivariable model.

Results: A total of 231 patients were analyzed (median age: 57 years; 83% male). At baseline, 119 patients (51%) had an LVEF < 50%, whereas at six months 115 patients (49%) had an LVEF < 50%. Multivariable analysis identified baseline LVEF, peak creatine kinase–myocardial band (CKMB) level, age, hypertension, and final Thrombolysis in Myocardial Infarction (TIMI) flow grade as independent predictors of follow-up LVEF (all $P < 0.05$).

Conclusion: Baseline LVEF and peak CK-MB level were the strongest independent predictors of six-month LVEF following STEMI. Age, hypertension, and final TIMI flow grade were identified as additional predictors. The proposed nomogram provides a practical tool for individualized follow-up planning and risk assessment in STEMI survivors.

Keywords: Left ventricular ejection fraction, nomogram, ST elevation myocardial infarction

ÖZET

Amaç: ST-segment elevasyonlu miyokard enfarktüsü (STEMI) sonrası sol ventrikül ejeksiyon fraksiyonunun (LVEF) doğru tahmini, uzun dönem yönetim ve kardiyovasküler risk sınıflaması açısından önemlidir. Bu çalışmada STEMI sonrası altıncı ay LVEF'nin belirleyicilerinin saptanması ve bireyselleştirilmiş prognostik değerlendirme için klinikte uygulanabilir bir nomogram geliştirilmesi amaçlandı.

Yöntem: Bu prospektif, tek merkezli kohort çalışmaya Temmuz 2018–Ekim 2018 tarihleri arasında STEMI tanısı ile başvuran ardışık hastalar dahil edildi. Başlangıç klinik, laboratuvar ve anjiyografik değişkenler toplandı. LVEF, indeks yatış sırasında ve altıncı ay izleminde transtorasik ekokardiyografi ile değerlendirildi. Hastalar izlem LVEF'sine göre dört gruba ayrıldı. Altıncı ay LVEF'nin belirleyicileri orantılı odds lojistik regresyon ile belirlendi ve nihai çok değişkenli modele dayalı bir nomogram oluşturuldu.

Bulgular: Toplam 231 hasta analiz edildi (medyan yaş: 57 yıl; %83 erkek). Başlangıçta 119 hastada (%51) LVEF <%50 saptanırken, altıncı ay izleminde 115 hastada (%49) LVEF < %50 olarak devam ettiği görüldü. Çok değişkenli analizde başlangıç LVEF, pik kreatin kinaz–miyokardiyal band (CK-MB) düzeyi, yaş, hipertansiyon varlığı ve final Thrombolysis in Myocardial Infarction (TIMI) akım derecesi, izlemdeki LVEF'nin bağımsız belirleyicileri olarak saptandı (tümü için $P < 0,05$).

Sonuç: Başlangıç LVEF ve pik CK-MB düzeyi, STEMI sonrası altıncı ay LVEF'nin en güçlü belirleyicileriydi. Yaş, hipertansiyon ve final TIMI akım derecesi de diğer belirleyiciler olarak tespit edildi. Geliştirilen nomogram, STEMI'den sağ kalan hastalarda bireyselleştirilmiş izlem planlaması ve risk değerlendirmesi için pratik bir araç sunmaktadır.

Anahtar Kelimeler: Sol ventrikül ejeksiyon fraksiyonu, nomogram, ST elevasyonlu miyokard enfarktüsü

Ischemic heart disease continues to represent the leading cause of morbidity and mortality worldwide, with ST-segment elevation myocardial infarction (STEMI) representing the most severe and life-threatening clinical manifestation of ischemic heart disease.[1] Despite major advances in reperfusion strategies, interventional techniques, and guideline-directed medical therapy, STEMI remains associated with substantial short- and long-term morbidity. In a contemporary study conducted in Türkiye, STEMI accounted for approximately 23.5% of admissions to coronary intensive care units,[2] underscoring its persistent clinical burden.

Although early and effective reperfusion has significantly reduced acute mortality, a considerable proportion of patients experience adverse left ventricular remodeling and develop heart failure during follow-up.[3] Reduced left ventricular ejection fraction (LVEF) is a central determinant of prognosis after myocardial infarction and is strongly associated with symptom burden, hospitalization rates, and long-term survival. Accordingly, international guidelines emphasize the pivotal role of LVEF in post-infarction risk stratification, optimization of medical therapy, and guidance of follow-up strategies.[4–6]

Early identification of patients at risk for persistently reduced LVEF following STEMI may facilitate closer surveillance and more timely therapeutic interventions. Such an approach has the potential to improve symptom control, prevent clinical deterioration, and reduce recurrent hospital admissions.[4] LVEF remains one of the most robust, widely validated, and clinically actionable parameters for prognostic assessment after myocardial infarction. However, reliable prediction of mid-term systolic recovery during the acute phase of STEMI remains challenging.

Left ventricular systolic function is highly dynamic in the post-infarction period and is influenced by multiple interacting mechanisms, including infarct size, microvascular obstruction, residual ischemia, neurohormonal activation, myocardial stunning, and the extent of ventricular remodeling.[7] Moreover, LVEF assessed during the acute phase may not reliably reflect intrinsic myocardial contractile function because of transient hemodynamic instability, sympathetic activation, arrhythmias, fluctuations in loading conditions, and myocardial edema. These factors limit the predictive value of isolated baseline LVEF measurements for mid-term functional recovery.

Several clinical, biochemical, and angiographic predictors of post-infarction ventricular recovery have been proposed, including infarct location, enzymatic markers of myocardial injury, Thrombolysis in Myocardial Infarction (TIMI) flow grade, and composite risk scores.[8] However, their predictive performance has been inconsistent, and none has achieved widespread clinical adoption for individualized LVEF estimation. Importantly, most existing risk models primarily focus on mortality or composite cardiovascular outcomes rather than directly addressing systolic functional recovery. Additionally, many rely on variables that are not universally available, limiting their applicability in real-world settings.[9,10]

In this context, a practical and user-friendly prediction tool incorporating readily obtainable clinical and biochemical parameters may address an important unmet clinical need. Such a model could enable individualized estimation of mid-term LVEF, support early identification of patients at risk for persistent systolic dysfunction, and inform decisions regarding imaging surveillance, optimization of medical therapy, and referral to cardiac rehabilitation or heart failure programs.

Therefore, the present study aimed to identify independent baseline predictors of six-month LVEF in patients presenting with STEMI and to develop a simple, clinically applicable nomogram to support personalized prognostic assessment in routine clinical practice.

ABBREVIATIONS

AIC	Akaike Information Criterion
BIC	Bayesian Information Criterion
CK-MB	Creatine kinase–myocardial band
EACTS	European Association for Cardio-Thoracic Surgery
ESC	European Society of Cardiology
ESH	European Society of Hypertension
HDL-C	High-density lipoprotein cholesterol
LDL-C	Low-density lipoprotein cholesterol
LVEF	Left ventricular ejection fraction
PCI	Percutaneous coronary intervention
STEMI	ST-segment elevation myocardial infarction
TIMI	Thrombolysis in Myocardial Infarction

Materials and Methods

Study Design and Population

This prospective, single-center observational study included consecutive adult patients (aged 18–90 years) who presented with STEMI between July 2018 and October 2018 and underwent primary percutaneous coronary intervention (PCI) at a tertiary cardiovascular care center.

Initially, 318 patients were enrolled. Patients were excluded if they had a documented history of heart failure or LVEF ≤ 50% prior to the index hospitalization, required coronary artery bypass grafting (CABG) following diagnostic angiography, or experienced recurrent myocardial infarction during the follow-up period. After applying these criteria, the final study population consisted of 231 patients.

Clinical Definitions

STEMI was diagnosed in accordance with the 2017 European Society of Cardiology (ESC) guidelines.[2] Diagnostic criteria included ischemic chest pain lasting longer than 30 minutes or equivalent symptoms, such as dyspnea, syncope, or diaphoresis, accompanied by characteristic electrocardiographic findings. These electrocardiographic features consisted of ST-segment elevation ≥ 2.5 mm in men younger than 40 years, ≥ 2.0 mm in men aged 40 years or older, or ≥ 1.5 mm in women in leads V2–V3, and/or ≥ 1.0 mm in two or more contiguous leads other than V2–V3, in the absence of left ventricular hypertrophy or left bundle branch block.[3]

In patients presenting with inferior myocardial infarction, right-sided precordial leads (V3R–V4R) were routinely evaluated to assess right ventricular involvement. Posterior myocardial infarction was suspected in the presence of ST-segment depression in leads V1–V3 with upright terminal T waves and was confirmed by concomitant ST-segment elevation ≥ 0.5 mm in posterior leads V7–V9.[3]

Hypertension was defined as a documented history of elevated blood pressure requiring antihypertensive therapy or previously recorded systolic blood pressure > 140 mmHg and/or diastolic blood pressure > 90 mmHg, in accordance with current recommendations of the ESC and the European Society of Hypertension (ESH).[11] Diabetes mellitus was defined by prior use of antidiabetic medication or fulfillment of established diagnostic criteria, including fasting plasma glucose ≥ 126 mg/dL, hemoglobin A1c (HbA1c) ≥ 6.5%, or random plasma glucose ≥ 200 mg/dL in the presence of classical hyperglycemic symptoms.[12]

Dyslipidemia was defined by the presence of at least one of the following abnormalities: total cholesterol ≥ 240 mg/dL, low-density lipoprotein cholesterol ≥ 130 mg/dL, high-density lipoprotein cholesterol < 40 mg/dL in men or < 50 mg/dL in women, or triglyceride levels ≥ 150 mg/dL.[13] Current smoking status was defined as active tobacco use or smoking cessation within 30 days prior to enrollment.[14]

Data Collection and Ethical Considerations

Baseline demographic, clinical, laboratory, and angiographic data were collected at the time of hospital admission. Follow-up clinical and echocardiographic evaluations were performed at six months. The study protocol was approved by the Haydarpaşa Numune Training and Research Hospital Clinical Research Ethics Committee (Approval Number: HNEAH-KAEK-2019/165-2858, Date: 02.12.2019) and was conducted in accordance with the principles of the Declaration of Helsinki. Written informed consent was obtained from all participants prior to study inclusion.

Laboratory and Imaging Assessments

Venous blood samples were obtained in the emergency department prior to coronary angiography. Complete blood count parameters were analyzed using a Beckman Coulter LH 750 hematology analyzer (Beckman Coulter, CA, USA), and biochemical analyses were performed using the Roche Cobas Integra 800 system (Roche Diagnostics, Switzerland).

Creatine kinase–myocardial band (CK-MB) levels were measured at admission and serially during hospitalization. The CK-MB value obtained at initial presentation was defined as baseline CK-MB, whereas the highest value recorded during the hospital stay was defined as peak CK-MB.

Fasting lipid profiles, including total cholesterol, low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), and triglycerides, were measured within 24 hours of admission.

Preprocedural SYNTAX (Synergy Between Percutaneous Coronary Intervention with TAXUS and Cardiac Surgery) scores were calculated using diagnostic coronary angiograms and the online SYNTAX Score calculator (version 2.1), in accordance with the SYNTAX II methodology and the 2018 ESC and European Association for Cardio-Thoracic Surgery (EACTS) myocardial revascularization guidelines.[15,16]

Final TIMI flow grade was assessed angiographically at the conclusion of the PCI procedure using the standardized TIMI flow classification.[17]

Interventional Procedure

All patients underwent primary PCI via femoral artery access using standard interventional techniques performed by experienced operators. Upon admission, patients received loading doses of aspirin and a P2Y12 inhibitor (clopidogrel, ticagrelor, or prasugrel), followed by administration of unfractionated heparin (50–70 IU/kg intravenously) to maintain an activated clotting time between 200 and 250 seconds throughout the procedure. The use of glycoprotein IIb/IIIa inhibitors, as well as stent selection and sizing, was left to the discretion of the operator, in accordance with contemporary guideline recommendations.[3]

Echocardiographic Evaluation

Transthoracic echocardiography was performed using an EPIQ 7 ultrasound system (Philips Healthcare, Andover, MA, USA) within the first 72 hours of hospital admission and was repeated at six months. Left ventricular ejection fraction was calculated using the modified biplane Simpson's method in accordance with the recommendations of the American Society of Echocardiography.[18] All echocardiographic measurements were performed by a single experienced operator using a standardized acquisition and analysis protocol to minimize measurement variability. LVEF measured during the index hospitalization was defined as baseline LVEF, whereas the value obtained at follow-up was defined as final LVEF.

Outcome

The primary outcome of the study was left ventricular ejection fraction assessed at the six-month echocardiographic follow-up.

Statistical Analysis

Statistical analyses were performed using the rms, ggplot2, and DynNom packages in R software version 3.5.1 (R Foundation for Statistical Computing, Vienna, Austria). Categorical variables were expressed as counts and percentages, while continuous variables were reported as mean ± standard deviation or median with interquartile range (25^{th}–75^{th} percentile), as appropriate.

Final LVEF at six months served as the primary outcome variable. For descriptive analyses, follow-up LVEF values were categorized into four ordinal groups: ≤ 40%, 41–50%, 51–60%, and > 60%. Candidate predictors were selected based on clinical plausibility and previously published evidence.

Proportional odds logistic regression was used to examine associations between candidate predictors and the ordinal LVEF outcome. This approach was chosen to account for the ordered nature of LVEF categories and to avoid information loss associated with dichotomization. To reduce the risk of overfitting and improve model stability, penalized proportional odds regression was applied. Continuous predictors were modeled using restricted cubic splines to account for potential non-linear relationships. The relative contribution of each predictor was quantified using the partial chi-square statistic divided by the total model chi-square.

To enhance clinical applicability, a reduced model was derived using backward step-down variable selection. Model performance was evaluated using likelihood ratio chi-square statistics, the Akaike Information Criterion (AIC), the Bayesian Information Criterion (BIC), Somers' D_{xy} rank correlation, and the coefficient of determination (R^2).

Table 1. Baseline demographic, clinical, and angiographic characteristics according to left ventricular ejection fraction (LVEF) at six-month follow-up echocardiography

Variables	LVEF ≤ 40% (n = 56)	LVEF 41–50% (n = 59)	LVEF 51–60% (n = 58)	LVEF ≥ 60% (n = 58)	*P*
Age (years)	61.3 ± 12.2	57.7 ± 11.0	56.2 ± 9.7	53.5 ± 8.1	0.001
Female sex	11 (19.6)	6 (10.2)	8 (13.8)	13 (22.4)	0.272
Hypertension	31 (55.3)	24 (40.7)	21 (36.2)	15 (25.9)	0.013
Diabetes mellitus	21 (37.5)	9 (15.2)	12 (20.7)	8 (13.8)	0.011
Smoking	37 (66.1)	46 (77.9)	48 (82.7)	43 (74.1)	0.206
Heart rate (beats/min)	92.3 ± 18.5	82.1 ± 19.8	79.6 ± 18.7	78.9 ± 16.7	<0.001
SBP (mmHg)	131.2 ± 30.8	137.8 ± 26.7	145.8 ± 29.1	138.3 ± 28.7	0.102
DBP (mmHg)	78.5 ± 17.5	81.9 ± 16.7	84.7 ± 17.6	80.6 ± 17.9	0.325
Killip class I	51 (91.1)	58 (98.3)	55 (94.8)	56 (96.5)	0.034
VT/VF	7 (12.5)	3 (5.1)	7 (12.1)	8 (13.8)	0.424
Glucose (mg/dL)	189.1 ± 72.4	145.0 ± 67.8	138.5 ± 57.8	153.5 ± 78.6	<0.001
HbA1c (%)	7.4 ± 2.4	6.3 ± 1.3	6.1 ± 1.1	6.5 ± 1.5	0.011
Leukocyte (×10³/mm³)	15.2 ± 5.8	12.5 ± 5.7	12.0 ± 3.9	11.8 ± 4.3	0.003
Hemoglobin (g/dL)	13.6 ± 2.0	13.6 ± 1.7	14.1 ± 2.1	14.0 ± 1.5	0.610
Platelet (×10³/mm³)	254.8 ± 62.7	248.1 ± 78.5	235.3 ± 52.5	258.4 ± 67.4	0.156
Total cholesterol (mg/dL)	175.7 ± 44.6	174.1 ± 45.8	185.8 ± 39.4	183.3 ± 45.5	0.433
LDL cholesterol (mg/dL)	109.1 ± 36.5	111.2 ± 37.1	120.5 ± 33.8	115.1 ± 44.7	0.363
HDL cholesterol (mg/dL)	34.1 ± 8.9	36.1 ± 8.8	35.7 ± 7.1	35.7 ± 7.4	0.671
CK-MB, baseline (IU/L)	251.3 ± 237.5	135.1 ± 112.1	78.1 ± 102.2	68.9 ± 63.7	<0.001
CK-MB, peak (IU/L)	323.1 ± 247.1	182.6 ± 138.5	115.2 ± 117.5	90.9 ± 75.8	<0.001
LVEF, baseline (%)	34.2 ± 6.6	43.7 ± 6.5	50.9 ± 5.8	54.1 ± 7.1	<0.001
LVEF, follow-up (%)	35.3 ± 5.4	48.1 ± 2.3	55.5 ± 2.1	60.1 ± 0.9	<0.001
SYNTAX score	21.1 ± 8.6	16.6 ± 7.1	12.1 ± 8.0	12.4 ± 8.7	<0.001
Residual SYNTAX score	7.2 ± 9.7	5.1 ± 6.4	4.1 ± 5.5	3.4 ± 6.1	0.069
Thrombus grade (0-1)	31 (55.3)	38 (64.4)	37 (63.8)	28 (48.3)	0.461
Myocardial blush grade III	38 (67.8)	48 (81.3)	48 (82.7)	50 (86.2)	0.066
Baseline TIMI flow grade 0	47 (83.9)	39 (66.1)	40 (68.9)	36 (62.1)	0.020
Final TIMI flow grade III	37 (66.1)	50 (84.7)	49 (84.5)	52 (89.6)	0.01
Infarct-related artery (LAD)	43 (76.8)	38 (64.4)	22 (37.9)	28 (48.3)	<0.001

Continuous variables are expressed as mean ± standard deviation (SD); categorical variables as n (%). p values were calculated using one-way analysis of variance (ANOVA) for continuous variables and the chi-square test for categorical variables. CK-MB, Creatine kinase–myocardial band; DBP, Diastolic blood pressure; HDL, High-density lipoprotein; LAD, Left anterior descending artery; LDL, Low-density lipoprotein; LVEF, Left ventricular ejection fraction; SBP, Systolic blood pressure; SYNTAX, Synergy Between Percutaneous Coronary Intervention with TAXUS and Cardiac Surgery; TIMI, Thrombolysis in Myocardial Infarction; VF, Ventricular fibrillation; VT, Ventricular tachycardia.

Results

Study Population

A total of 231 patients were included in the final analysis. At baseline, 119 patients (51%) had LVEF below 50%. At the six-month follow-up, reduced systolic function (LVEF < 50%) persisted in 115 patients (49%). According to follow-up LVEF values, patients were categorized into four groups: LVEF ≤ 40% (n = 56), 41–50% (n = 59), 51–59% (n = 58), and ≥ 60% (n = 58).

Baseline Characteristics According to Follow-Up LVEF

Patients with markedly reduced LVEF at follow-up (≤ 40%) were significantly older and had a higher prevalence of hypertension and diabetes mellitus compared with those who achieved preserved systolic function. This group also exhibited higher admission heart rates and blood glucose levels.

Markers of myocardial injury were substantially elevated in patients with reduced LVEF. Both baseline and peak CK-MB levels were significantly higher in this subgroup (all P < 0.001). In addition, the final TIMI flow grade was significantly lower among patients with impaired systolic recovery (P = 0.01).

Anatomical disease burden differed significantly across LVEF categories. Patients with reduced follow-up LVEF demonstrated higher SYNTAX and residual SYNTAX scores (both P < 0.001), indicating more complex coronary artery disease and less

Table 2. Independent predictors of left ventricular ejection fraction (LVEF) at six-month follow-up echocardiography after ST-segment elevation myocardial infarction (STEMI)

Variables	RC (95% CI)	*P*
Age, years (change from 50 to 63.5)	-0.513 (-0.998, -0.027)	0.050
Sex (male vs. female)	0.232 (-0.298, 0.763)	0.389
Hypertension (yes vs. no)	-0.455 (-0.853, -0.057)	0.024
Diabetes mellitus (yes vs. no)	-0.289 (-0.741, 0.162)	0.209
Smoking (yes vs. no)	-0.056 (-0.671, 0.387)	0.808
Prior revascularization (previous PCI and/or CABG) (yes vs. no)	-0.142 (-0.671, 0.387)	0.598
VT/VF (yes vs. no)	-0.099 (-0.446, 0.645)	0.721
Baseline hemoglobin, g/dL (change from 12 to 15.1)	-0.076 (-0.343, 0.191)	0.671
Peak CK-MB, IU/L (change from 44.45 to 262.8)	-0.347 (-0.779, 0.085)	<0.001
Baseline LVEF, % (change from 40 to 53.5)	1.683 (1.309, 2.056)	<0.001
Infarct-related artery (non-LAD vs. LAD)	0.191 (-0.228, 0.612)	0.371
Final TIMI flow grade (change from 0 to 3)	0.936 (0.099, 1.772)	0.028
SYNTAX score (change from 9 to 21.5)	-0.305 (-0.623, 0.012)	0.116

CABG, Coronary artery bypass grafting; CK-MB, Creatine kinase–myocardial band; LAD, Left anterior descending artery; LVEF, Left ventricular ejection fraction; PCI, Percutaneous coronary intervention; RC, Regression coefficient; SYNTAX, Synergy Between Percutaneous Coronary Intervention with TAXUS and Cardiac Surgery; TIMI, Thrombolysis in Myocardial Infarction; VF, Ventricular fibrillation; VT, Ventricular tachycardia.

complete revascularization. The left anterior descending artery was more frequently identified as the infarct-related vessel in patients with lower LVEF. Baseline LVEF was also significantly lower in this group.

Detailed baseline demographic, clinical, laboratory, and angiographic characteristics stratified by follow-up LVEF are summarized in Table 1.

Multivariable Predictors of Six-Month LVEF

Multivariable proportional odds logistic regression analysis identified several independent predictors of LVEF at the six-month follow-up.

Baseline LVEF demonstrated the strongest positive association with follow-up systolic function (regression coefficient: 1.683; 95% confidence interval [CI]: 1.309–2.056; P < 0.001). In contrast, peak CK-MB level was inversely associated with final LVEF (regression coefficient: –0.347; 95% CI: –0.779 to –0.085; P < 0.001), consistent with the adverse impact of greater myocardial injury. Increasing age was independently associated with lower follow-up LVEF (regression coefficient: –0.513; 95% CI: –0.998 to –0.027; P = 0.050). A history of hypertension was also independently associated with impaired systolic recovery (regression coefficient: –0.455; 95% CI: –0.853 to –0.057; P = 0.024). Conversely, a higher final TIMI flow grade was positively associated with improved LVEF at follow-up (regression coefficient: 0.936; 95% CI: 0.099–1.772; P = 0.028).

The complete results of the multivariable regression analysis are presented in Table 2. Figure 1 presents the partial effect plots for key predictors, while Figure 2 depicts the relative contribution of each variable, underscoring baseline LVEF as the most influential determinant of six-month systolic function.

Model Reduction and Performance

To improve clinical applicability, a reduced prediction model was generated using backward step-down variable selection.

Table 3. Performance metrics of the full and reduced models

	dF	Likelihood ratio χ^2	R^2	Dxy	AIC	BIC
Full model	13	197	0.632	0.783	738	856
Reduced model	3	201	0.626	0.783	736	809

AIC, Akaike information criterion; BIC, Bayesian information criterion; dF, Degrees of freedom; Dxy, Somers' D rank correlation; R^2, Coefficient of determination; X^2, Likelihood ratio chi-square.

This simplified model retained three independent predictors: baseline LVEF, peak CK-MB, and a history of hypertension.

Despite the reduction in the number of variables, the simplified model demonstrated performance metrics comparable to those of the full model. Likelihood ratio chi-square statistics, the Akaike Information Criterion, the Bayesian Information Criterion, Somers' D_{xy} rank correlation, and the coefficient of determination (R^2) showed minimal attenuation, as detailed in Table 3. External validation was not performed.

Nomogram-Based Prediction

Based on the reduced model, a nomogram was constructed to enable individualized prediction of six-month LVEF. Although the primary analyses were conducted using ordinal LVEF categories, the nomogram was derived from the underlying continuous latent scale of the proportional odds model.

For illustrative purposes, a hypothetical patient with hypertension, a peak CK-MB value of 300 IU/L, and a baseline LVEF of 35% would yield a total nomogram score of 63. This score corresponds to a predicted mean LVEF of approximately 40%, a median LVEF of 37%, and estimated probabilities of achieving LVEF thresholds > 55%, > 50%, > 45%, and > 40% of < 10%, 13%, 30%, and 52%, respectively. The graphical representation of the nomogram is shown in Figure 3.

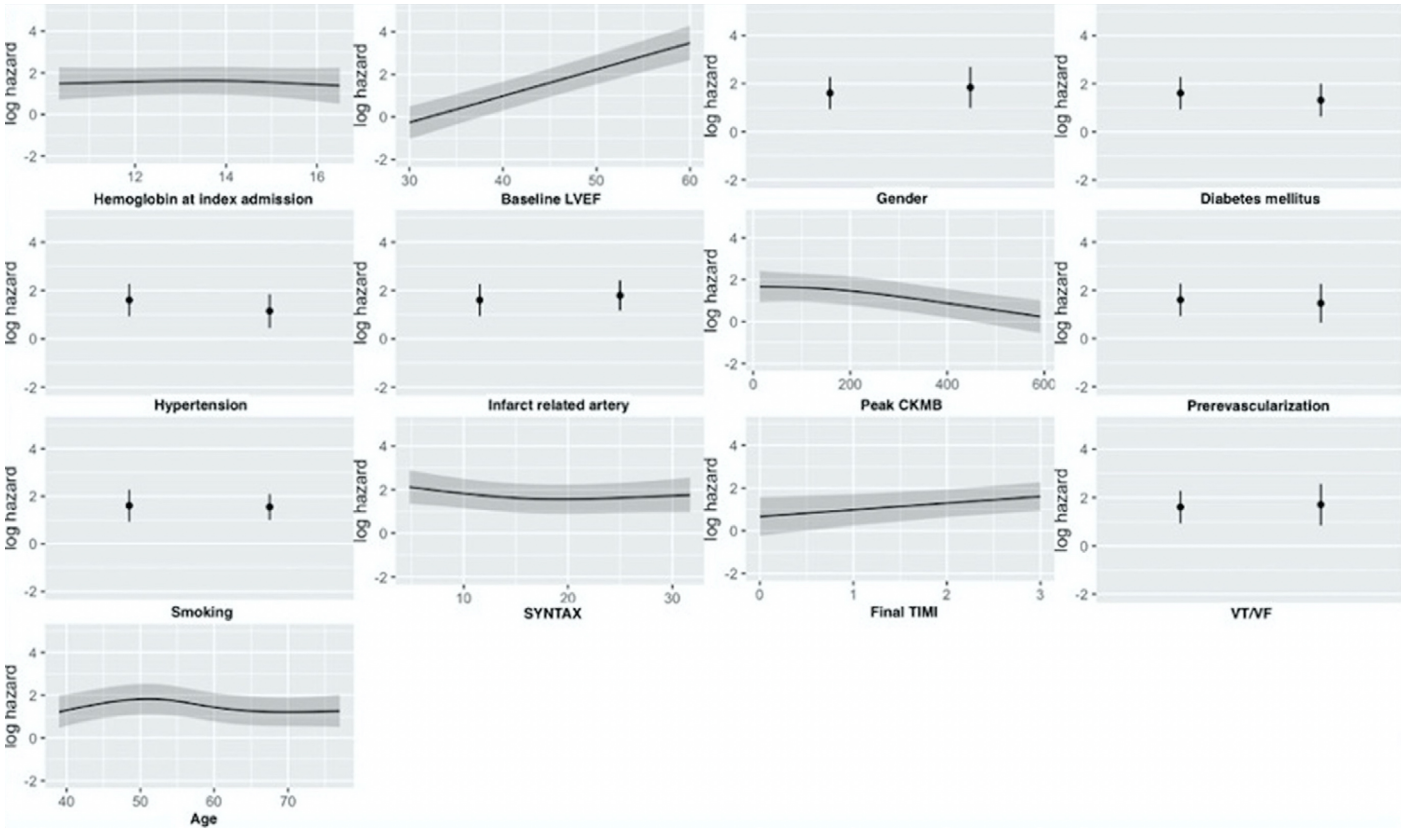

Figure 1. Partial effect plots of independent variables for prediction of six-month left ventricular ejection fraction (LVEF) in patients with ST-segment elevation myocardial infarction (STEMI). The solid lines represent the estimated partial effects, and the shaded areas indicate the 95% confidence intervals. For categorical variables, the points represent effect estimates with corresponding 95% confidence intervals.

CK-MB, Creatine kinase–myocardial band; LVEF, Left ventricular ejection fraction; SYNTAX, Synergy Between Percutaneous Coronary Intervention with TAXUS and Cardiac Surgery; TIMI, Thrombolysis in Myocardial Infarction; VF, Ventricular fibrillation; VT, Ventricular tachycardia.

Discussion

The present study provides several clinically relevant insights into left ventricular systolic recovery following ST-segment elevation myocardial infarction. First, baseline LVEF, peak CK-MB level, age, hypertension, and final TIMI flow grade were identified as independent predictors of six-month LVEF. Second, nearly half of the study population continued to exhibit impaired systolic function (LVEF < 50%) at mid-term follow-up. Finally, these predictors were integrated into a practical nomogram to facilitate individualized estimation of post-STEMI ventricular recovery.

Among all evaluated variables, baseline LVEF emerged as the strongest independent determinant of systolic function at six-month follow-up. This finding aligns with prior evidence demonstrating that early post-infarction LVEF reflects the combined effects of infarct size, myocardial stunning, and early remodeling processes.[19–21] Previous echocardiographic and cardiac magnetic resonance studies have consistently shown that severely reduced LVEF during the acute phase of myocardial infarction is associated with persistent systolic dysfunction at short- and mid-term follow-up.[20] Although some patients with initially reduced LVEF may exhibit relative improvement over time, a substantial proportion continue to demonstrate impaired systolic function.[22–24] Collectively, these findings underscore the dominant prognostic role of baseline LVEF and justify its central contribution to the proposed nomogram.

Peak creatine kinase–myocardial band level was also identified as a strong independent predictor of six-month LVEF, reflecting the extent of myocardial injury. Prior studies have consistently demonstrated a close relationship between peak CK-MB levels, infarct size, and residual systolic function.[9,25,26] Hartman et al.[25] reported that peak CK-MB reliably estimated infarct size assessed by cardiac magnetic resonance imaging and independently predicted LVEF and short-term mortality. Although cardiac troponins are currently preferred for the diagnosis of myocardial infarction, CK-MB remains clinically informative due to its well-characterized release kinetics and its ability to reflect the magnitude of myocardial necrosis. Necropsy-based studies have demonstrated a closer correlation between CK-MB levels and histopathological infarct size compared with troponins,[27] and registry data suggest comparable or superior prognostic performance of CK-MB for early adverse outcomes following acute myocardial infarction.[28,29] These findings support the inclusion of CK-MB as a practical biomarker in predictive models of post-infarction ventricular recovery.

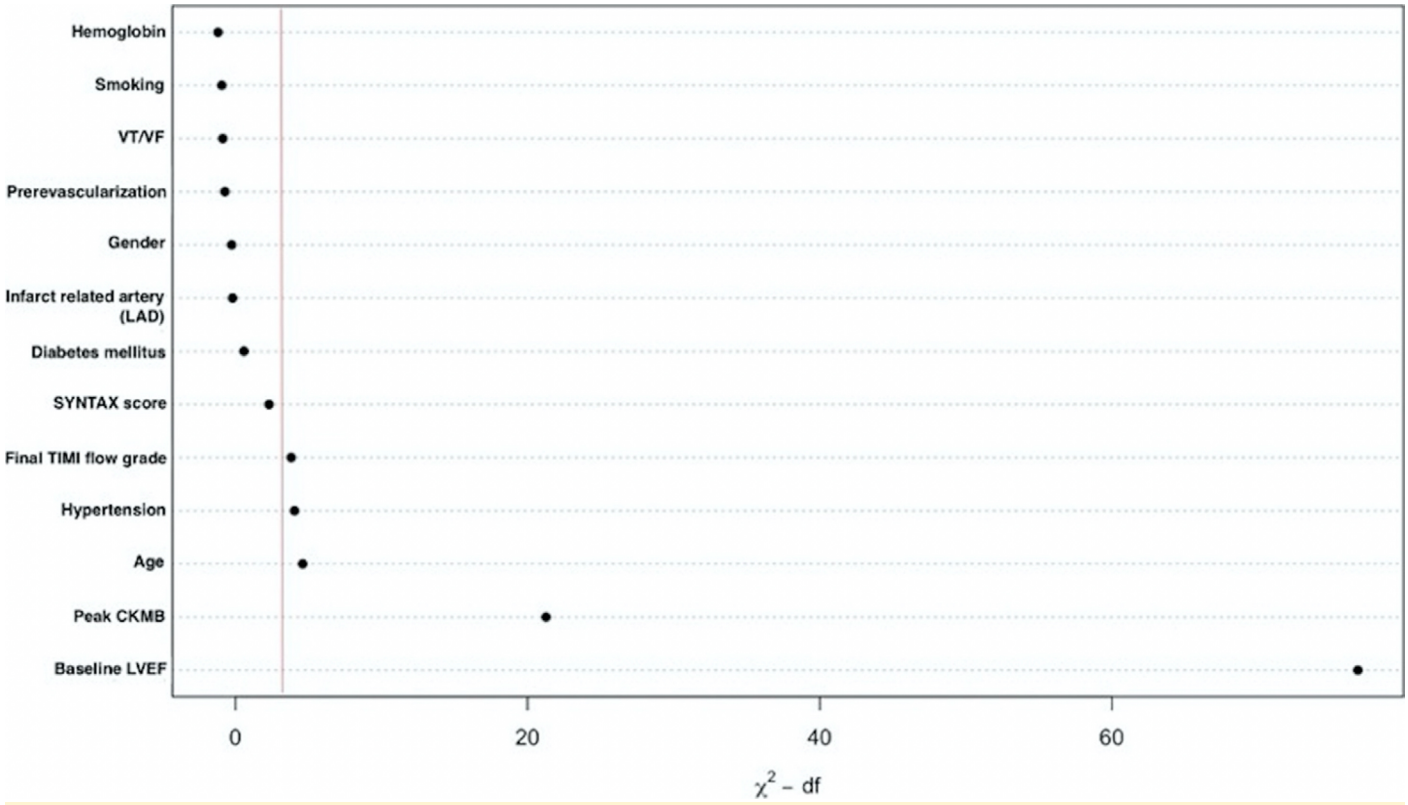

Figure 2. Importance of variables for predicting six-month left ventricular ejection fraction (LVEF). This figure illustrates the relative importance of each variable included in the final model, based on χ^2 minus degrees of freedom values.

CK-MB, Creatine kinase–myocardial band; LAD, Left anterior descending artery; LVEF, Left ventricular ejection fraction; SYNTAX, Synergy Between Percutaneous Coronary Intervention with TAXUS and Cardiac Surgery; TIMI, Thrombolysis in Myocardial Infarction; VF, Ventricular fibrillation; VT, Ventricular tachycardia.

Age was identified as an independent predictor of reduced left ventricular systolic function at six-month follow-up. This observation is consistent with prior studies showing that advanced age is associated with an increased risk of heart failure and impaired myocardial recovery after myocardial infarction.[21,30,31] Older patients often present with a higher burden of comorbid conditions, including microvascular dysfunction, endothelial impairment, and reduced myocardial reserve, all of which may limit the capacity for functional recovery after ischemic injury.[32,33] In addition, age-related alterations in inflammatory response and myocardial repair mechanisms may further contribute to less favorable systolic recovery trajectories in this population.

Hypertension was also independently associated with impaired systolic recovery at six months. Prior studies have shown that antecedent hypertension is linked to heightened neurohormonal activation, increased myocardial fibrosis, and adverse ventricular remodeling following myocardial infarction.[30,34] Structural and functional alterations related to chronic hypertension may further exacerbate ischemic myocardial injury and compromise left ventricular recovery. In addition, hypertension is strongly associated with greater coronary artery disease severity and complexity, which may limit myocardial salvage despite successful epicardial revascularization.[35,36]

The present study further demonstrated a significant association between final postprocedural TIMI flow grade and follow-up LVEF. Suboptimal TIMI flow has been consistently linked to larger infarct size, reduced myocardial salvage, and unfavorable long-term outcomes.[37,39] In previous investigations, patients with impaired postprocedural TIMI flow exhibited significantly lower predischarge LVEF and reduced survival rates. Achieving optimal TIMI flow likely preserves viable myocardium by improving microvascular perfusion and limiting infarct expansion, thereby promoting more favorable ventricular remodeling.[40]

Based on the strong predictive contributions of baseline LVEF, peak CK-MB, and hypertension, a simplified nomogram incorporating only these three readily available parameters was developed. Unlike most existing risk models, which primarily focus on mortality or composite adverse cardiovascular events, the proposed nomogram was specifically designed to estimate systolic functional recovery. Previous nomogram-based approaches have incorporated a broader range of clinical and laboratory variables to predict post-STEMI outcomes.[41] However, by relying on fewer and more routinely collected parameters, the present model offers a pragmatic and easily applicable tool that may enhance feasibility and generalizability in daily clinical practice. In clinical terms, this nomogram may facilitate early risk stratification at the time of index hospitalization, enabling clinicians to identify patients with a lower likelihood of mid-term LVEF recovery who may benefit from closer follow-up, more aggressive optimization of guideline-directed medical therapy, earlier referral to cardiac rehabilitation, and timely consideration

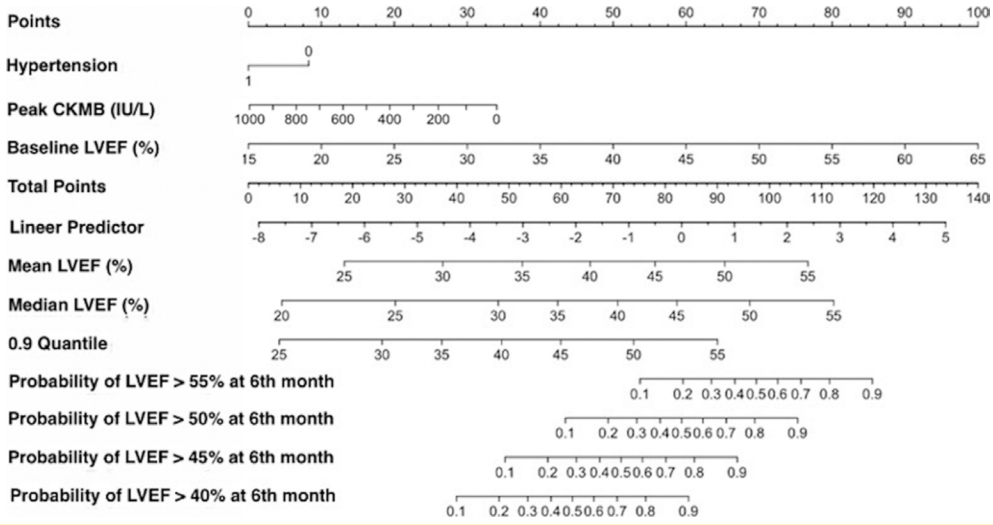

Figure 3. Nomogram for predicting six-month left ventricular ejection fraction (LVEF) after ST-segment elevation myocardial infarction (STEMI).

CK-MB, Creatine kinase–myocardial band; IU/L, International units per liter; LVEF, Left ventricular ejection fraction; STEMI, ST-segment elevation myocardial infarction.

of advanced heart failure surveillance strategies. Moreover, individualized risk estimation may support shared decision-making with patients regarding prognosis and the intensity of post-discharge management.

Limitations

Several limitations of this study should be acknowledged. First, the observational design introduces the potential for residual confounding and selection bias. Second, baseline LVEF was assessed during the acute phase of myocardial infarction and may have been influenced by transient sympathetic activation, potentially leading to overestimation of baseline systolic function. Third, the single-center design and relatively modest sample size may limit the generalizability of the findings. Fourth, variability in angiographic characteristics and procedural strategies may have contributed to heterogeneity. Fifth, post-discharge medication adherence and longitudinal treatment modifications were not systematically assessed, which may have influenced mid-term LVEF recovery. Finally, the backward step-down variable selection approach may increase the risk of overfitting and the exclusion of clinically relevant predictors; therefore, external validation of the proposed nomogram is warranted.

Conclusion

In conclusion, baseline LVEF, peak CK-MB level, age, hypertension, and final TIMI flow grade were identified as independent predictors of left ventricular systolic function at six months following STEMI. The proposed nomogram integrates these variables into a clinically applicable tool that may support individualized risk stratification and optimization of follow-up strategies in STEMI survivors.

Ethics Committee Approval: Ethics committee approval was obtained from Haydarpaşa Numune Training and Research Hospital Clinical Research Ethics Committee (Approval Number: HNEAH-KAEK-2019/165-2858, Date: 02.12.2019).

Informed Consent: Written informed consent was obtained from all participants prior to study inclusion.

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Serum Thiol/Disulfide Homeostasis as a Marker of Left Atrial Remodeling in Atrial Fibrillation

Atriyal Fibrilasyonda Sol Atriyal Yeniden Yapılanmanın Bir Göstergesi Olarak Serum Tiyol/Disülfit Homeostazı

ABSTRACT

Objective: Oxidative stress has been implicated in the pathogenesis of atrial fibrillation (AF), contributing to atrial remodeling through redox imbalance. This study aimed to evaluate the relationship between serum thiol/disulfide homeostasis (TDH) parameters and echocardiographic indices of left atrial (LA) structural remodeling in patients with AF.

Method: This cross-sectional study included 123 patients diagnosed with AF and 58 healthy controls. Demographic, biochemical, and echocardiographic data were collected for all participants. Serum native thiol, total thiol, and disulfide levels were analyzed using a fully automated spectrophotometric method. LA dimensions, volume, sphericity, and volume index were measured using transthoracic echocardiography. Correlation and multiple linear regression analyses were performed to identify factors independently associated with LA volume index.

Results: Patients with AF exhibited significantly increased LA diameters, LA volume, and LA volume index compared with controls (all $P < 0.001$). TDH parameters did not differ significantly between the AF and control groups ($P > 0.05$). Within the AF cohort, native thiol and total thiol levels were inversely correlated with LA longitudinal diameter and LA dimension index, respectively. In multivariate analysis, native thiol level ($\beta = -0.235$, $P = 0.001$), body surface area ($\beta = -0.143$, $P = 0.03$), independently predicted LA volume index.

Conclusion: Native thiol levels showed a modest association with indices of left atrial remodeling in AF. Given the absence of between-group differences and the relatively weak correlations, these findings should be interpreted as hypothesis-generating rather than definitive.

Keywords: Atrial fibrillation, echocardiography, left atrial remodeling, oxidative stress

ÖZET

Amaç: Oksidatif stresin, redoks dengesizliği yoluyla atriyal yeniden yapılanmaya katkıda bulunarak atriyal fibrilasyonun (AF) patogenezinde rol oynadığı gösterilmiştir. Bu çalışmanın amacı, atriyal fibrilasyonu olan hastalarda serum tiyol/disülfit homeostazı (TDH) parametreleri ile sol atriyumun (LA) yapısal yeniden yapılanmasını gösteren ekokardiyografik göstergeler arasındaki ilişkiyi değerlendirmektir.

Yöntem: Bu kesitsel çalışmaya AF tanısı konmuş 123 hasta ve 58 sağlıklı kontrol dahil edildi. Tüm katılımcıların demografik, biyokimyasal ve ekokardiyografik verileri toplandı. Serum doğal tiyol, total tiyol ve disülfit düzeyleri tam otomatik spektrofotometrik bir yöntem kullanılarak analiz edildi. LA boyutları, hacmi, sferisite ve hacim indeksi transtorasik ekokardiyografi ile ölçüldü. LA hacim indeksi ile bağımsız olarak ilişkili faktörleri belirlemek amacıyla korelasyon ve çoklu doğrusal regresyon analizleri yapıldı.

Bulgular: AF hastalarında kontrol grubuna kıyasla LA çapı, LA hacmi ve LA hacim indeksinin anlamlı derecede arttığı saptandı (tüm $P < 0.001$). TDH parametreleri açısından AF ve kontrol grupları arasında anlamlı fark bulunmadı ($P > 0.05$). AF grubunda doğal tiyol ve total tiyol düzeyleri sırasıyla LA longitudinal çapı ve LA boyut indeksi ile ters korelasyon gösterdi. Çok değişkenli analizde doğal tiyol düzeyi ($\beta = -0.235$, $P = 0.001$), vücut yüzey alanı ($\beta = -0.143$, $P = 0.03$) ve LA hacim indeksinin bağımsız belirleyicileri olarak saptandı.

Sonuç: Doğal tiyol düzeyleri, AF'de sol atriyal yeniden yapılanma göstergeleri ile sınırlı düzeyde ilişki göstermektedir. Gruplar arasında anlamlı fark bulunmaması ve korelasyonların görece zayıf olması nedeniyle bu bulgular kesin sonuçlardan ziyade hipotez oluşturucu nitelikte değerlendirilmelidir.

Anahtar Kelimeler: Atriyal fibrilasyon, ekokardiyografi, sol atriyal yeniden yapılanma, oksidatif stres

ORIGINAL ARTICLE
ARAŞTIRMA MAKALESİ

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Atrial fibrillation (AF) represents the most prevalent sustained cardiac arrhythmia worldwide and constitutes a major contributor to cardiovascular morbidity and mortality. The arrhythmia is characterized by disorganized atrial electrical activity, resulting in impaired atrial mechanical function and adverse hemodynamic consequences. In clinical practice, atrial fibrillation is recognized as a condition that significantly increases the risks of ischemic stroke, progression to heart failure, and all-cause mortality, underscoring the importance of elucidating its underlying mechanisms and identifying markers of disease progression.[1,2]

A central feature in the development and persistence of AF is atrial remodeling, a multifaceted process involving structural, electrical, and functional alterations of the atrial myocardium. Structural remodeling of the left atrium (LA), manifested by chamber enlargement, increased atrial volume, and altered geometry, facilitates conduction heterogeneity and promotes re-entrant circuits, thereby sustaining the arrhythmogenic substrate.[3] Echocardiographic evaluation of LA morphology and function has therefore become an essential component of AF assessment. Parameters such as LA diameter, left atrial volume index (LAVI), and LA sphericity index have been shown to carry important diagnostic and prognostic implications across various AF populations.[4,5]

Accumulating data indicate that oxidative stress is a key pathophysiological driver in AF initiation and maintenance.[6,7] Excessive generation of reactive oxygen species (ROS) contributes to atrial fibrosis, ion channel dysfunction, and disruption of intracellular signaling pathways, ultimately leading to electrical instability within the atrial myocardium. In this context, thiol/disulfide homeostasis (TDH) has emerged as a novel and dynamic indicator of systemic redox balance. Thiol groups function as major endogenous antioxidants, neutralizing free radicals, while oxidative conditions promote their conversion into disulfide bonds. The reversible balance between thiol and disulfide forms reflects the adaptive capacity of the antioxidant defense system in response to oxidative challenges.[8] Beyond redox-related mechanisms, recent evidence suggests that systemic inflammatory and metabolic status also play a pivotal role in atrial substrate vulnerability. Composite hematological indices integrating inflammatory and nutritional components have been shown to provide prognostic information in AF. In a contemporary cohort of patients undergoing cryoballoon ablation, Kalenderoğlu et al.[9] demonstrated that the hemoglobin, albumin, lymphocyte, and platelet (HALP) score independently predicted AF recurrence, highlighting the contribution of systemic inflammation and metabolic dysregulation to atrial remodeling and arrhythmia persistence.

Despite growing recognition of oxidative stress in AF pathophysiology, the relationship between TDH parameters and echocardiographic markers of LA structural remodeling remains insufficiently characterized. While prior studies have reported associations between oxidative biomarkers and atrial enlargement or fibrosis, findings regarding TDH are limited and inconsistent. Accordingly, further investigation is warranted to clarify whether alterations in thiol/disulfide balance reflect the extent of atrial structural remodeling in AF.

ABBREVIATIONS

AF	Atrial fibrillation
BSA	Body surface area
CI	Confidence interval
LA	Left atrium
LAVI	Left atrial volume index
LVEF	Left ventricular ejection fraction
OR	Odds ratio
TDH	Thiol/disulfide homeostasis

Therefore, the present study aimed to evaluate the association between serum thiol/disulfide homeostasis parameters and echocardiographic indices of left atrial remodeling in patients with atrial fibrillation. By addressing this relationship, we sought to explore the potential role of TDH as a biochemical correlate of atrial structural changes and to enhance the mechanistic understanding of AF progression.

Materials and Methods

Study Design and Population

This study was designed as a retrospective cross-sectional analysis and comprised 181 consecutive individuals evaluated at a tertiary cardiology outpatient clinic. The study population consisted of 123 patients with a confirmed diagnosis of atrial fibrillation and 58 control subjects. Enrollment was conducted between March 2018 and December 2019. Controls were selected to be comparable in terms of sex distribution, although full age matching could not be achieved. Atrial fibrillation was diagnosed in accordance with contemporary European Society of Cardiology (ESC) guidelines, based on electrocardiographic evidence of irregular RR intervals in the absence of clearly discernible P waves.

Patients were excluded if they had valvular AF, heart failure with reduced left ventricular ejection fraction (LVEF < 50%), moderate or severe valvular heart disease, a history of coronary artery bypass grafting, thyroid dysfunction, acute infectious conditions, hepatic or renal insufficiency, or any known systemic inflammatory disorder. All participants underwent comprehensive clinical evaluation, routine laboratory testing, and transthoracic echocardiographic examination.

Echocardiographic Evaluation

Transthoracic echocardiography was conducted using a Philips EPIQ 7 ultrasound system with a 2.5–3.5 MHz transducer. Patients were examined in the left lateral decubitus position according to standardized imaging procedures.

Left atrial size was evaluated by measuring transverse and longitudinal dimensions in the apical four-chamber view. Left atrial volume was determined using a biplane area–length method and normalized to body surface area to obtain the left atrial volume index. Left atrial geometry was further characterized by calculating the sphericity index, defined as the proportion of the short-axis to long-axis dimensions of the atrial cavity.[10] In addition, routine left ventricular parameters, including end-diastolic diameter, end-systolic diameter, and ejection fraction, were recorded.

Table 1. Demographic and laboratory characteristics of the study population

Variables	AF group (n = 123)	Control group (n = 58)	*P*
Age (years)	68 ± 12	57 ± 13	<0.001*
Male sex, n (%)	67 (54)	32 (55)	0.93
Diabetes mellitus, n (%)	30 (24)	19 (32)	0.23
Hypertension, n (%)	72 (58)	32 (55)	0.66
Body mass index (kg/m²)	28 (25–31)	27 (24–33)	0.96
Body surface area (m²)	1.84 ± 0.16	1.82 ± 0.21	0.41
History of coronary artery disease, n (%)	42 (34)	19 (32)	0.85
AF duration (months)	14 (9–33)	–	–
Mild valvular involvement, n (%)	45 (36.6)	–	–
Non-valvular AF, n (%)	78 (63.4)	–	–
Hemoglobin (g/dL)	13.3 ± 1.9	13.6 ± 1.7	0.38
LDL cholesterol (mg/dL)	97 ± 35	100 ± 36	0.54
TSH (IU/mL)	1.75 (1.0–2.6)	1.42 (0.79–2.07)	0.06
T4 (ng/dL)	1.3 (1.1–1.4)	1.2 (1.1–1.4)	0.38
Creatinine (mg/dL)	0.86 (0.71–1.08)	0.83 (0.67–0.99)	0.30
GFR (mL/min)	83 (64–96)	89 (79–99)	0.02*
Neutrophil-to-lymphocyte ratio (NLR)	2.31 (1.68–3.0)	2.0 (1.5–3.3)	0.60
Red cell distribution width (RDW, %)	14.4 (13.5–15.3)	13.7 (13.1–14.5)	0.001*

AF, Atrial fibrillation; BMI, Body mass index; BSA, Body surface area; CAD, Coronary artery disease; GFR, Glomerular filtration rate; LDL, Low-density lipoprotein; NLR, Neutrophil-to-lymphocyte ratio; RDW, Red cell distribution width; TSH, Thyroid-stimulating hormone. Normally distributed continuous variables are expressed as mean ± standard deviation; non-normally distributed variables are expressed as median (interquartile range). A P-value < 0.05 was considered statistically significant.

Biochemical Analysis

Fasting venous blood samples were collected from all participants following a minimum of 12 hours of fasting. Serum samples were separated by centrifugation and stored at –80°C until biochemical analysis. Serum native thiol, total thiol, and disulfide concentrations were measured using a fully automated spectrophotometric assay as previously described by Erel and Neselioğlu.[8]

Total thiol concentrations were determined after chemical reduction of disulfide bonds, whereas disulfide levels were calculated as half of the numerical difference between total and native thiol concentrations. In addition, disulfide/native thiol, disulfide/total thiol, and native/total thiol ratios were calculated to comprehensively evaluate thiol/disulfide homeostasis.

Statistical Analysis

Statistical processing was carried out using the SPSS statistical package (version 29.0; IBM, Armonk, NY, USA). Distributional characteristics of continuous variables were evaluated using both the Kolmogorov–Smirnov and Shapiro–Wilk tests. Variables exhibiting a symmetric distribution are presented as mean values with corresponding standard deviations, whereas asymmetrically distributed data are expressed as medians with interquartile ranges.

For between-group analyses, parametric comparisons were performed using the independent samples t-test when distributional assumptions were met, whereas the Mann–Whitney U test was applied for non-parametric data. Comparisons of categorical variables were conducted using the chi-square test. The relationships between thiol/disulfide homeostasis parameters and echocardiographic measurements were explored using Pearson or Spearman correlation coefficients, depending on variable distribution. To account for potential confounding due to age imbalance between groups, analysis of covariance (ANCOVA) was performed with age included as a covariate.

To determine factors independently associated with the left atrial volume index, multiple linear regression modeling was applied. Receiver operating characteristic analysis was not performed, as the study did not include a dichotomous outcome measure. Statistical significance was defined as a two-tailed P value < 0.05.

Ethical Approval

The research protocol was reviewed and approved by the Yıldırım Beyazıt University Faculty of Medicine Clinical Research Ethics Committee (Approval Number: 26379996/47, Date: 21.01.2018) and was conducted in accordance with internationally accepted ethical standards. Written informed consent was obtained from all participants prior to inclusion in the study.

Results

A total of 181 participants were enrolled in the study, including 123 patients with atrial fibrillation and 58 healthy controls. The mean age of the AF group was significantly higher than that of the control group (68 ± 12 vs. 57 ± 13 years, P < 0.001). The distribution of sex, diabetes mellitus, hypertension, and coronary artery disease was comparable between groups. While hemoglobin, lipid profile, and thyroid parameters were similar, the estimated glomerular filtration rate (GFR) was significantly lower and red cell distribution width (RDW) was higher in the AF group compared with controls (P = 0.02 and P = 0.001, respectively) (Table 1).

Table 2. Echocardiographic parameters of the study population

Echocardiographic parameters	AF group (n = 123)	Control group (n = 58)	*P*
LVEF (%)	55 (50–60)	65 (55–65)	<0.001*
LVEDD (cm)	4.9 (4.5–5.2)	4.5 (4.2–4.9)	0.002*
LVESD (cm)	3.0 (2.5–3.6)	2.6 (2.2–3.1)	0.002*
Interventricular septum (cm)	1.2 (1.1–1.3)	1.1 (1.0–1.2)	0.02*
Posterior wall thickness (cm)	1.2 (1.0–1.2)	1.1 (1.0–1.2)	0.02*
LA transverse diameter (cm)	5.1 ± 0.9	4.1 ± 0.7	<0.001*
LA longitudinal diameter (cm)	6.5 ± 0.9	4.9 ± 0.8	<0.001*
LA dimension index	2.6 ± 0.5	1.9 ± 0.3	<0.001*
LA sphericity index	0.7 ± 0.1	0.8 ± 0.1	0.04*
Log (LA volume) (mL)	1.91 ± 0.19	1.57 ± 0.21	<0.001*
Log (LA volume index) (mL/m²)	1.65 ± 0.20	1.31 ± 0.20	<0.001*

AF, Atrial fibrillation; LA, Left atrium; LVEDD, Left ventricular end-diastolic diameter; LVEF, Left ventricular ejection fraction; LVESD, Left ventricular end-systolic diameter. Normally distributed continuous variables are expressed as mean ± standard deviation; non-normally distributed variables are expressed as median (interquartile range). A P-value < 0.05 was considered statistically significant.

Table 3. Serum thiol/disulfide homeostasis parameters of the study population

Parameters	AF group (n = 123)	Control group (n = 58)	*P*
Native thiol (μmol/L)	411 ± 61	428 ± 77	0.11
Total thiol (μmol/L)	443 (399–469)	450 (386–507)	0.23
Disulfide (μmol/L)	13.6 (7.5–18)	10.9 (5.1–16)	0.11
Disulfide/native thiol ratio	0.03 (0.02–0.05)	0.03 (0.01–0.04)	0.07
Disulfide/total thiol ratio	0.03 (0.02–0.04)	0.02 (0.01–0.04)	0.09
Native/total thiol ratio	0.94 (0.91–0.97)	0.95 (0.93–0.98)	0.054

AF, Atrial fibrillation; TDH, Thiol/disulfide homeostasis. Normally distributed continuous variables are expressed as mean ± standard deviation; non-normally distributed variables are expressed as median (interquartile range). A P-value < 0.05 was considered statistically significant.

Table 4. Serum thiol parameters according to atrial fibrillation type

Parameters	Paroxysmal AF (n = 31)	Chronic AF (n = 90)	*P*
Native thiol (μmol/L)	428 ± 52	405 ± 63	0.05
Total thiol (μmol/L)	460 (421–488)	442 (392–464)	0.12
Disulfide (μmol/L)	13.6 (6.4–16.2)	13.7 (7.5–19.3)	0.27
Disulfide/native thiol ratio	0.03 (0.02–0.04)	0.03 (0.02–0.05)	0.16
Disulfide/total thiol ratio	0.03 (0.02–0.04)	0.03 (0.02–0.05)	0.07
Native/total thiol ratio	0.94 (0.93–0.96)	0.94 (0.91–0.97)	0.15

AF, Atrial fibrillation. Normally distributed continuous variables are expressed as mean ± standard deviation; non-normally distributed variables are expressed as median (interquartile range). A P-value < 0.05 was considered statistically significant.

Echocardiographic evaluation revealed that indices of left atrial size and geometry were markedly increased in the AF group (Table 2). Specifically, LA transverse and longitudinal diameters, LA dimension index, and log-transformed LA volume and volume index were all significantly higher in patients with AF compared to controls (all P < 0.001). Conversely, the left ventricular ejection fraction was significantly lower in the AF group (P < 0.001). In addition, the LA sphericity index was slightly but significantly reduced in the AF group (P = 0.04), indicating alterations in atrial geometry associated with AF.

The comparison of serum thiol/disulfide homeostasis parameters between groups demonstrated no statistically significant differences (Table 3). Native thiol, total thiol, and disulfide levels, as well as their derived ratios (disulfide/native thiol, disulfide/total thiol, and native/total thiol), were comparable between the AF and control groups (all P > 0.05).

When AF patients were stratified according to arrhythmia type, no significant differences in TDH parameters were found between paroxysmal and chronic AF subgroups (Table 4). Mean native and total thiol levels were slightly lower in the chronic AF subgroup but did not reach statistical significance (P = 0.05 and P = 0.12, respectively).

Correlation analyses in the AF cohort demonstrated significant inverse relationships between serum thiol parameters and echocardiographic markers of LA remodeling (Table 5). Native thiol levels showed a negative correlation with LA longitudinal diameter (r = –0.19, P = 0.03), while total thiol levels were

Table 5. Correlation analysis between serum thiol parameters and echocardiographic left atrial indices in patients with AF

Variables	Total thiol (r)	*P*	Native thiol (r)	*P*	Disulfide (r)
LA transverse diameter	-0.08	0.37	-0.09	0.31	0.06
LA longitudinal diameter	-0.16	0.07	-0.19	0.03*	0.10
LA dimension index	-0.18	0.03*	-0.17	0.055	0.07
LA sphericity index	+0.10	0.26	+0.10	0.26	-0.01
Log (LA volume)	-0.12	0.16	-0.16	0.07	0.15
Log (LA volume index)	-0.13	0.12	-0.16	0.06	0.12

AF, Atrial fibrillation; LA, Left atrium. Correlation coefficients (r) are presented with corresponding p-values. A P-value < 0.05 was considered statistically significant.

Table 6. Multivariable linear regression analysis for predictors of left atrial volume index

Variables	B	SE	β	*P*	95% CI
Native thiol	–0.088	0.042	–0.201	0.036	–0.171 to –0.006
Age	–0.456	0.202	–0.212	0.026	–0.857 to –0.056
Body surface area	–36.690	15.057	–0.218	0.016	–66.506 to –6.874
AF duration	0.578	0.441	0.118	0.192	–0.294 to 1.451

Values represent unstandardized regression coefficients (B), standard errors (SE), standardized beta coefficients (β), and 95% confidence intervals (CI) derived from multivariable linear regression analysis.

inversely correlated with the LA dimension index (r = –0.18, P = 0.03). Other correlations between TDH indices and LA parameters were not statistically significant.

To account for the age imbalance between groups, analysis of covariance was performed with age included as a covariate. After adjustment for age, native thiol, total thiol, and disulfide levels remained comparable between AF patients and controls (native thiol: P = 0.639; total thiol: P = 0.475; disulfide: P = 0.291).

In multivariable linear regression analysis, native thiol level (B = –0.088, β = –0.201, P = 0.036), age (B = –0.456, β = –0.212, P = 0.026), and body surface area (B = –36.690, β = –0.218, P = 0.016) were independently associated with left atrial volume index (Table 6).

Discussion

In the present study, we evaluated the relationship between serum thiol/disulfide homeostasis parameters and echocardiographic indicators of left atrial remodeling in patients with atrial fibrillation. Three principal findings were identified. First, patients with AF demonstrated markedly increased LA dimensions and volumes compared with control subjects, indicating the presence of advanced structural remodeling. Second, TDH parameters did not differ significantly between AF patients and controls or across AF subtypes. Third, within the AF cohort, lower native and total thiol levels were significantly associated with greater LA dimensions, and native thiol level remained associated with LA volume index in multivariable analysis, although the strength of this association was modest.

Atrial fibrillation is widely recognized as both a cause and a consequence of atrial structural remodeling. Progressive LA enlargement and alterations in atrial geometry reflect underlying myocardial stretch and fibrotic changes, which in turn facilitate conduction heterogeneity and re-entrant electrical activity, thereby sustaining the arrhythmia.[11] Previous investigations have consistently shown that LA volume index provides superior prognostic information compared with simple linear or area-based measurements, particularly with respect to cardiovascular morbidity and mortality.[12,13] In this context, our findings further support the close association between structural atrial alterations and the presence of AF.

Oxidative stress has been increasingly implicated in the initiation and maintenance of AF.[14,15] Excessive generation of reactive oxygen species may induce electrophysiological instability by modifying ion channel activity, promoting cardiomyocyte apoptosis, and activating profibrotic signaling pathways. Thiol/disulfide homeostasis represents a dynamic marker of systemic redox status, reflecting the reversible oxidation of thiol groups to disulfide bonds.[16] In the present study, the inverse relationship between serum thiol levels and echocardiographic indices of LA remodeling suggests that oxidative imbalance may contribute to atrial structural changes. These observations are in line with previous reports demonstrating associations between oxidative and inflammatory biomarkers, such as oxidized low-density lipoprotein (LDL) and high-sensitivity C-reactive protein, and LA enlargement or pulmonary vein dilation in patients with AF.[17]

Notably, although TDH parameters did not differ significantly between groups, the observed negative correlations between thiol levels and LA dimensions indicate that oxidative stress may exert gradual and cumulative effects on atrial structure rather than presenting as overt biochemical alterations. Importantly, age-adjusted analyses using ANCOVA confirmed that the absence of differences in TDH parameters between AF patients and controls was not confounded by age, strengthening the robustness of the primary findings. This observation may be related to the chronic nature of AF and the dynamic equilibrium of thiol/disulfide exchange. In accordance with inflammatory mechanisms previously linked to atrial remodeling and AF recurrence after cardioversion, oxidative imbalance may

represent an additional biochemical reflection of atrial substrate alteration.[18,19] Furthermore, consistent with earlier studies, acute variations in redox markers may be more pronounced during paroxysmal AF episodes, whereas chronic AF may reflect a relatively stabilized oxidative state.[20,21] Consequently, single time-point measurements may underestimate the overall burden of oxidative stress in these patients.

Beyond oxidative stress, structural and clinical factors such as body surface area (BSA) and AF duration were independently associated with LA volume index in our regression analysis. This observation is consistent with prior evidence indicating that LA size is influenced by both anatomical characteristics and disease-related factors.[22,23] The identification of native thiol as an independent determinant of LA volume index suggests that redox imbalance may serve as a biochemical marker reflecting the extent of atrial remodeling. Given the established prognostic value of LA volume index in predicting stroke and cardiovascular mortality,[24,25] incorporation of TDH parameters into clinical assessment may offer additional value for early detection of remodeling and risk stratification.

Overall, our findings support the concept that oxidative stress contributes to atrial remodeling in patients with AF. Although serum TDH parameters were comparable between groups, their inverse association with LA measurements and the independent predictive role of native thiol for LA volume index highlight a potential mechanistic link between redox imbalance and atrial structural changes.

Limitations

This study has certain limitations that warrant consideration. Primarily, its cross-sectional nature does not allow conclusions regarding a cause–effect relationship between oxidative imbalance and left atrial remodeling. Accordingly, the observed associations cannot determine whether thiol depletion contributes to atrial enlargement or represents a consequence of structural remodeling.

Second, biochemical parameters were assessed at a single time point. Given the dynamic nature of thiol/disulfide balance and its potential fluctuation during acute AF episodes, serial measurements might have provided a more comprehensive assessment of oxidative status.

Third, this study was conducted at a single tertiary center with a relatively modest sample size, which may limit the generalizability of the findings. Larger, multicenter prospective studies involving more diverse patient populations are warranted to validate and extend these results.

An important limitation of this study is the significant age difference between the AF and control groups, which may have influenced both oxidative stress markers and echocardiographic parameters. Although age was considered in multivariable analyses, residual confounding cannot be excluded.

Conclusion

In this study, patients with atrial fibrillation demonstrated significant left atrial structural remodeling, as evidenced by increased LA diameter, volume, and sphericity index compared with healthy controls. Although serum thiol/disulfide homeostasis parameters did not differ significantly between the two groups, native thiol levels were independently associated with LA volume index, indicating a potential link between oxidative imbalance and atrial structural changes.

These findings suggest that native thiol, a key component of the antioxidant defense system, may serve as a biochemical marker reflecting the extent of atrial remodeling in AF. Given the established prognostic importance of LA volume index in cardiovascular outcomes, integrating TDH parameters into clinical evaluation might enhance early risk stratification and provide insights into the oxidative mechanisms underlying AF progression. Further prospective, large-scale studies are warranted to validate these associations and explore the temporal relationship between redox status and atrial remodeling.

Ethics Committee Approval: Ethics committee approval was obtained from Yıldırım Beyazıt University Faculty of Medicine Clinical Research Ethics Committee (Approval Number: 26379996/47, Date: 21.01.2018).

Informed Consent: Written informed consent was obtained from all participants prior to inclusion in the study.

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Psychometric Evaluation of the Turkish Version of the Control Attitudes Scale–Revised for Heart Disease

Kalp Hastalıkları için Kontrol Tutumları Ölçeği-Revize'nin Türkçe Versiyonunun Psikometrik Değerlendirmesi

ABSTRACT

Objective: Perceived control is an important issue that needs to be addressed in patient groups with chronic diseases where self-management plays a critical role. Patients with a high perception of control demonstrate greater success in symptom management and adaptation to chronic illness.

Method: This methodological adaptation study was conducted to investigate the psychometric properties of the Control Attitudes Scale–Revised in Turkish patients with heart failure. In the reliability analysis of the scale, Cronbach's alpha was used to determine internal consistency, and item homogeneity was assessed using item-total and item-item correlations. For validity testing, confirmatory factor analysis, hypothesis testing for known relationships, discriminant validity, and test-retest reliability were applied.

Results: Confirmatory factor analysis (CFA) of the scale demonstrated supportive fit indices for the original Control Attitudes Scale–Revised (CAS-R) single-factor structure ($P < 0.001$ for all items). The Cronbach's alpha reliability coefficient of the Turkish version of the Control Attitudes Scale–Revised (TCAS-R) scale was found to be 0.99. In the hypothesis test used for construct validity, a moderate positive relationship ($r = 0.568$, $P < 0.05$) was found between the Turkish version of the Control Attitudes Scale–Revised and the nine-item European Heart Failure Self-Care Scale.

Conclusion: Based on these results, it can be concluded that the Turkish version of the Control Attitudes Scale–Revised is a valid and reliable tool for use with Turkish patients. The findings are expected to be useful for both healthcare professionals and patients.

Keywords: Control attitudes, heart failure, psychometric, reliability, validity

ÖZET

Amaç: Algılanan kontrol, öz yönetimin önemli olduğu kronik hastalıkları olan hasta gruplarında ele alınması gereken bir konudur. Kontrol algısı yüksek olan hastalar, kronik hastalık semptomlarının yönetimi ve hastalığa uyum konusunda yüksek başarı oranına sahiptir.

Yöntem: Bu çalışma, kalp yetersizliği olan Türk hastalarda Kontrol Tutumları Ölçeği-Revize'nin psikometrik özelliklerini araştırmak için tasarlanmış metodolojik bir uyarlamadır. Ölçeğin güvenilirlik testlerinde, iç tutarlılığı belirlemek için Cronbach alfa katsayısı kullanılmış, madde homojenliği ise madde-toplam ve madde-madde korelasyonları kullanılarak değerlendirilmiştir. Ölçeğin geçerlilik testlerinde ise doğrulayıcı faktör analizi ve bilinen ilişkiler için hipotez testi, ayırt edici geçerlilik ve test-tekrar test güvenilirliği kullanılmıştır.

Bulgular: Ölçeğin doğrulayıcı faktör analizi (CFA) testi orijinal CAS-R'nin tek faktörlü yapısının destekleyici uyum indeksleri ile sonuçlanmıştır (tüm maddeler için $P < 0,001$). Ölçeğin Cronbach alpha güvenilirlik katsayısı 0,99 olarak hesaplanmıştır. Yapı geçerliliği için kullanılan hipotez testinde Türkçe Kontrol Tutumları Ölçeği-Revize ile dokuz maddelik Avrupa Kalp Yetersizliği Öz Bakım Ölçeği arasında $r = 0,568$ ($P < 0,05$) orta düzeyde korelasyon saptanmıştır.

Sonuç: Bu sonuçlara dayanarak, Kontrol Tutumları Ölçeği-Revize'nin Türk hastalar için uygun ve güvenilir bir araç olduğu sonucuna varılabilir. Bulguların hem sağlık profesyonelleri hem de hastalar için yararlı olması beklenmektedir.

Anahtar Kelimeler: Kontrol tutumları, kalp yetersizliği, psikometrik, güvenilirlik, geçerlilik

ORIGINAL ARTICLE
ARAŞTIRMA MAKALESİ

This study was presented as an oral presentation at the 12th International Acharaka Congress on Medicine, Nursing, Midwifery, and Health Sciences, held in September 2025.

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Perceived control is defined as the belief that individuals have the ability to regulate and influence their own behavior and that this ability can be improved through appropriate training and counseling.[1] Patients with a high perception of control demonstrate greater success in symptom management and disease adaptation.[2] Studies have shown that a decrease in perceived control is associated with an increase in anxiety and depression, which negatively affects quality of life.[3,4] In this respect, perceived control is an issue that should be addressed in patient groups with chronic diseases where self-management is important.[5,6]

Heart failure (HF), a common chronic disease, occurs when the heart is unable to pump sufficient blood throughout the body.[6] As HF is not fully curable and patients must live with the condition for life, it is common for individuals to experience a sense of loss of control. This loss has been shown to have a detrimental effect on patients' health-related quality of life.[7] However, identifying the modifiable determinants of perceived control can provide guidance for planning effective interventions to promote health and improve health-related quality of life. Therefore, individuals with HF should adapt to the disease and adopt lifestyle changes to manage the condition effectively. Patients' psychological state and their management of disease symptoms play an important role in this process.[6,8]

The Control Attitudes Scale–Revised (CAS-R) was developed by Moser et al.[9] to measure patients' perceptions of control over heart failure. The CAS-R is a psychometric tool that assesses patients' perceived control over their current health problems. To date, the psychometric properties of the CAS-R have been evaluated in Portuguese, Mandarin Chinese, Korean, and Brazilian samples.[3,10-13] Our study aimed to conduct a psychometric evaluation of the CAS-R in Turkish patients with heart failure.

Materials and Methods

Language Translation Procedure

The first author obtained permission to translate the scale from the developer of the original instrument.

The linguistic validity of the scale was established through three stages, in accordance with recommended guidelines.[14-16] First, the original scale was translated into Turkish and back-translated into English by a certified linguist who is fluent in both English and Turkish. At the second stage, the Turkish version of the scale was translated back into English by a native English speaker who had never seen the original English version of the scale. At the third stage, the latest version of the scale was subjected to independent evaluation by experts participating in the study to ensure conceptual equivalence.[17-18] The experts involved in the translation process were from various institutions to ensure impartiality. The scale was sent to the experts via e-mail. The expert panel consisted of five experts, including nursing professors and a cardiology clinic nurse. All panelists had extensive knowledge of both languages and their respective cultures. According to the manual, each item of the Turkish version of the CAS-R was independently evaluated by five experts for language and content validity.[14-16]

Study Design

The present study was methodologically designed in accordance with the COSMIN (COnsensus-based Standards for the selection of health Measurement Instruments) methodology to evaluate the cross-cultural adaptation of the CAS-R and the psychometric properties of the Turkish version.[15,17]

ABBREVIATIONS

CAS-R	Control Attitudes Scale–Revised
CFA	Confirmatory factor analysis
CFI	Comparative fit index
GFI	Goodness-of-fit index
HF	Heart failure
I-CVI	Item content validity index
IFI	Incremental fit index
NFI	Normed fit index
NYHA	New York Heart Association
RFI	Relative fit index
RMR	Root mean square residual
RMSEA	Root mean square error of approximation
S-CVI	Scale content validity index
TCAS-R	Turkish version of the Control Attitudes Scale–Revised
TLI	Tucker-Lewis Index

Study Sample

The study sample consisted of patients with heart failure aged 18 years and older who were hospitalized in a hospital in Ankara, Türkiye, and classified into New York Heart Association (NYHA) classes I through IV.

Data were collected between November 2022 and November 2023. Participants were Turkish-literate patients without diagnosed cognitive impairment, dementia, or severe mental illness. Prior to the main data collection, the language validity of the scale was assessed by administering the questionnaire to five patients with heart failure. The study was completed with a total of 117 heart failure patients.

Data Collection

In this study, data were collected using the Patient Information Form, the Turkish Control Attitude Scale–Revised (TCAS-R), and the Turkish version of the nine-item European Heart Failure Self-Care Behaviour Scale. After the participants were verbally informed about the study by the researcher, their written informed consent was obtained, and the measurement tools were administered. The participants completed the paper-based instruments in approximately 15 minutes.

Measures

Patient Information Form

This form, developed by the researchers based on the literature, consists of nine questions related to age, gender, educational status, marital status, family type, comorbid diseases, medication use, and NYHA functional class.[9,19,20]

Turkish Control Attitudes Scale–Revised (TCAS-R)

This scale is derived from the Attitude Control Scale and the Cardiac Attitudes Index developed by Moser et al.[9] The scale consists of eight items, each scored from 1 to 5. Two items (items 5 and 8) are reverse-coded. The total score obtained from the scale ranges from 8 to 40, with higher scores indicating a higher perception of control. The CAS-R is used to identify current health problems related to heart disease that patients perceive to be within their control. The Cronbach's alpha value of the original

scale was reported as 0.76.9 In this study, the Cronbach's alpha coefficient of the Turkish CAS-R was found to be 0.99.

Nine-Item European Heart Failure Self-Care Behaviour Scale (EHFScBS-9)

This psychometric instrument was originally developed by Jaarsma et al.[19] and later adapted into Turkish by Yıldız and Erci.[20] The scale consists of nine items, each scored from 1 to 5. The scale does not have a cut-off point. Higher scores indicate better self-care behavior. There are no reverse-coded items in the scale. The scale has two subdimensions. Items 2, 4, 9, 3, and 6 constitute the first subdimension (counseling behavior), while items 8, 7, 5, and 1 constitute the second subdimension (adherence to treatment). The Cronbach's alpha value of the original scale was reported as 0.82,[20] while it was 0.91 in this study.

Statistical Analysis

The data obtained in this study were analyzed using the IBM Statistical Package for the Social Sciences (SPSS, version 24.0, Armonk, NY, USA) and IBM SPSS AMOS 24 (IBM Corp., Armonk, NY, USA) software. Descriptive data were used to describe the characteristics of the patients participating in the study. Skewness and kurtosis values were examined to determine whether the scale items showed a normal distribution. According to the relevant literature, skewness and kurtosis values between + ±1.5 or ±2.0 are considered indicative of normal distribution. The analysis showed that the scale items were normally distributed.[21,22]

In this study, only confirmatory factor analysis (CFA) was applied to test the construct validity of the scale. Within the scope of the analysis, structural relationships or causal pathways between latent variables were not examined. Therefore, no structural model was established within the framework of structural equation modeling (SEM) in this study; the analysis focused solely on the measurement model. Confirmatory factor analysis is a measurement model approach within the general framework of structural equation modeling that tests the fit of observed variables to a predefined factor structure.[23,24] In addition, the goodness-of-fit index (GFI), comparative fit index (CFI), root mean square residual (RMR), root mean square error of approximation (RMSEA), normed fit index (NFI), incremental fit index (IFI), Tucker-Lewis index (TLI), and chi-square/degrees of freedom (χ^2/df) were used to evaluate model fit.[25] Pearson correlation analysis was used to assess construct validity through hypothesis testing.[17] The internal consistency of the scale was evaluated using Cronbach's alpha reliability coefficient.[26] Additionally, item-total correlations and inter-item correlations were examined to assess item reliability.[27] Discriminant validity and test-retest reliability were assessed to evaluate the validity of the Turkish CAS-R.[14]

Ethical Consideration and Permissions

Permission to conduct the study was obtained from the developer of the original scale through electronic correspondence. Ethical approval was obtained from Lokman Hekim University Scientific Research Ethics Committee (Approval Number: 2022/180, Date: 15.11.2022). After the patients were informed about the research, both verbal and written informed consent were obtained from the participants. The study was conducted in accordance with the principles of the Declaration of Helsinki. No artificial intelligence tools were used during the data collection or manuscript preparation process.

Table 1. Characteristics of the patients (n = 117)

	n	%
Age (years), mean ± SD = 61.17 ± 12.98		
Gender		
Female	39	33.3
Male	78	66.7
Education level		
Primary school	37	31.6
Middle school	6	5.2
High school	57	48.7
University	17	14.5
Marital status		
Single	33	28.2
Married	84	71.8
Family type		
Nuclear family	107	91.5
Extended family	10	8.5
Comorbid diseases		
Yes	98	83.8
No	19	16.2
Medication use		
Yes	110	94
No	7	6
NYHA functional class		
I	14	12
II	40	34.1
III	45	38.5
IV	18	15.4

SD, Standard deviation; NYHA, New York Heart Association.

Results

Patient Characteristics

The present study included 117 patients diagnosed with heart failure. The mean age of the patients was 61.17 ± 12.98 years. Most of the patients (66.7%) were male, 48.7% were high school graduates, 71.8% were married, and 91.5% belonged to nuclear families. Additionally, 83.8% of the patients had comorbid diseases other than heart failure. Among these patients, 41.8% had hypertension, and 94% were taking medication regularly. According to the NYHA functional classification, 34.2% of the patients were classified as Class II and 38.5% as Class III (Table 1).

Validity

Content Validity

In accordance with the guidelines, after the translation stages were completed by linguists and translators, the scale was submitted to experts to evaluate its validity. Experts assessed the content validity of each item using the Davis technique on a 4-point Likert scale ranging from 1 (not relevant) to 4 (very relevant). After

Table 2. Confirmatory factor analysis of the Turkish version of the Control Attitudes Scale–Revised (TCAS-R)

Items and factors		β	Std. β	S. Error	t	*P*
1. I feel helpless about my heart problems.	F1	1.000	0.807			
2. I feel I have a great deal of control over my heart condition.	F1	0.968	0.796	0.060	16.122	< 0.001
3. I am coping effectively with my heart condition.	F1	0.897	0.636	0.074	12.103	< 0.001
4. No matter what I do, or how hard I try, I just cannot seem to get relief from my symptoms.	F1	1.021	0.838	0.059	17.258	< 0.001
5. I have considerable ability to control my symptoms.	F1	0.975	0.815	0.059	16.631	< 0.001
6. When I manage my personal life well, my heart condition does not bother me as much.	F1	0.974	0.675	0.075	13.025	< 0.001
7. I can do many things myself to cope with my heart condition.	F1	0.789	0.647	0.064	12.337	< 0.001
8. If I do everything right, I can successfully manage my heart condition.	F1	0.895	0.756	0.059	15.042	< 0.001

Goodness-of-fit indices	Pre-covariance adjustment values	Post-covariance adjustment values	Acceptable value
χ^2	99.835	50.604	
df	20	18	
χ^2/df (CMIN/DF)	4.992	2.811	$0 \leq \chi^2/df \leq 5$
RMR	0.047	0.029	$0.05 \leq RMR \leq 0.08$
GFI	0.932	0.963	$0.80 \leq GFI \leq 0.95$
NFI	0.936	0.968	$0.90 \leq NFI \leq 1.00$
RFI	0.911	0.950	$0.90 \leq RFI \leq 1.00$
IFI	0.948	0.979	$0.80 \leq IFI \leq 1.00$
TLI	0.927	0.967	$0.80 \leq TLI \leq 1.00$
CFI	0.948	0.979	$0.90 \leq CFI \leq 1.00$
RMSEA	0.110	0.074	≤ 0.08

CFI, Comparative fit index; df, Degrees of freedom; GFI, Goodness-of-fit index; IFI, Incremental fit index; NFI, Normed fit index; RMSEA, Root mean square error of approximation; RMR, Root mean square residual; TLI, Tucker-Lewis index; χ^2, Chi-square.

obtaining evaluations from five experts, content validity analyses were conducted, and the item content validity index (I-CVI) and scale content validity index (S-CVI) were calculated.[18,27]

For the content validity of the CAS-R scale and its items translated into Turkish, the validity index was calculated by dividing by the number of experts after expert opinions were obtained. According to the guidelines, items with a CVI value lower than 0.80 should be removed from the scale.[14,16] In the present study, the CVI value for each item was higher than 0.80.

Corrections were made to items 7 and 8, which had I-CVI values lower than 1, in accordance with expert opinions. In the original scale, item 7 reads, "*Regarding my heart problems, I feel lots of control*." However, the statement "*I feel I have a great deal of control over my heart condition*" was found to be difficult for responders to understand in the direct Turkish translation of the scale. Similarly, in the original scale, item 8 reads, "*Regarding my heart problems, I feel helpless*." However, the statement "*I feel helpless about my heart problems*" was also found to be difficult for responders to understand in the direct translation. The final Turkish wording of these items was reviewed by the researchers, and the most appropriate expressions were selected.

Construct Validity

In this study, confirmatory factor analysis was applied to test the construct validity of the scale. CFA is a measurement model approach within the general framework of structural equation modeling that evaluates the fit of observed variables to a predefined factor structure. Additionally, goodness-of-fit indices were used to assess model fit.[23,24] In converting the model to a conceptual model, it was suggested that the error terms of items 3 and 6 and items 7 and 8 be allowed to covary. The goodness-of-fit criteria for the confirmatory factor analysis are presented below. As part of the modifications made to improve model fit, covariance was specified between the error terms of items 3–6 and 7–8, which belong to the same factor and show high similarity in terms of content and wording. The fact that these items measure similar behavioral and conceptual dimensions may lead to shared variance that cannot be fully explained by the latent variable. The defined error covariances were determined based on theoretical considerations rather than purely statistical reasons and were limited to items within the same factor. The alternative model showed satisfactory fit to the data after modification (Figure 1), and the results are presented in Table 2.

This study demonstrated that the model's goodness-of-fit indices were acceptable for CFA. The χ^2/df value was 2.81. The GFI, NFI, relative fit index (RFI), IFI, TLI, and CFI indices were calculated as 0.96, 0.96, 0.95, 0.97, 0.96, and 0.97, respectively, indicating values slightly above the acceptable thresholds. The RMSEA value was 0.07 and the RMR value was 0.03, both of which fall within the acceptable range.[23,24] The analysis results indicate that the fit statistics obtained from confirmatory factor analysis were acceptable and consistent with the previously determined factor structure of the scale. Overall, the model demonstrated acceptable fit, and the factor loadings and corresponding t-values are presented in Table 2.

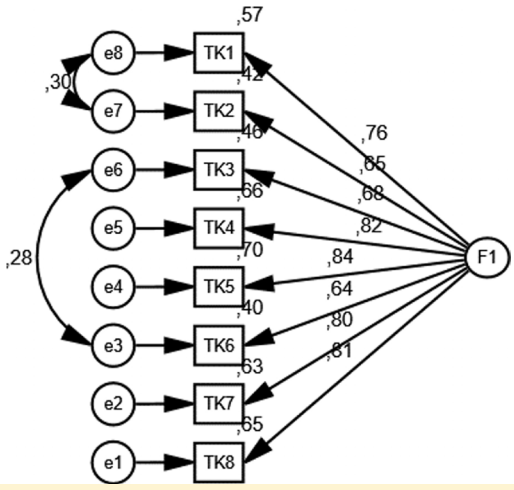

Figure 1. Path diagram of the Turkish version of the Control Attitudes Scale–Revised.

A statistically significant relationship was found between the factor loadings of the items and the relevant factor (P < 0.001). This result was supported by the analysis of all items. Examination of the standardized coefficients showed that the factor loadings were high, the standard error values were low, and the t-values were statistically significant (Table 2).

In hypothesis testing used for construct validity, the aim is verify the construct by examining the correlations between scales that measure related constructs.[14,15,23] In this study, hypotheses proposed in previous studies were used to investigate construct validity.[3,12] To support the construct validity of the scale, the relationship between perceived control and the Turkish version of the EHFScBS-9 was examined using correlation analysis. Accordingly, the objective of this study was to test the hypothesis that the Turkish CAS-R and the Turkish EHFScBS-9 are related. A moderate positive correlation (r = 0.568, P < 0.05) was identified between the two scales. The results of the analysis indicated a strong positive correlation (Table 3).

Table 3. Correlation analysis between the Turkish version of the Control Attitudes Scale–Revised (CAS-R) and the nine-item European Heart Failure Self-Care Behaviour Scale

	TCAS-R
Nine-Item European Heart Failure Self-Care Behaviour Scale	
r	0.568*
p	0.000

*P < 0.01; Pearson correlation analysis.

Reliability

The item-total correlation coefficients ranged between 0.95 and 0.98. When the item–total correlations and Cronbach's alpha values after item deletion were examined, no item was found to decrease the internal consistency of the scale. The Cronbach alpha reliability coefficient for the Turkish CAS-R was 0.99, indicating the scale's high reliability (Table 4).

According to the guidelines, at this stage of validity testing, the Turkish version of the CAS-R should clearly distinguish between two extreme groups defined as the lower 27% and upper 27%. Analyses conducted for the Turkish CAS-R revealed a statistically significant difference between these groups. The independent samples t-test results also showed a significant difference between the two groups (P < 0.001). These findings support the conclusion that the scale is a valid measurement tool (Table 5).

The Turkish CAS-R test yielded a mean score of 34.524, while the retest conducted two weeks later yielded a mean score of 33.952. Statistical analysis of the test–retest results revealed no significant difference between the two measurements. Furthermore, the Intraclass Correlation Coefficient (ICC) indicated strong consistency, with a value of 0.879 (P < 0.001). This result indicates that the Turkish CAS-R demonstrates stability over time (Table 6).

Table 4. Item descriptive statistics and factor loadings for the psychometric evaluation of the Turkish version of the Control Attitudes Scale–Revised

Items	Item-total correlation	Cronbach's alpha if item deleted
1. If I do everything right, I can successfully manage my heart condition.	0.974	0.992
2. I can do many things myself to cope with my heart condition.	0.974	0.992
3. When I manage my personal life well, my heart condition does not bother me as much.	0.971	0.992
4. I have considerable ability to control my symptoms.	0.961	0.992
5. No matter what I do, or how hard I try, I just cannot seem to get relief from my symptoms.	0.961	0.992
6. I am coping effectively with my heart condition.	0.975	0.992
7. I feel I have a great deal of control over my heart condition.	0.981	0.991
8. I feel helpless about my heart problems.	0.955	0.993

Table 5. Comparison of lower and upper 27% groups for the Turkish version of the Control Attitudes Scale–Revised (TCAS-R)

Groups	Lower 27% (n = 32)		Upper 27% (n = 32)		t[a]	SD	*P*
	Mean	SD	Mean	SD			
CAS-R	23.750	7.679	38.156	2.316	-10.161	62	0.000

a, Independent samples t-test; SD, Standard deviation.

Table 6. Test–retest results for the Turkish version of the Control Attitudes Scale–Revised (TCAS-R)

Measurements	Test		Retest		t	*P*[a]	ICC	*P*[b]
	Mean	SD	Mean	SD				
Control Attitudes Scale–Revised	34.524	3.108	33.952	2.783	1.351	0.192	0.879	0.000

a, Dependent samples t-test; b, Intraclass correlation coefficient; ICC, Intraclass correlation coefficient; SD, Standard deviation.

Discussion

The aim of this study was to translate the CAS-R into Turkish and examine its psychometric properties in patients with HF in Türkiye. In evaluating the accuracy and reliability of translated scale items, it is imperative to conduct a rigorous language validity assessment. Such assessments are recommended to be carried out by experts who are professionals in their respective fields.[14,15,17]

CFA is used to examine the structure of the items in the scale and to determine whether the scale demonstrates internal consistency. The analysis indicated that the fit statistics obtained from confirmatory factor analysis were consistent with the previously established factor structure of the scale, with only minor discrepancies. These findings support the construct validity of the previously identified factor structure. However, in the Mandarin version of the scale, the factor loadings of the two inverted items were found to be too low, and these items were therefore removed from the final instrument.[3,12]

According to COSMIN guidelines, confirmatory factor analysis is recommended to examine the factor structure in cross-cultural adaptation studies.[15] In this study, the construct validity of the CAS-R was evaluated using confirmatory factor analysis. After modification, the parameters reached the required thresholds and demonstrated acceptable goodness-of-fit for the 8-item Turkish CAS-R. Subsequently, principal component analysis was conducted, and the results indicated that the optimal structure for the Turkish CAS-R was a single-factor structure, consistent with previous studies. The correlations between the items loading onto the single factor ranged between 0.64 and 0.84 and were found to be consistent with the original factor structure.9

In this study, the hypothesis that perceived control would be related to various outcome measures was examined using the EHFScBS-9 to provide further evidence for construct validity.[14-16] The Korean version of the scale examined the relationships between self-efficacy, self-confidence, and self-care, and reported a moderate positive correlation.[12]

When a scale is adapted into a new language, testing its psychometric properties is essential to establish reliability.[14-16] When evaluating the internal consistency of a Likert-type scale, the Cronbach's alpha coefficient should ideally be close to 1, and for attitude scales it should be above 0.70.[28-30]

According to the reliability analysis, the Cronbach's alpha coefficient of the Turkish CAS-R was 0.99. The high Cronbach's alpha value in this study may be attributed to the small number of items (8), high inter-item correlations, and minor modifications made during the cultural adaptation process. Based on these results, it can be concluded that the scale provides reliable measurements over time. The Cronbach's alpha value of the CAS-R has been reported as 0.76 in the original scale and between 0.65 and 0.93 in other validated versions.[3,9-13]

Our study found that the Turkish CAS-R provides sensitive measurements regarding group differences. According to the manual, distinctiveness is based on the reliability of the adapted scale and the statistical measurement of the score differences between individuals with low and high scores on the scale (defined as two extreme groups: the lower 27% and the upper 27%).[14,31] The findings of this study showed that the Turkish CAS-R successfully distinguishes between these groups, indicating good distinctiveness. Distinctiveness analysis is another parameter recommended in the manual and indicates that the adapted scale is appropriate in terms of reliability.[31] In this study, the aim of the distinctiveness analysis was to determine whether the score differences between individuals with low and high scores on the scale were statistically significant. This distinctiveness analysis has not been reported in other versions of the scale.[3,10-13]

As recommended in the guidelines, the scale was re-administered to 20 patients two weeks later to assess the reliability of the Turkish CAS-R.[14] The ICC is a statistical measure used to determine the proportion of observed variance that cannot be attributed to measurement error. In this study, the ICC value above 0.87 indicated almost perfect reliability.[15,28] This procedure has not been reported in other versions of the scale.[3,10-13]

Limitations

Several limitations should be considered when interpreting the results of this study. First, because the study was conducted in a single hospital, the sample may not represent the entire Turkish population with HF. Second, the original CAS-R scale has been applied to patient groups with different cardiac conditions. However, in this study, the sample was limited to patients with HF. Therefore, these limitations should be taken into account in future research.

Conclusion

The lack of a tool to assess perceived control in Türkiye limits research on this concept among patients. It also prevents the identification of individuals who may require appropriate nursing interventions. The primary aim of nursing interventions is to increase patients' perceptions of control and psychological adjustment while improving their clinical outcomes. Determining the perceived control levels of patients with HF is important for coping with their current health status, facilitating disease management, and improving overall health outcomes. This study represents the first investigation of the psychometric properties of the Turkish version of the CAS-R. The findings indicate that the Turkish CAS-R demonstrates satisfactory reliability and validity in Turkish patients with HF. The use of this reliable and valid instrument is expected to be beneficial for both healthcare professionals and patients.

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A Case of Double-Inlet Left Ventricle Reaching Adulthood Without Surgery

Opere Edilmeden Erişkinliğe Ulaşmış Çift Girişli Sol Ventrikül Olgusu

ABSTRACT

Double-inlet left ventricle (DILV) is a rare congenital heart defect, also referred to as a single-ventricle defect. It has a complex structure in which blood from both atria flows into a single ventricle, accounting for approximately 1.5% of all congenital heart diseases. A 37-year-old female patient with no prior history of cardiac disease visited our outpatient clinic for routine cardiological evaluation. Transthoracic echocardiography (TTE) was performed after a 3/6 pansystolic murmur was heard at the mesocardiac focus and a 3/6 systolic ejection murmur at the pulmonary focus on cardiac auscultation. The patient's TTE revealed that the atrioventricular valves opened into one ventricular chamber in four-chamber apical imaging. There was no noticeable interventricular septum, while a rudimentary right ventricle and a ventricular septal defect (VSD) were observed. A gradient of 38 mmHg was measured in the pulmonary valve, and mild-to-moderate pulmonary stenosis was present. In the transesophageal echocardiography (TEE), a rudimentary interventricular septum and right ventricle were observed. Because the patient did not have any symptoms or cyanosis, she was informed about the potential need for occasional infective endocarditis prophylaxis and phlebotomy, and close medical follow-up was planned. A double-inlet left ventricle is known as a severe congenital heart anomaly that is typically diagnosed symptomatically in childhood and requires surgical intervention. However, very rarely, asymptomatic cases without surgical intervention have been reported in the literature to reach adulthood.

Keywords: Congenital heart diseases, double-inlet left ventricle, pulmonary stenosis, single ventricle, ventricular septal defect

ÖZET

Çift girişli sol ventrikül (DİLV), tek ventrikül defektleri olarak da bilinen, nadir görülen konjenital kalp defektlerindendir ve her iki atriyumdan çıkan kanın tek bir ventriküle aktığı karmaşık bir yapıya sahiptir ve tüm konjenital kalp hastalıklarının yaklaşık %1,5'ini oluşturur. Kalp hastalığı öyküsü olmayan 37 yaşındaki kadın hasta, rutin kardiyolojik değerlendirmeler için polikliniğimize başvurdu. Kardiyak oskültasyonda, mezokardiyak odakta 3/6 pansistolik ve pulmoner odakta 3/6 sistolik ejeksiyon üfürümü duyulması üzerine transtorasik ekokardiyografi (TTE) yapıldı. Hastanın TTE'sinde, dört odacıklı apikal görüntülemede atriyoventriküler kapakların tek bir ventriküler boşluğa açıldığı görüldü. Belirgin bir interventriküler septum görülmezken, rudimenter bir sağ ventrikül ve ventriküler septal defekt (VSD) izlendi. Pulmoner kapakta 38 mmHg'lik bir gradient vardı. Hafif-orta şiddette pulmoner stenoz mevcuttu. Daha sonra yapılan transözofageal ekokardiyografide (TEE) de rudimenter interventriküler septum ve sağ ventrikül gözlendi. Hastanın VSD'sinde şantın küçük düzeyde olması, pulmoner vasküler direncin normal sınırlarda bulunması ve belirgin semptom vermeden, siyanoz gelişmeden erişkin yaşa ulaşması da göz önüne alınarak ayrıca hastaya enfektif endokardit profilaksisi, ara ara flebotomi gerekebileceği anlatılarak yakın tıbbi takip kararı alındı. Çift girişli sol ventrikül, genellikle çocukluk çağında semptomatik olarak teşhis edilen ve cerrahi müdahale gerektiren ciddi bir konjenital kalp anomalisi olarak bilinir. Ancak literatürde, çok nadir de olsa cerrahi müdahale olmaksızın erişkinliğe ulaşan asemptomatik seyirli vakalar bildirilmiştir.

Anahtar Kelimeler: Konjenital kalp hastalıkları, çift girişli sol ventrikül, pulmoner stenoz, tek ventrikül, ventriküler septal defekt

CASE REPORT
OLGU SUNUMU

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Double-inlet left ventricle (DILV) and double-outlet right ventricle (DORV) are rare congenital heart defects, also referred to as single-ventricle defects. They constitute approximately 1.5% of all congenital heart diseases.[1] In 70-75% of DILV cases, the main ventricle is in the form of a left ventricle (Figure 1). In most

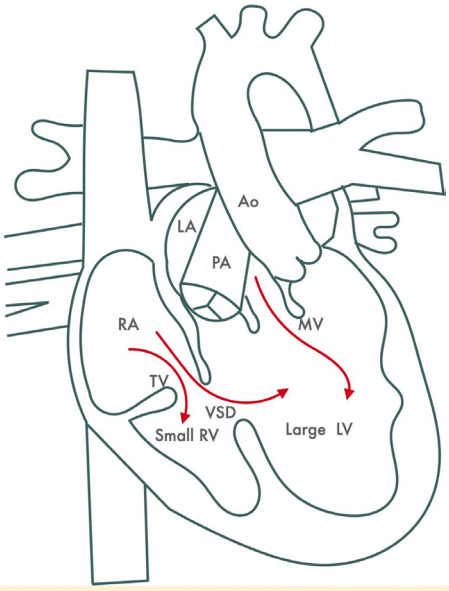

Figure 1. Schematic illustration of double-inlet left ventricle.

Ao, Aorta; LA, Left atrium; LV, Left ventricle; MV, Mitral valve; PA, Pulmonary artery; RA, Right atrium; RV, Right ventricle; TV, Tricuspid valve; VSD, Ventricular septal defect.

patients, the aorta arises from the hypoplastic right ventricle.[2] The prognosis of these cases is usually poor, and patients very rarely reach adulthood.[3] In general, diagnosis is made based on cyanotic symptoms in the early postpartum period, and surgical intervention is often required in the first years of life. Without surgical treatment, these cases usually result in death during infancy. This article presents a case of DILV in a patient who reached adulthood without diagnosis, complaint, or surgery.

Case Report

The 37-year-old female patient with no history of cardiac disease visited our outpatient clinic for routine cardiological assessments. She did not report cardiovascular symptoms such as dyspnea, chest pain, palpitations, or syncope. Her medical history revealed only diabetes mellitus (DM), without other systemic or comorbid cardiac conditions. She had no history of cardiac medication use. The patient demonstrated normal physical and mental appearance and development. Her height was 162 cm, and her weight was 110 kg. The patient's functional capacity was classified as NYHA (New York Heart Association Functional Classification) class I. Her hemoglobin value was 16.0, and her hematocrit was 46.6%. Arterial blood gas analysis showed a partial oxygen pressure of 59.1 mmHg and a saturation of 90.3% (Table 1). Her blood pressure was 123/81 mmHg, heart rate 92 bpm, and respiratory rate 20 breaths per minute. She did not have cyanosis, and finger clubbing was not observed. On physical examination, a 3/6 pansystolic murmur was heard at the mesocardiac focus, and a 3/6 systolic ejection murmur was heard at the pulmonary focus on cardiac auscultation. Electrocardiography (ECG) showed a normal sinus rhythm. The ECG axis was normal, and the left ventricle was dominant. On telecardiography, the cardiothoracic ratio was normal.

ABBREVIATIONS

CT	Computed tomography
DILV	Double-inlet left ventricle
DM	Diabetes mellitus
NYHA	New York Heart Association Functional Classification
TEE	Transesophageal echocardiography
TTE	Transthoracic echocardiography
VSD	Ventricular septal defect

Table 1. The patient's laboratory values on admission

Parameter	Patient value	Reference range
Glucose (mg/dL)	240	74–109
Sodium (mmol/L)	135	135–145
Potassium (mmol/L)	4.7	3.5–5.1
Chloride (mmol/L)	100	98–107
Calcium (mg/dL)	10	8.8–10.2
Creatinine (mg/dL)	0.7	0.7–1.2
Blood urea nitrogen (mg/dL)	18	8–23
AST (U/L)	27	10–50
ALT (U/L)	21	< 41
Albumin (g/dL)	45	35–52
TSH (mUI/mL)	2.1	0.4–4.0
pH	7.40	7.35–7.45
pCO_2 (mmHg)	33	32–48
pO_2 (mmHg)	59 (low)	83–108
sO_2 (%)	90 (low)	95–99
HCO_3 (mmol/L)	22	22–28
White blood cells (10^9/L)	10.1	4.45–10.95
Red blood cells (10^{12}/L)	6.15 (high)	4.54–6.11
Hemoglobin (g/dL)	16 (high)	12–15.9
Hematocrit (%)	46.6 (high)	36–46
Platelet (10^9/L)	364	162–367

ALT, Alanine aminotransferase; AST, Aspartate aminotransferase; HCO_3, Serum bicarbonate; pCO_2, Partial pressure of carbon dioxide; pO_2, Partial pressure of oxygen; sO_2, Oxygen saturation.

Transthoracic echocardiography revealed that the atrioventricular valves opened into a single ventricular chamber in four-chamber apical imaging. No noticeable interventricular septum was seen, while a rudimentary right ventricle and a ventricular septal defect (VSD) were observed (Video 1). Using the Simpson method, the ejection fraction of the common ventricle was calculated as 62%. There was a gradient of 38 mmHg across the pulmonary valve. Mild-to-moderate pulmonary stenosis was present. To observe the patient's cardiac anatomy in more detail, transesophageal echocardiography (TEE) was planned (Figure 2). In the TEE, the aortic valve had a tricuspid structure, the left atrial appendage was clear, and the interatrial septum was intact. A rudimentary interventricular septum and right ventricle were observed. The VSD was identified, and flow through the VSD was observed (Figure 3, Videos 2–6). A large portion of the VSD was covered by the septal leaflet of the tricuspid valve, with only a small

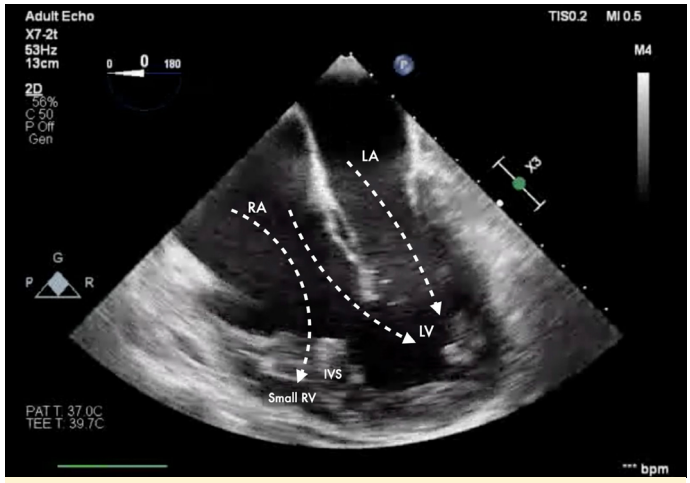

Figure 2. Double-inlet left ventricle in mid-esophageal four-chamber view on transesophageal echocardiography (when the atrioventricular valves are open).

IVS, Interventricular septum; LA, Left atrium; LV, Left ventricle; RA, Right atrium; RV, Right ventricle.

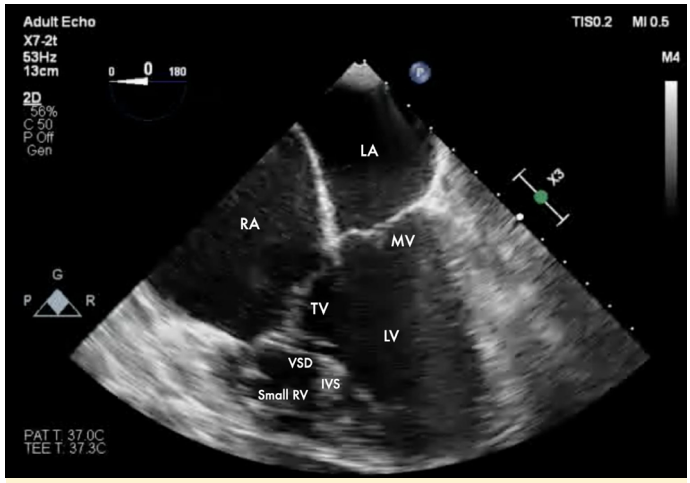

Figure 3. Double-inlet left ventricle in mid-esophageal four-chamber view on transesophageal echocardiography.

IVS, Interventricular septum; LA, Left atrium; LV, Left ventricle; MV, Mitral valve; RA, Right atrium; RV, Right ventricle; TV, Tricuspid valve; VSD, Ventricular septal defect.

segment showing right-to-left shunt flow. The right atrium was noticeably dilated. Cardiac catheterization was recommended. During cardiac catheterization, the pulmonary capillary wedge pressure was 15 mmHg, pulmonary artery pressure was 27/15/21 mmHg, right atrial pressure was 7 mmHg, and aortic pressure was 115/78 mmHg. Pulmonary vascular resistance was 1.9 Wood U, while systemic vascular resistance was 17.8 Wood U. Coronary angiography was also performed during the same session, and normal coronary arteries were observed. No anomalies such as coronary fistulae were detected. Computed tomography (CT) imaging was then performed. The CT results, compatible with echocardiography results, revealed a hypoplastic right ventricle, a rudimentary interventricular septum, and a VSD. No aortopulmonary collaterals were observed, and there was no transposition of the great arteries on CT. As the patient had no symptoms or cyanosis, she was counseled regarding the potential need for occasional infective endocarditis prophylaxis and phlebotomy, and close medical follow-up was recommended.

Discussion

Single-ventricle anomalies may be frequently accompanied by pulmonary stenosis, pulmonary atresia, transposition of the great arteries, or aortic coarctation.[4] Moreover, in some DILV cases, the presence of anatomical and physiological factors that preserve hemodynamic balance may lead to an asymptomatic course of the disease and delayed diagnosis for years. A long-term asymptomatic course may be possible in the presence of pulmonary vascular resistance, atrioventricular valve structure, and minor comorbid anatomical variations.

In patients with single ventricles, anatomical features determine the prognosis, the severity of clinical findings, and the success of surgical methods.[5] Patients should be evaluated for the condition of the atrioventricular valves, major vascular anomalies, and ventricular type. Among single-ventricle defects, the left ventricular type is seen in 70-75% of cases, while the right ventricular type is seen in 10-15%. The ventricular type with both right and left ventricular features is known as the indeterminate type and is seen in 10-20% of cases. In follow-up studies based on anatomical features, a better prognosis was observed in the presence of DILV, transposition of the great arteries, and mild pulmonary stenosis.[6] In this combination, oxygenated blood arriving at the ventricle from the left atrium is directed toward the aorta due to pulmonary stenosis, while an amount of blood sufficient to prevent severe cyanosis but not cause volume overload passes to the pulmonary artery. The patient in our case fits the description of this combination.

Double inlet left ventricle is a rare congenital anomaly in which the atrioventricular valves open into a single left ventricle. The etiology of DILV is not clearly known; however, it is believed to involve genetic predisposition in addition to multiple factors. All patients with DILV have hypoxia, the severity of which is associated with the degree of shunting. In general, clinical symptoms are observed shortly after birth in these patients. The most common signs are dyspnea, tachycardia, cyanosis, and progressive cardiac insufficiency. In advanced cases, erythrocytosis and finger clubbing may develop.[7] These symptoms were not observed in our patient, who had reached adulthood, which is very rare.

Transposition of the great arteries is seen in 80-90% of patients, while pulmonary stenosis is present in 51%.[1] The long-term prognosis of DILV cases depends on the degree of pulmonary stenosis. In unoperated cases without pulmonary stenosis, a broad left-to-right shunt develops, leading to progressive cardiac insufficiency, fatal volume overload, and increased pulmonary blood flow. In the presence of pulmonary stenosis, pulmonary blood flow depends on the severity of the stenosis. Oliver et al.[3] reported that patients with L-transposition and pulmonary stenosis had the most favorable prognosis. In contrast, in a study of 83 unoperated patients with single-ventricle defects, Moodie et al.[8] argued that the severity of pulmonary stenosis did not have a significant effect on mortality.

The prognosis of patients with any form of single-ventricle defect and the onset of clinical symptoms largely depend on pulmonary arterial blood flow and pressure, which are influenced by the presence and severity of pulmonary stenosis and the level of pulmonary vascular resistance.[9,10] The degree of pulmonary blood flow and the severity of cyanosis determine the timing of surgical repair. In this case, mild-to-moderate pulmonary stenosis may have prevented pulmonary hypertension and maintained hemodynamic balance, allowing the patient to reach adulthood without symptoms.

The most important symptom in patients with single-ventricle defects is cyanosis observed after birth. Later in life, nonspecific complaints such as syncope, growth retardation, and exercise intolerance may also be observed. In patients with single-ventricle defects, ventricular systolic function supports both pulmonary and systemic circulation. This ventricular function, which is initially normal, may be impaired by pressure overload, volume overload, and comorbid pathologies.

Echocardiography, cardiac catheterization, and cardiac magnetic resonance imaging can be used in the diagnosis of DILV. In adults with complex congenital heart defects, echocardiography may be insufficient for functional assessments due to distorted ventricular geometry.

The most frequently encountered causes of mortality in these patients are arrhythmias, cardiac insufficiency, and sudden cardiac arrest. The survival rate of patients with single-ventricle defects within the first year of life is 30%.[11] The average life expectancy of non-operated patients ranges from 4 to 14 years.[8] This is why diagnosing and treating these patients at an early age is important.

In single-ventricle defects, step-by-step surgical treatment beginning in the neonatal period is the accepted form of treatment worldwide. It has been reported that the 10-year survival rate in patients suitable for the Fontan procedure reaches 81%.[12] While surgical treatment is unquestionable in neonatal cases, the situation differs for those detected in adulthood. According to Ammash et al.,[13] patients with well-developed pulmonary circulation may reach the sixth decade of life with good functional capacity. Deciding to keep these patients under follow-up is still difficult, as deterioration in their general condition during follow-up may render them unsuitable for the Fontan procedure. Cardiac transplantation is the last-resort treatment option for patients who have lost eligibility for the Fontan procedure.[14] The patient in our case was the fourth reported in adulthood in Türkiye. The other patients reached adulthood after refusing surgery after following diagnosis in childhood. Our patient did not show any symptoms until adulthood and therefore was not diagnosed. This suggests that she is a very rare case.

In the literature, the first report of a patient with a single-ventricle defect reaching adulthood was published by Goldberg et al.[10] Cases similar to ours, in which patients reached adulthood without surgery, have also been reported, although they are rare. While a few patients reaching the fifth to sixth decades of life have been described worldwide, before our case, only three such cases had been reported in Türkiye. Belgi et al.[15] presented a 21-year-old patient with a single-ventricle defect. Demir et al.[16] reported a 28-year-old male patient. Duran Karaduman et al.[17] described a 45-year-old female patient. In reports from outside Türkiye, Benelli et al.[18] reported a 63-year-old female patient diagnosed with congestive heart failure in advanced stages of life. Salame-Waxman et al.[19] reported a 28-year-old male patient diagnosed with pulmonary hypertension and aortic coarctation, who was followed without surgical intervention. David Gregg[20] described a male patient in his 50s with DILV who maintained stable vital signs and had an oxygen saturation of 80%.

The surgical option and the potential future consequences of not undergoing surgery were explained to our patient; however, she declined surgical intervention, stating that she currently had no significant symptoms. We decided to schedule regular follow-ups, as her VSD had only a small shunt, her pulmonary vascular resistance was within normal limits, and she had reached adulthood without noticeable symptoms or cyanosis. The patient was also informed that she might require infective endocarditis prophylaxis and phlebotomy. Diuretic treatment was not necessary.

This case highlights the protective role of pulmonary stenosis and the rare possibility of reaching adulthood without surgery, while underlining the importance of close follow-up and prophylactic measures.

Conclusion

A double-inlet left ventricle is a severe congenital heart disease that is rarely seen in adulthood, is usually diagnosed in childhood, and requires surgical intervention. Our case demonstrated that double-inlet left ventricle has a broad clinical spectrum: some patients may have a long-term asymptomatic course, and in rare instances, the condition may first be diagnosed in adulthood. The importance of routine cardiological assessments, physical examination, and meticulous imaging techniques in diagnosing congenital heart defects with a silent course was also highlighted. Such cases diagnosed in adulthood serve as a reminder of the need to consider congenital heart disease not only in the pediatric population but also in adults.

Ethics Committee Approval: This is a single case report, and therefore ethics committee approval was not required in accordance with institutional policies.

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Video 1. Double-inlet left ventricle in apical four-chamber view on transthoracic echocardiography.

Video 2. Double-inlet left ventricle in mid-esophageal four-chamber view on transesophageal echocardiography.

Video 3. Double-inlet left ventricle in mid-esophageal four-chamber view on transesophageal echocardiography (180º).

Video 4. Double-inlet left ventricle on transesophageal echocardiography.

Video 5. Double-inlet left ventricle on transesophageal echocardiography (slow motion).

Video 6. Double-inlet left ventricle in mid-esophageal four-chamber view on transesophageal echocardiography.

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Left Bundle Branch-Optimized Cardiac Resynchronization Therapy in a Patient with a Carillon Annuloplasty Device: Challenges and Solutions

Karillon Anüloplasti Cihazı Bulunan Bir Hastada Sol Dal Demeti Optimizasyonlu Kardiyak Resenkronizasyon Tedavisi: Zorluklar ve Çözümler

ABSTRACT

Cardiac resynchronization therapy (CRT) improves outcomes in heart failure, but prior interventions like percutaneous mitral annuloplasty may hinder lead placement. We present a 70-year-old male with ischemic cardiomyopathy and severe functional mitral regurgitation who previously received a Carillon device. Due to appropriate coronary sinus branch inaccessibility, left bundle branch optimized cardiac resynchronization therapy (LOT-CRT) was performed. The procedure was successful, with improved QRS duration. This case highlights LOT-CRT as a viable alternative in patients with challenging anatomy, offering physiological pacing when conventional CRT is not feasible.

Keywords: Carillon mitral contour system, conduction system pacing, left bundle branch-optimized cardiac resynchronization therapy

ÖZET

Kardiyak resenkronizasyon tedavisi (KRT), kalp yetersizliği olan hastalarda klinik sonuçları iyileştirmektedir. Ancak daha önce uygulanan perkütan mitral anüloplasti gibi girişimler, sol ventrikül lead yerleşimini engelleyebilir. Bu yazıda, iskemik kardiyomiyopati ve ciddi fonksiyonel mitral yetersizliği olan, daha önce Karillon cihazı implante edilmiş 70 yaşında erkek bir hasta sunulmaktadır. Koroner sinüs yolunun erişilemez olması nedeniyle, sol dal demeti optimize KRT (LOT-KRT) uygulanmıştır. İşlem başarılı olmuş; QRS süresi iyileşmiştir. Bu olgu, anatomik zorlukların bulunduğu hastalarda, konvansiyonel KRT'nin uygulanamadığı durumlarda fizyolojik bir alternatif olarak LOT-KRT yönteminin uygulanabilirliğini göstermektedir.

Anahtar Kelimeler: Carillon mitral kontur sistemi, İletim sistemi pili, sol dal demeti optimizasyonlu kardiyak resenkronizasyon tedavisi

CASE REPORT
OLGU SUNUMU

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Ventricular dyssynchrony is common in patients with reduced left ventricular ejection fraction and contributes to worsening heart failure.[1] Cardiac resynchronization therapy (CRT) has been shown to improve left ventricular function, reduce mitral regurgitation (MR), and enhance clinical outcomes.[2] While conventional biventricular pacing is the standard approach, left bundle branch-optimized cardiac resynchronization therapy (LOT-CRT) has emerged as a promising alternative, utilizing the native conduction system to achieve more physiological ventricular activation.[3]

Mitral regurgitation frequently coexists with heart failure due to left ventricular dilation. The Carillon Mitral Contour System, a transvenous mitral annuloplasty device, has been developed to reduce MR through external annular restriction.[4] However, its presence may complicate the implantation of coronary sinus leads. The literature on LOT-CRT in patients with Carillon devices is sparse, with only one previously reported case.[5] This report presents the second known case, demonstrating that LOT-CRT can be a viable approach in selected patients.

Case Report

A 70-year-old male with ischemic cardiomyopathy and severe functional MR presented with worsening dyspnea and reduced exercise tolerance (New York Heart Association [NYHA] class III) despite optimal guideline-directed medical therapy. Previously, he had Carillon device implantation due to severe MR (2014). However, his clinical condition deteriorated, and coronary artery bypass grafting (CABG) along with mitral valve replacement were performed eight years after (2022) Carillon device implantation.

A year after the cardiac surgery, he had an implantable cardioverter-defibrillator (ICD) implantation for primary prevention. At the time of ICD implantation, a 12-lead electrocardiogram (ECG) showed atrial fibrillation (AF) and right bundle branch block (RBBB) with a QRS duration of 130 ms. One year after ICD implantation, follow-up 12-lead ECG revealed a paced rhythm with a markedly prolonged QRS duration (> 200 ms) (Figure 1). Device interrogation showed a ventricular pacing rate of 78%. Underlying rhythm at 40 bpm revealed AF with complete atrioventricular (AV) block. Transthoracic echocardiography demonstrated a severely reduced left ventricular ejection fraction (LVEF) of 20% with a markedly dilated left ventricle (LV) end-diastolic diameter: 62 mm), consistent with advanced heart failure and significant ventricular dyssynchrony. Additionally, the patient had markedly elevated N-terminal pro-B-type natriuretic peptide (NT-proBNP) levels (11,705 pg/mL), further supporting the presence of severe heart failure.

Given his worsening symptoms, significant ventricular pacing burden, and echocardiographic findings, an upgrade to either conventional CRT or left bundle branch-optimized cardiac resynchronization therapy with defibrillator (LOT-CRT-D) was planned.

ABBREVIATIONS

AF	Atrial fibrillation
AV	Atrioventricular
CABG	Coronary artery bypass graft
CRT	Cardiac resynchronization therapy
CS	Coronary sinus
CSP	Conduction system pacing
ECG	Electrocardiogram
HRS	Heart Rhythm Society
ICD	Implantable cardioverter-defibrillator
LBB	Left bundle branch
LBBAP	Left bundle branch area pacing
LBBB	Left bundle branch block
LOT-CRT-D	Left bundle branch-optimized cardiac resynchronization therapy with defibrillator
LV	Left ventricle
LVEF	Left ventricular ejection fraction
LVSP	Left ventricular septal pacing
MR	Mitral regurgitation
NT-proBNP	N-terminal pro-B-type natriuretic peptide
NYHA	New York Heart Association
RBBB	Right bundle branch block
RV	Right ventricular

After obtaining both verbal and written consent, the patient was taken to the laboratory. A coronary sinus (CS) venogram revealed distal narrowing due to the distal anchor of the Carillon device but a well-developed posterolateral branch, which was considered for lead placement (Figure 2A). However, due to high thresholds obtained from all polarities of the quadripolar lead, we considered adding an additional left bundle branch area lead. Left bundle branch area pacing (LBBAP) was attempted

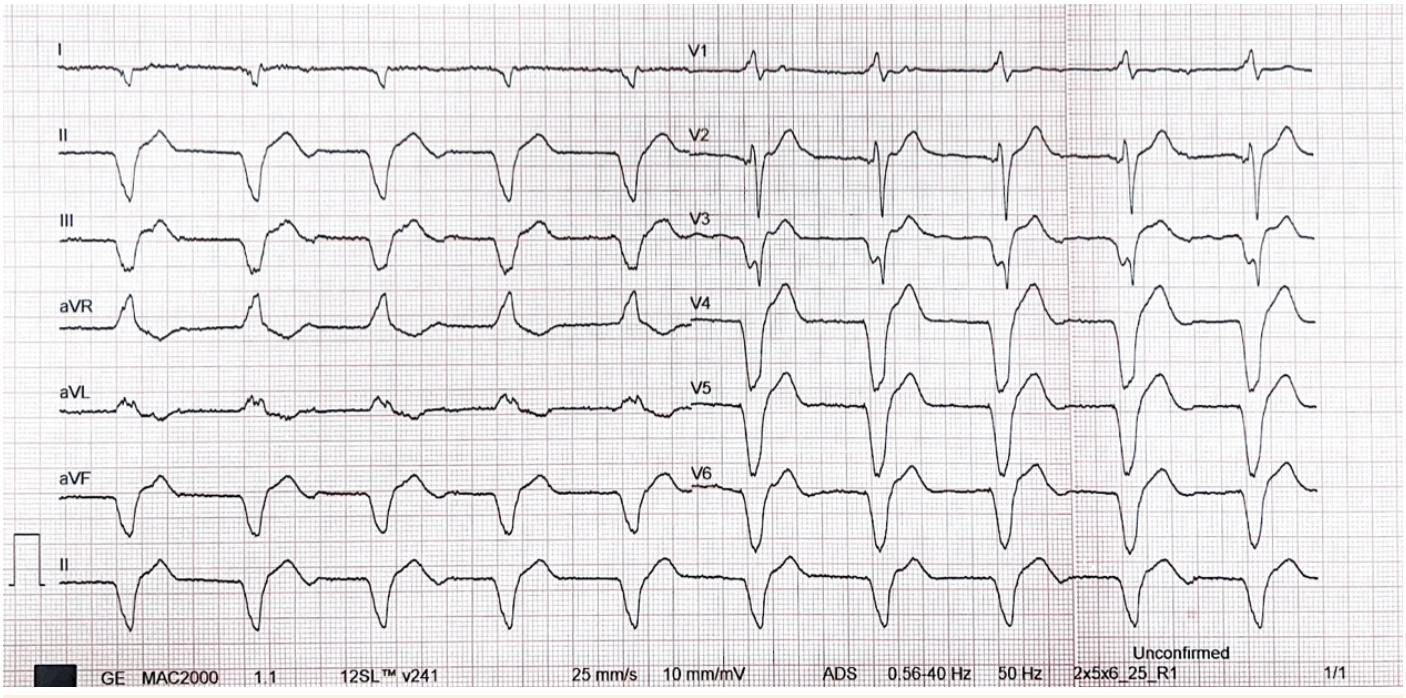

Figure 1. Baseline 12-lead electrocardiogram (ECG) recorded in a ventricular paced rhythm, demonstrating a widened paced QRS complex (240 ms).

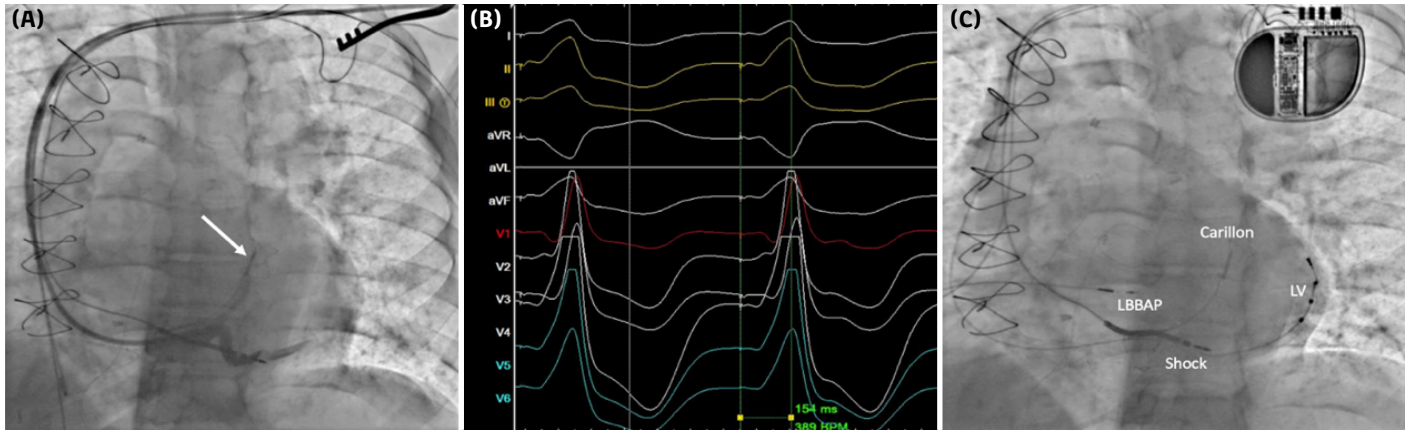

Figure 2. (A) Coronary sinus venography showing the Carillon Mitral Contour System; arrow indicates the distal anchor causing narrowing of the distal CS, with a well-developed posterolateral branch targeted for LV lead placement. (B) Intraprocedural findings during LBBAP, demonstrating an R-wave peak time (RWPT) of 154 ms in lead V5 with a latency of 40 ms. (C) Final fluoroscopic view demonstrating the positions of the LV lead, LBBAP lead, and ICD shock lead relative to the Carillon device, enabling LOT-CRT configuration.

with a Selectra 55/42 sheath and Solia S 60 leads (Biotronik, Germany). Despite multiple attempts, we were unable to penetrate the septum with the stylet-driven lead (Solia S 60). Then we switched to the lumenless lead (Medtronic 3830 lead, Minnesota, MN, US). This time we were able to penetrate the septum and capture the conduction system. Although we had a nice qR morphology in lead V1, the R-wave peak time in leads V5 and V6 was very prolonged (154 ms) (Figure 2B). Therefore, we decided to use both LV and LBBAP leads to obtain better synchronization (Figure 2C). The previous right ventricular (RV) shock lead was DF-4, and due to permanent AF, the LBBAP lead was placed in the atrial port. The device was programmed as DDDR (dual chamber, dual sensed, dual response, rate-modulated) at 60 bpm, paced AV delay 15 ms, and LV > RV offset 100 ms. The LBBaP lead was programmed in a bipolar configuration with a pacing threshold of 1.0 V at 0.5 ms. Final 12-lead ECG showed a paced rhythm with a QRS duration of 155 ms (Figure 3). Procedure and fluoroscopy times were 83 minutes and 21 minutes, respectively. The patient was discharged the day after the procedure without any complication.

Discussion

Heart failure is frequently associated with conduction system abnormalities, including left bundle branch block (LBBB), which can further impair ventricular synchrony and exacerbate symptoms.[6] Cardiac resynchronization therapy has been a cornerstone in addressing these electrical dyssynchronies, leading to improved functional status, reduced hospitalizations, and enhanced survival rates.[7] Despite its benefits, CRT implantation can be technically challenging, especially in patients with prior structural interventions, such as percutaneous annuloplasty devices, which may limit coronary sinus lead placement.[7]

Emerging evidence supports conduction system pacing (CSP), particularly LBBAP, as an alternative to traditional biventricular pacing. The 2023 Heart Rhythm Society (HRS) Conduction System Pacing guidelines acknowledge CSP as an effective alternative when standard CRT is not feasible, offering improved electrical synchrony by engaging the native conduction system.[8] In cases where coronary sinus lead placement is challenging due to anatomic constraints, CSP provides a promising solution for achieving cardiac resynchronization.[9]

The presence of an annuloplasty device in the coronary sinus alters lead placement strategies, necessitating pre-procedural imaging and careful planning. LV lead implantation through the Carillon device might be challenging due to altered geometry and risk of CS dissection. Our case demonstrates the feasibility of LOT-CRT in a patient with a Carillon annuloplasty device, an approach supported by recent reports. Jamil et al.[10] described CRT implantation in a patient with a Carillon device, highlighting the technical feasibility and potential for synergistic benefits. Similarly, Aschacher et al.[5] presented a case of LOT-CRT in a patient with both a Carillon device and a percutaneous tricuspid valve repair, demonstrating that conduction system pacing can be effectively employed in patients with complex structural heart disease. Previous reports of LOT-CRT in patients with Carillon devices are summarized (Table 1). In our case, the decision to pursue LOT-CRT instead of either conventional CRT or LBBAP was guided by two factors: high LV thresholds and very prolonged RWPT (R-wave peak time). Measurement of RWPT in patients with very dilated LV and septal fibrosis (latency) is not reliable. Therefore, without clear demonstration of left bundle branch (LBB) or fascicular potential as well as in the absence of transition, it is difficult to make a diagnosis of whether we achieved left ventricular septal pacing (LVSP) or LBBAP. Therefore, adding an extra LV lead might improve the clinical outcomes if LBBAP alone fails, which has been proposed by experts in the field.[3,11]

Another interesting point in our case was that switching from the stylet-driven lead to the lumenless lead allowed successful septal penetration and capturing of the conduction system. Although stylet-driven leads allow better antegrade force, in selected cases, particularly in cases with septal fibrosis, switching to the lumenless lead might provide better penetration due to the fixed, extended helix.

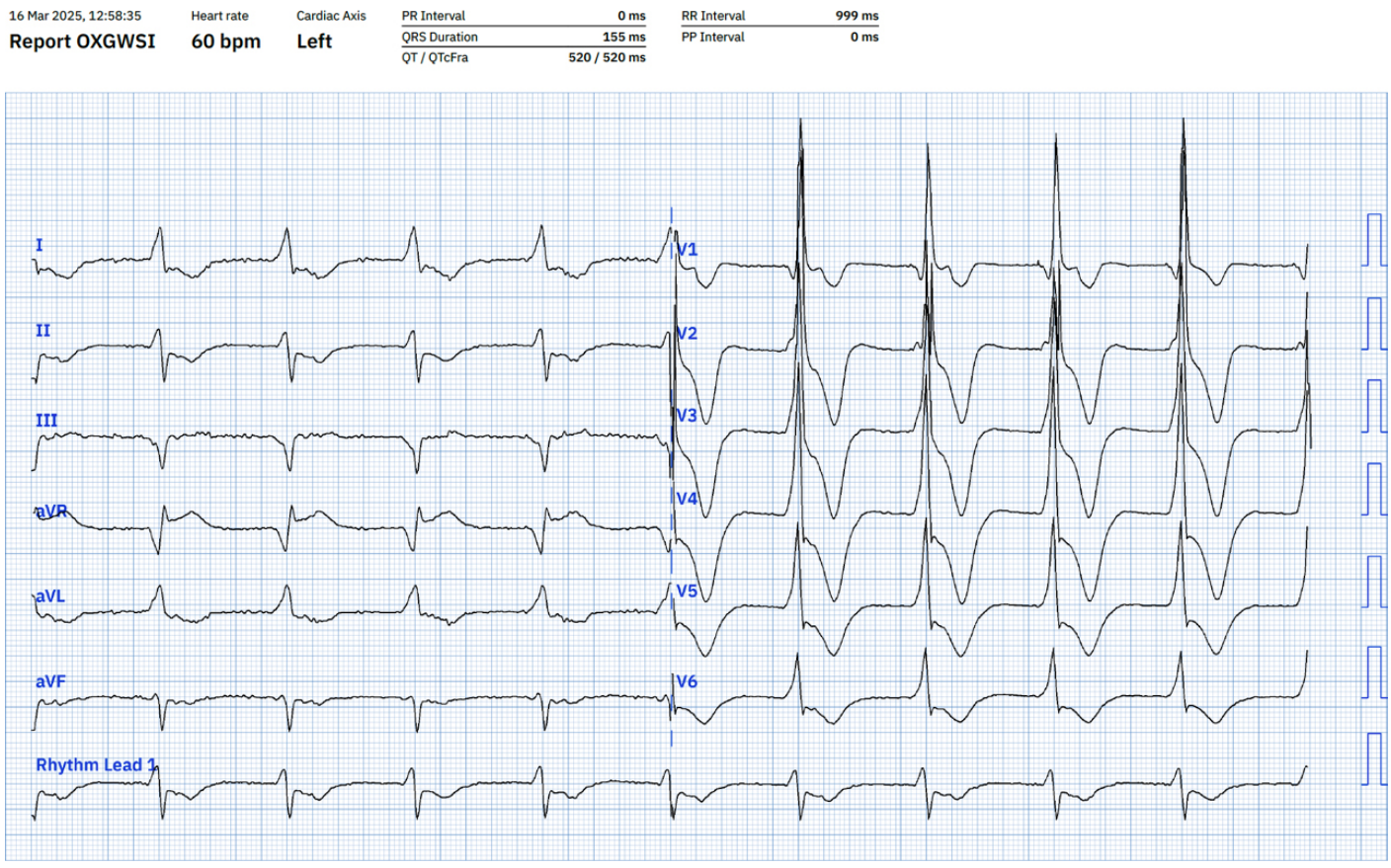

Figure 3. Final ECG following LOT-CRT, showing a narrower QRS complex (155 ms), indicative of improved ventricular synchrony (PMcardio (Powerful Medical, Slovakia), an AI-based ECG interpretation software, was used post-procedurally to confirm QRS narrowing and to standardize measurement of QRS duration. The software was not used to guide intra-procedural decision-making).

Table 1. Clinical, electrocardiographic, and procedure characteristics of patients with carillon annuloplasty device undergoing LOT-CRT

	Present case	Aschacher et al.[5]
Year	2025	2024
Origin	–	Austria
Age, years	70	80
Sex	M	M
Indication	ICM, LBBB	DCM, AVB
AF	Yes	Yes
QRS, ms	240	249
LVEF, %	20	30-35
Procedure	LOT-CRT	LOT-CRT
Lead type	LL	SDL
PD, min	83	NA
FT, min	21	NA
pQRS, ms	155	132
Complications	None	None
FU, weeks	0	2

AF, Atrial fibrillation; AVB, Atrioventricular block; DCM, Dilated cardiomyopathy; FT, Fluoroscopy time; FU, Follow-up; ICM, Ischemic cardiomyopathy; LBBB, Left bundle branch block; LL, Lumenless lead; LOT-CRT, Left bundle branch-optimized cardiac resynchronization therapy; PD, Procedure duration; SDL, Stylet-driven lead.

This case also highlights an important practical point: operators should consider LOT-CRT when conventional BiVP-CRT (biventricular pacing cardiac resynchronization therapy) is not feasible due to high LV lead thresholds or anatomic barriers (e.g., annuloplasty devices), or when LBBAP alone yields inadequate resynchronization such as excessively prolonged RWPT. In such scenarios, combining LV and LBBAP leads offers an effective alternative strategy. Further studies are needed to establish standardized approaches and assess the long-term outcomes of LOT-CRT in patients with transvenous annuloplasty devices. Beyond the present case, the hybrid LOT-CRT approach may also have broader implications for patients undergoing transcatheter valve therapies, such as transcatheter mitral, tricuspid, and combined interventions. As the utilization of percutaneous valve repair strategies increases, challenges related to lead placement and optimal ventricular resynchronization are expected to become more frequent. In such anatomically complex scenarios, hybrid strategies integrating conduction system pacing with conventional coronary venous pacing could provide a reproducible solution for maintaining electrical synchrony. Given these trends, the integration of CSP into heart failure management algorithms will be crucial, and as collective experience grows, LOT-CRT may become an increasingly viable option, aligning with the evolving recommendations of international pacing guidelines.

Conclusion

This case demonstrates that LOT-CRT can be successfully performed in patients with a Carillon annuloplasty device when other standard options are not optimal. Advanced imaging, meticulous procedural planning, and alternative pacing strategies should be kept in mind in patients with complex anatomies.

Ethics Committee Approval: This is a single case report, and therefore ethics committee approval was not required in accordance with institutional policies.

Informed Consent: The author/s confirm that written consent for submission and publication of this case report including image(s) and associated text has been obtained from the patient in line with COPE (Committee on Publication Ethics) guidance.

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Percutaneous Intervention for Left Internal Mammary Artery Side Branch, Subclavian, and Coronary Artery Stenosis in Chronic Coronary Syndrome

Kronik Koroner Sendromda Sol İnternal Mammarian Arter Yan Dalı ile Subklavyen ve Koroner Arter Darlıklarına Yönelik Perkütan Girişim

CASE IMAGE
OLGU GÖRÜNTÜSÜ

A 55-year-old male with hypertension and coronary artery disease (CAD) presented with effort-induced Canadian Cardiovascular Society (CCS) class III angina and severe left arm pain occurring even at rest, without movement. His medical history included coronary artery bypass grafting (CABG) 10 years prior, with aorta-saphenous (Ao-S) grafts to the obtuse marginal (OM) branch, right coronary artery (RCA), and left anterior descending artery (LAD), as well as a left internal mammary artery (LIMA) graft to the intermediate artery (IM). Blood pressure measured 115/65 mmHg in the left arm and 140/70 mmHg in the right arm. Physical examination was unremarkable except for surgical scars on the legs and chest wall. Laboratory findings were within normal limits, except for a low-density lipoprotein (LDL) level of 122 mg/dL. The electrocardiogram (ECG) showed normal sinus rhythm with a left anterior hemiblock. Transthoracic echocardiography revealed a left ventricular ejection fraction of 52%, with hypokinesia of the lateral and inferior walls, and no significant valvular disease. Due to the patient's severe left arm pain, bilateral upper extremity Doppler ultrasonography was performed, revealing significant stenosis in the left subclavian artery with a retrograde flow pattern. Additionally, during exercise provocation testing, a marked drop in blood pressure and worsening pain in the left arm were observed.

The patient's prior medical therapy included acetylsalicylic acid 100 mg/day, metoprolol 50 mg/day, ramipril 5 mg/day, atorvastatin 20 mg/day, trimetazidine 35 mg twice daily, and ranolazine 500 mg twice daily. Despite this comprehensive anti-ischemic regimen, the patient continued to experience anginal symptoms. Coronary and peripheral angiography revealed an occluded RCA and circumflex artery, with 70% stenosis at the Ao-S-OM anastomosis (Figure 1A), multiple lesions in the LAD, and an occluded Ao-S-LAD graft. The LIMA-IM graft showed no stenosis. However, a well-developed side branch of the LIMA (Figure 1B) was causing a significant reduction in coronary flow due to the coronary steal phenomenon (Figure 1C). Subclavian artery angiography also demonstrated severe proximal stenosis (Figure 1D).

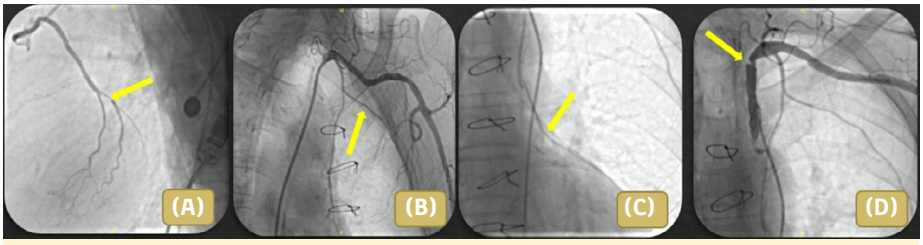

Figure 1. (A) Severe stenosis in the aorta-saphenous (Ao-S) to obtuse marginal (OM) graft. This in-graft narrowing reduces coronary perfusion and contributes to anginal symptoms. (B) Well-developed side branch of the left internal mammary artery (LIMA). This abnormal branch causes myocardial ischemia by diverting blood from the main coronary flow (coronary steal). (C) Coronary steal syndrome caused by the LIMA side branch. The image shows how the side branch from the LIMA diverts graft flow. (D) Severe stenosis in the proximal left subclavian artery. This narrowing reduces total blood flow to the LIMA.

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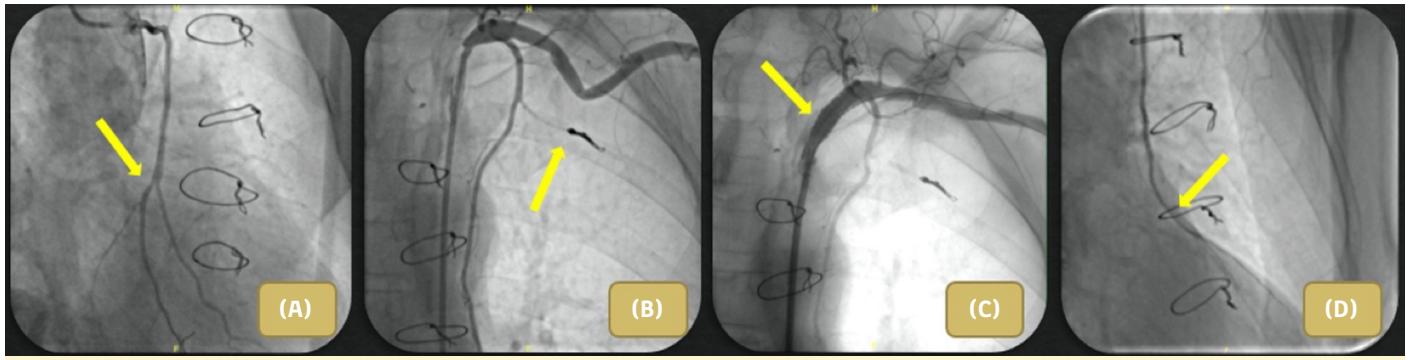

Figure 2. (A) Drug-eluting stent implantation for severe stenosis in the aorta-saphenous (Ao-S) to obtuse marginal (OM) graft. (B) Complete occlusion of the left internal mammary artery (LIMA) side branch following coil embolization. Blood flow through the side branch is fully eliminated after embolization. (C) Peripheral stent implantation in the proximal left subclavian artery. (D) Improved flow through the internal mammary artery (IMA) after subclavian artery stent implantation and LIMA side branch coil embolization. Coronary perfusion is significantly improved following the intervention.

The LIMA side branch was diverting a substantial portion of blood flow (steal phenomenon), thereby reducing blood flow to the LIMA-IM graft and contributing to myocardial ischemia. Additionally, the severe stenosis in the subclavian artery further limited total blood flow to the entire LIMA, exacerbating graft dysfunction. These two pathologies (the LIMA side branch and subclavian stenosis) acted synergistically to worsen coronary steal syndrome. Embolization of the LIMA side branch was planned to eliminate the steal phenomenon and improve coronary perfusion.

Revascularization was planned due to the patient's prior cardiac surgery and unsuitable coronary anatomy for repeat CABG. A drug-eluting stent (2.25 × 9 mm) was implanted at the Ao-S-OM graft anastomosis (Figure 2A). Embolization of the LIMA side branch was performed using 4 mm × 8 cm and 3 mm × 8 cm coils, resulting in complete occlusion (Figure 2B). A peripheral stent (8 × 18 mm) was placed in the subclavian artery (Figure 2C), which improved flow through the LIMA-IM graft (Figure 2D). The patient was discharged without complications and remained asymptomatic at the three-month follow-up.

Well-developed LIMA side branches can cause coronary steal. Subclavian artery atherosclerosis is common in patients with CAD, underscoring the importance of ruling out subclavian stenosis before CABG. Advances in percutaneous interventions provide effective treatment options for such patients, avoiding the challenges associated with repeat surgery.

Ethics Committee Approval: This is a single case image, and therefore ethics committee approval was not required in accordance with institutional policies.

Informed Consent: Written and verbal consent was obtained from the patient for the publication of this case image.

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Fusion, Pseudofusion, and Pseudo-Pseudofusion in a Dual-Chamber Implantable Cardioverter Defibrillator: From Confusion to Clarity in a Single Image

Çift Odacıklı İmplante Edilebilir Defibrilatörde Füzyon, Psödofüzyon ve Psödo-Psödofüzyon: Tek Görüntüde Karmaşadan Açıklığa

CASE IMAGE
OLGU GÖRÜNTÜSÜ

A 58-year-old man with nonischemic cardiomyopathy and a dual-chamber implantable cardioverter-defibrillator (ICD) presented to the emergency department after two presyncopal episodes associated with ICD shocks triggered by premature ventricular contractions (PVC). During an electrophysiological study, the tracing shown in Figure 1 was obtained. What is the mechanism underlying the different QRS morphologies observed in this dual-chamber pacemaker tracing?

Pseudomalformations such as fusion (F), pseudofusion (PF), and pseudo-pseudofusion (PPF) are considered normal pacemaker behaviors. Although these findings usually indicate normal device function, they may result in unnecessary energy consumption; therefore, it is important to determine whether pacing truly contributes to cardiac activation. Careful analysis of the electrocardiography reveals wide and similar QRS complexes in all beats except the second, seventh, and eighth beats, indicating that these are pure paced QRS complexes (P in Figure 2). Ventricular fusion represents the electrical summation of an intrinsic cardiac beat (sinus or premature beat) and depolarization from a pacing stimulus, resulting in a morphology that lies between a fully paced beat and a purely intrinsic beat (eighth beat in Figure 2). In contrast, a pseudofusion beat occurs when the intrinsic rhythm competes with the pacemaker timing cycle, producing a QRS shape similar to the intrinsic QRS activity with a superimposed pacing spike from the same chamber. This reflects inappropriate timing and occurs when pacing output coincides with intrinsic

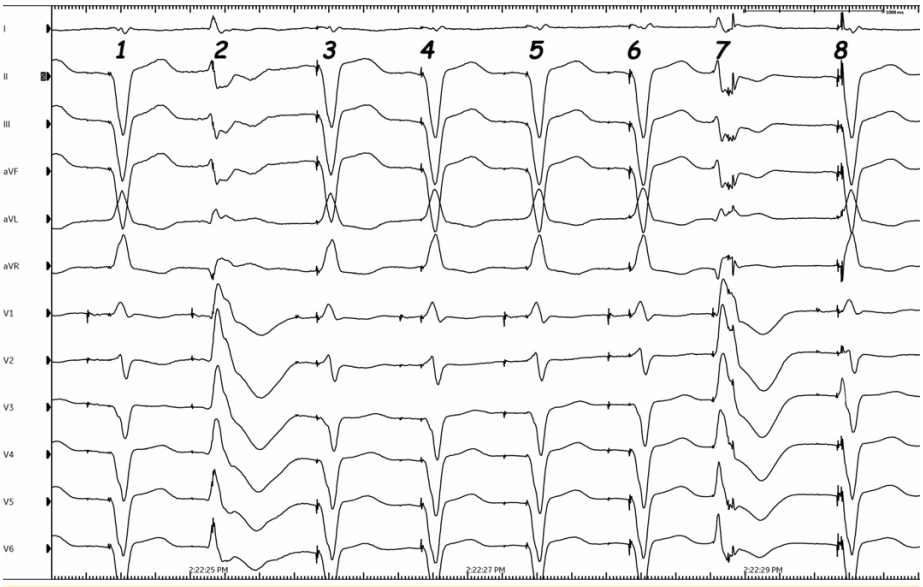

Figure 1. Twelve-lead electrocardiogram obtained from a patient with a dual-chamber ICD.

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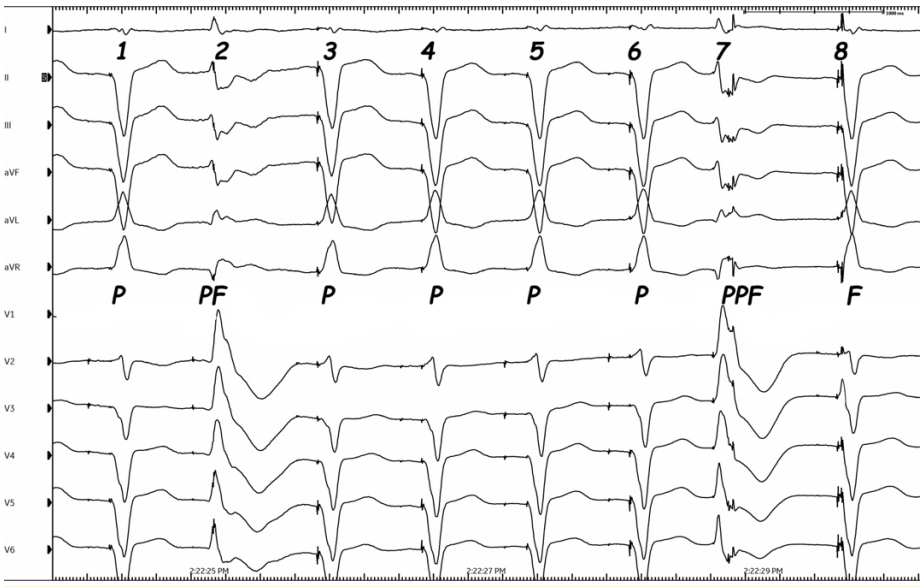

Figure 2. Pacing artifacts occurring simultaneously with premature ventricular contractions (PVCs), creating the appearance of fusion (F), pseudofusion (PF), and pseudo-pseudofusion (PPF). A ventricular spike is observed within the QRS complex (second beat), and an atrial spike appears immediately before the QRS complex (seventh beat).

activation, resulting in a spike superimposed on an intrinsic QRS event (second beat in Figure 2). The QRS morphology is consistent with intrinsic depolarization. Pseudofusion does not confirm or exclude capture and is not dangerous to the patient; however, it may lead to unnecessary battery depletion. In contrast to PF, cross-chamber pacing in PPF does not alter the morphology of the intrinsic P wave or R wave. It is characterized by an intrinsic or fully paced QRS complex overlapping with a cross-chamber pacing spike originating from the atrium rather than the ventricle (seventh beat in Figure 2). Reprogramming the lower rate limit to avoid PPF and/or adjusting the atrioventricular (AV) delay to prevent pacing during vulnerable periods following PPF may successfully prevent further ventricular tachycardia or ventricular fibrillation (VT/VF) episodes. Alternatively, elimination of PVCs through medical therapy or ablation may also be considered.

Ethics Committee Approval: This is a case image, and therefore ethics committee approval was not required in accordance with institutional policies.

Informed Consent: Informed consent was obtained from the patient for publication of anonymized clinical data, in accordance with the Committee on Publication Ethics guidelines.

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When the Appendage is Clear: A Giant Left Atrial Roof Thrombus

Apandiksin Temiz Olduğu Durumda: Sol Atriyum Tavanında Dev Bir Trombüs

CASE IMAGE
OLGU GÖRÜNTÜSÜ

A 50-year-old woman with a history of hypertension presented with progressive exertional dyspnea (New York Heart Association class III) and worsening palpitations for one month. Electrocardiography revealed atrial fibrillation (AF) with a ventricular rate of 117 bpm. Transthoracic echocardiography demonstrated normal left and right ventricular size and function (left ventricular [LV] ejection fraction 55%), mild mitral, aortic, and tricuspid regurgitation, and severe rheumatic mitral stenosis (mitral valve area 1.4 cm^2; peak gradient 18 mmHg; mean gradient 11 mmHg). Biatrial enlargement, an estimated pulmonary artery systolic pressure of 45 mmHg, and a minimal (6 mm) pericardial effusion adjacent to the LV inferolateral wall were also noted. In addition, a well-circumscribed heterogeneous mass with internal echolucent areas was identified at the roof (superior wall) of the left atrium (LA). The mass was round to ovoid, exhibited broad-based mural attachment without a pedunculated stalk, demonstrated limited mobility throughout the cardiac cycle, and did not prolapse into the mitral valve (Figure 1A, Video 1). Transesophageal echocardiography

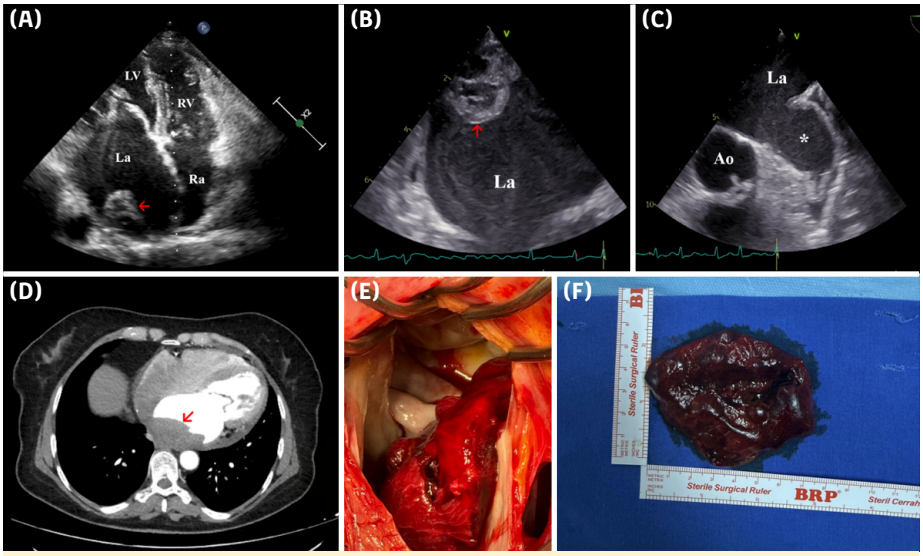

Figure 1. Multimodality imaging of a giant left atrial (LA) roof thrombus. (A) Transthoracic echocardiography showing a well-circumscribed heterogeneous mass (red arrow) at the left atrial roof with broad-based attachment and no mitral prolapse. (B and C) Transesophageal echocardiography demonstrating: (B) a markedly dilated LA with dense spontaneous echo contrast (SEC) and a large roof-adjacent mass (red arrow) lacking a pedunculated stalk, with focal internal lytic areas; (C) a dilated left atrial appendage (asterisk) with dense SEC; however, no definite thrombus or sludge is observed. (D) Contrast-enhanced computed tomography revealing a non-enhancing hypodense mass (red arrow) arising from the LA roof without wall invasion or extracardiac extension. (E) Intraoperative view of the giant thrombus arising from the LA roof. (F) Gross specimen of the excised thrombus showing a large, dark-red organized mass.

Ao, Aorta; LA, Left atrium; LV, Left ventricle; RA, Right atrium; RV, Right ventricle.

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(TEE) confirmed a markedly dilated LA with dense (grade 3–4) spontaneous echo contrast (SEC) and a large heterogeneous mass adjacent to the atrial roof. The lesion showed broad-based contact with the atrial wall, lacked a definite stalk, and had limited mobility. Focal internal lytic areas suggested partial organization or internal degeneration (Figure 1B, Video 2). The left atrial appendage (LAA) was dilated and exhibited dense SEC; however, no definite thrombus or sludge was identified (Figure 1C, Video 3). Contrast-enhanced chest computed tomography revealed a well-defined hypodense intracavitary mass measuring 76 × 62 × 36 mm arising from the LA roof. The lesion demonstrated no contrast enhancement during the arterial phase and contained small calcifications. It appeared markedly hypoattenuating compared with the contrast-opacified atrial cavity and showed no evidence of atrial wall invasion or extracardiac extension (Figure 1D). In the context of severe rheumatic mitral stenosis, AF, and marked atrial enlargement, the imaging constellation (absence of contrast enhancement, lack of a pedunculated attachment, broad-based mural contact, and low attenuation relative to the opacified blood pool) strongly favored the diagnosis of a giant LA thrombus over a primary cardiac tumor, particularly atrial myxoma. The patient underwent successful surgical thrombectomy with complete removal of the mass (Figures 1E and 1F) and implantation of a mechanical mitral valve prosthesis. The postoperative course was uneventful, with no neurologic complications.

Left atrial thrombus formation in rheumatic mitral stenosis (MS) with AF has traditionally been associated with the LAA. However, prior studies have demonstrated that in advanced MS, thrombus distribution frequently extends beyond the appendage, with a substantial proportion arising within the left atrial cavity itself. This reflects the presence of a diffuse thrombogenic milieu driven by severe atrial enlargement, chronic blood stasis, and impaired intra-atrial flow dynamics, rather than an isolated appendage-related phenomenon. In the present case, multimodality imaging, including dedicated TEE evaluation of the LAA in multiple planes, demonstrated no definite thrombus or sludge within the appendage despite dense SEC. In contrast, a giant, well-organized thrombus was identified along the atrial roof, highlighting the heterogeneous spatial distribution of thrombogenesis in advanced rheumatic disease. Rather than representing a purely unexpected localization, this case illustrates the extreme end of atrial remodeling, in which thrombus formation may occur at sites of relative flow stagnation within the atrial body and roof. Accordingly, the principal clinical message is not limited to the absence of appendage thrombus, but rather emphasizes that comprehensive multimodality assessment of the entire LA, including both appendage and non-appendage regions, is essential in high-risk valvular AF. This approach is particularly important for accurate diagnosis, differentiation from cardiac tumors, and appropriate therapeutic planning.

Ethics Committee Approval: This is a single case image, and therefore ethics committee approval was not required in accordance with institutional policies.

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Video 1. Transthoracic echocardiography showing a well-circumscribed heterogeneous mass with internal echolucent areas at the left atrial roof, with broad-based attachment and no mitral prolapse.

Video 2. Transesophageal echocardiography demonstrating a markedly dilated left atrium with dense spontaneous echo contrast and a large roof-adjacent mass lacking a pedunculated stalk, with focal internal lytic areas.

Video 3. Transesophageal echocardiography demonstrating a dilated left atrial appendage with dense spontaneous echo contrast; however, no definite thrombus or sludge is observed.

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Two Overlooked Issues in Hypertension Management: Risk Thresholds and Obesity Integration

Hipertansiyon Tedavisinde Gözden Kaçan İki Konu: Risk Eşikleri ve Obezitenin Tedaviye Dahil Edilmesi

LETTER TO THE EDITOR
EDİTÖRE MEKTUP

To the Editor,

I read the Turkish Hypertension Consensus Report 2025 with great interest.[1] The report provides a comprehensive and pragmatic framework for hypertension management tailored to national realities. However, in Türkiye—where adult obesity prevalence is among the highest in Europe[2]—two interconnected issues merit further consideration: the use of high SCORE2 (Systematic Coronary Risk Evaluation 2) treatment thresholds and the limited integration of obesity into cardiovascular risk stratification.

The report recommends initiating antihypertensive therapy in patients with elevated blood pressure (130–139/80–89 mmHg) when diabetes mellitus, chronic kidney disease, established cardiovascular disease (CVD), prior stroke, or SCORE2 ≥ 15% (Systematic Coronary Risk Evaluation 2 – Older Persons [SCORE2-OP] ≥ 20%) is present. Although this recommendation is justified by the absence of statistically significant benefit in lower-risk subgroups,[3] lack of statistical significance should not be equated with absence of a clinically meaningful effect—particularly in younger individuals with prolonged exposure to elevated blood pressure.

According to the original SCORE2 derivation study, risk categories are age-dependent, and a SCORE2 value > 10% in individuals aged 50–69 years already corresponds to very high cardiovascular risk, even in low-risk countries.[4] Thus, applying a uniform ≥ 15% threshold in a high-risk setting may delay timely preventive treatment in patients who are already on an adverse trajectory.

From a preventive cardiology perspective, it is difficult to justify withholding antihypertensive therapy in a 53-year-old man who is an active smoker and has a blood pressure of 135/80 mmHg, a non–high-density lipoprotein (non-HDL) cholesterol level of 185 mg/dL, and a calculated SCORE2 risk of 11%. If obesity is also present—an independent risk factor for CVD not incorporated into SCORE2—the likelihood of risk underestimation becomes even more pronounced.[5]

This concern is reinforced by the fact that SCORE2 does not include measures of adiposity such as body mass index or waist circumference. In populations with a high burden of obesity and metabolic syndrome, reliance on models and thresholds that omit adiposity may increase the risk of systematic misclassification. Notably, obesity is not included among the decision-modifying conditions in the elevated blood pressure algorithm, potentially leaving patients with substantial adiposity outside pharmacological consideration despite their heightened cardiovascular burden.

Obesity is not merely a lifestyle issue but a structural determinant of hypertension and CVD, promoting neurohumoral activation and vascular remodeling and independently associated with incident hypertension and cardiovascular mortality.[5]

In this context, we respectfully suggest that future updates adopt a more nuanced risk framework, including age-specific risk interpretation and stronger outcome-based justification for specific SCORE2 thresholds in patients with elevated blood pressure. Incorporation of anthropometric measures—specifically height, weight, and waist circumference—into the baseline evaluation table of the report would reinforce adiposity

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as a clinically relevant risk determinant. A dedicated subsection entitled "Obesity and Hypertension" could further clarify its implications for cardiovascular risk stratification in high-prevalence settings such as Türkiye.

In summary, high SCORE2 thresholds combined with limited integration of obesity may contribute to cardiovascular risk under-recognition in Türkiye. More precise risk interpretation and explicit acknowledgment of adiposity as a determinant of cardiovascular burden may strengthen preventive cardiology practice.

Conflict of Interest: The author have no conflicts of interest to declare.

Funding: The author declared that this study received no financial support.

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Reply to the Letter to the Editor: Two Overlooked Issues in Hypertension Management: Risk Thresholds and Obesity Integration

Editöre Mektup Yanıtı: Hipertansiyon Tedavisinde Gözden Kaçan İki Konu: Risk Eşikleri ve Obezitenin Tedaviye Dahil Edilmesi

LETTER TO THE EDITOR REPLY
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To the Editor,

We would like to express our sincere gratitude to Dr. Oğuz Abdullah Uyaroğlu,[1] who evaluated our article.[2] The author focused on two points, and we would like to share our thoughts on these issues separately:

1. The Threshold for Defining High Risk in the SCORE-2 Risk Scoring System

As is well-known, the SCORE-2 and SCORE-2 OP risk assessment systems were developed jointly by the SCORE-2 working group and the Cardiovascular Risk sections of the European Society of Cardiology. These systems aim to predict the development of fatal or non-fatal atherosclerotic cardiovascular disease in patients without known cardiovascular disease or significant comorbidities, based on parameters such as age, gender, systolic blood pressure, and non-HDL cholesterol.[3,4] These scores provide a numerical value representing the 10-year risk of developing atherosclerotic cardiovascular disease for patients. Guidelines that use these scores also categorize risks according to these numbers.

In the latest European Society of Cardiology hypertension guidelines, patients with SCORE-2 or SCORE-2 OP risks ≥ 10% are considered high risk. In our guidelines, however, we have set a risk threshold of 15% for SCORE-2 and 20% for SCORE-2 OP in individuals without hypertension but with elevated blood pressure. This corresponds to a higher threshold than that used in the European Society of Cardiology Guidelines. The primary reason for this is that the potential positive effects of lowering blood pressure on mortality and morbidity in patients with elevated blood pressure have not been universally accepted. As the author mentions, the lack of clear proof of benefit does not mean the intervention is ineffective. However, since our report aims to convey clear messages, we chose to base our decision solely on the available evidence. We also believe that individualizing treatment and starting it earlier, especially in younger patients, may be appropriate.

Furthermore, risk markers are constantly changing and evolving to provide better results. We must keep in mind that the SCORE2 and SCORE2-OP risk markers we use may not provide perfect results. In this regard, a study published in our journal showed that the Pooled Cohort Equation risk calculator, another marker used by the American Heart Association and the American College of Cardiology, had better predictive power than SCORE2 markers in the Turkish population.[5]

2. Obesity

The authors of this consensus report agree that obesity plays a crucial role in the development and progression of hypertension. As noted by the author of the letter to the editor, obesity is not included in the SCORE-2 and SCORE-2 OP risk markers utilized in our report.[3,4] The American Heart Association and the American College of Cardiology's 2025 hypertension guidelines use the PREVENT risk calculator for risk assessment.[6,7] Although body mass index (BMI) is included in this scoring system, it is not used to determine the risk of cardiovascular disease

or atherosclerotic cardiovascular disease. Instead, it is only employed to calculate the risk of developing heart failure. The exclusion of obesity as a parameter in determining the risk of cardiovascular disease or atherosclerotic cardiovascular disease in two of the most widely used hypertension guidelines may be due to insufficient data from studies on this topic. Furthermore, the risk-determining algorithms currently in use do not practically include all risk factors.

Although not directly included in risk assessment guidelines, the importance of obesity is discussed in detail in our report. This report is specifically prepared for primary care, so we have made every effort to ensure it is as simple, understandable, and practical as possible. Our recommendations are not meant to override clinicians' assessments but to assist them. Therefore, a comprehensive evaluation of all risk factors, especially in such a broad topic as hypertension, could compromise the integrity of this report.

Weight and height measurements, which are indispensable components of a physical examination, enable us to detect obesity in patients. From the summary onward, we have tried to emphasize that obesity is a risk factor. We also mentioned obesity as a risk factor when recommending treatment for patients with Diabetes Mellitus. In Türkiye, 60% of type 2 diabetes patients are obese, and treatment is indicated for these patients.[8] Furthermore, the treatment of this risk factor is examined in detail under the section on lifestyle changes. Of course, considering the recent developments in obesity treatment, we will consider addressing this topic as a separate section in future versions of our report.

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Letter to the Editor: Clinical Outcomes of Using Drug-Coated Balloons During Primary Percutaneous Coronary Intervention for ST-Elevation Myocardial Infarction Patients – Insights from High-Risk Groups: A Single-Center Experience

Editöre Mektup: ST Yükselmeli Miyokard Enfarktüsü Hastalarında Primer Perkütan Koroner Girişim Sırasında İlaç Kaplı Balonların Kullanımının Klinik Sonuçları – Yüksek Risk Gruplarından Elde Edilen Bulgular: Tek Merkez Deneyimi

LETTER TO THE EDITOR
EDİTÖRE MEKTUP

To the Editor,

We read the article by Darwish et al.,[1] titled "Clinical Outcomes of Using Drug-Coated Balloons During Primary Percutaneous Coronary Intervention for ST-Elevation Myocardial Infarction Patients – Insights from High-Risk Groups: A Single-Center Experience," published in Archives of the Turkish Society of Cardiology, with great interest. Whether drug-coated balloons (DCB) can replace drug-eluting stents (DES) or serve as an alternative treatment strategy in patients with ST-elevation myocardial infarction (STEMI) remains an important clinical question. This clinical trial suggests the potential for a safe and effective alternative strategy, given the non-inferior outcomes observed in comparable patient populations. However, we would like to offer several constructive comments regarding the generalizability of these results to broader patient populations.

Previous studies have demonstrated that DCB angioplasty is effective, particularly in small-vessel lesions and in cases of in-stent restenosis.[2] However, in the REC-CAGEFREE I randomized trial (Randomized Evaluation of a Drug-Coated Balloon Strategy vs. Drug-Eluting Stent in De Novo Non-Complex Coronary Artery Lesions), DCB angioplasty in 2,272 patients with de novo non-complex coronary lesions failed to demonstrate non-inferiority to DES with respect to major adverse cardiac events (MACE) at two-year follow-up. Evidence regarding the use of DCB in patients presenting with STEMI remains relatively limited.[3]

Although no statistically significant difference was observed between the two groups in terms of target vessel distribution, 55% of interventions in the DCB group involved major epicardial coronary arteries, whereas 82% of interventions in the DES group involved major epicardial coronary arteries. Patients with smaller vessel diameters were significantly more common in the DCB group. The higher frequency of interventions in larger vessels and multiple epicardial coronary arteries may suggest that the DES group included patients with more complex or higher-risk coronary disease. These findings may therefore limit the generalizability of the results to patients presenting with STEMI.

Another important issue is the potential development of coronary dissection during DCB angioplasty, which may impair coronary flow. Patients with this complication were excluded from the study; however, the number of excluded patients was not reported. The proportion of such patients may be clinically relevant when selecting the optimal revascularization strategy in STEMI, as it may indicate how many patients ultimately require DES implantation.

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In a Japanese registry reported by Takahashi et al.,[4] the one-year outcomes of uncomplicated and successful DCB angioplasty in de novo lesions in patients with acute coronary syndrome were comparable to those observed with DES. Taken together with the existing literature, the results of the current study suggest that DCB use may be safe in cases where no dissection occurs and adequate vessel patency is achieved after the procedure.

Despite these limitations, the study provides important evidence suggesting that DCB use may be safe in STEMI patients with lesions involving non-major epicardial coronary arteries and small vessels. Further prospective studies with long-term follow-up are needed to evaluate the safety of DCB use in STEMI patients, particularly in lesions involving major epicardial coronary arteries.

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Reply to the Letter to the Editor: Clinical Outcomes of Using Drug-Coated Balloons During Primary Percutaneous Coronary Intervention for ST-Elevation Myocardial Infarction Patients – Insights from High-Risk Groups: A Single-Center Experience

Editöre Mektup Yanıtı: ST Yükselmeli Miyokard Enfarktüsü Hastalarında Primer Perkütan Koroner Girişim Sırasında İlaç Kaplı Balonların Kullanımının Klinik Sonuçları – Yüksek Risk Gruplarından Elde Edilen Bulgular: Tek Merkez Deneyimi

LETTER TO THE EDITOR REPLY
EDİTÖRE MEKTUP YANITI

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To the Editor,

We sincerely thank the Editor for forwarding this letter to us and for providing the opportunity to share our insights. We also thank the author[1] for their interest in our research article[2] and for the valuable comments provided.

In response to the author's comments, we would like to address the following points:

We agree that drug-coated balloons (DCB) were used more frequently in small vessels in our study. This is largely justified by evidence in the literature suggesting poorer outcomes with drug-eluting stents (DES) in small vessels compared with larger vessels. In addition, DCBs were initially introduced for the treatment of small-vessel disease rather than large-vessel disease, where they subsequently began to gain supporting clinical evidence.

Furthermore, the more frequent use of DES in larger vessels does not necessarily imply that these lesions were more complex. The SYNTAX score (Synergy Between Percutaneous Coronary Intervention With TAXUS and Cardiac Surgery), which is the most validated scoring system for evaluating coronary artery disease (CAD) complexity in clinical practice, considers factors such as calcification, bifurcation lesions, tortuosity, lesion length, and thrombus burden. In our study, there was no significant difference between the two groups in terms of the culprit vessel, native versus in-stent culprit lesions, lesion size and length, presence of calcification, bifurcation lesions, or TIMI (Thrombolysis in Myocardial Infarction) flow before and after the intervention.

Regarding the patients excluded due to significant dissections after DCB treatment, these accounted for 10 patients out of a total of 138 DCB cases (approximately 7%). These patients were excluded to avoid potential bias in follow-up outcomes, as it would not have been possible to clearly determine whether any adverse outcomes were related to the DCB itself or to the stent subsequently implanted to treat the dissection.

Finally, as highlighted in the limitations section of our article, the present study is a retrospective observational study and is therefore subject to multiple confounders. Although the larger sample size improves sensitivity compared to smaller cohorts, the study was only powered to detect relatively large absolute differences. Smaller but potentially clinically meaningful differences—particularly subgroup effects—may not have been reliably detected. Therefore, subgroup analyses should be considered exploratory and interpreted with caution. Accordingly, we plan to extend this work with a large randomized double-blind clinical trial comparing DCB and DES during primary percutaneous coronary intervention.

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Albumin as a Pharmacokinetic Confound and the Temporal Validity of the MAPH Score in Atrial Fibrillation

Atriyal Fibrilasyonda Farmakokinetik Bir Karıştırıcı Faktör Olarak Albümin ve MAPH Skorunun Zamansal Geçerliliği

LETTER TO THE EDITOR
EDİTÖRE MEKTUP

To the Editor,

I read with great interest the article by Konte et al.,[1] which evaluated the MAPH score (Mean platelet volume–Age–total Protein–Hematocrit) as a predictor of left atrial appendage thrombus (LAAT) in patients with atrial fibrillation (AF) scheduled for ablation. The authors demonstrated that the MAPH score outperformed the CHA_2DS_2-VASc score (Congestive heart failure–Hypertension–Age ≥ 75 (2 points)–Diabetes mellitus–Stroke/TIA/thromboembolism (2 points)–Vascular disease–Age 65–74–Sex category (female)) in discriminating LAAT presence on transesophageal echocardiography (TEE), and they appropriately flagged the extreme odds ratio (OR) observed for serum albumin (OR: 1328.5) as a likely statistical artifact. I wish to expand on two points that I believe merit further discussion: the pharmacokinetic interpretation of the albumin finding and the temporal validity of MAPH score components in chronically anticoagulated patients.

The multivariable model revealed that higher albumin was independently associated with LAAT presence. This association warrants pharmacokinetic scrutiny, particularly given the overwhelming predominance of warfarin use in the thrombus group. Warfarin circulates approximately 97–99% protein-bound, primarily to human serum albumin (HSA).[2] Well-established pharmacokinetic literature consistently demonstrates that it is hypoalbuminemia—not hyperalbuminemia—that increases the free, pharmacologically active fraction of warfarin, thereby enhancing its anticoagulant effect and elevating bleeding risk.[3,4] Conversely, higher serum albumin is associated with greater warfarin protein binding, which increases the dose requirement needed to maintain the same anticoagulant effect and, under conditions of fixed dosing, may result in a reduced free drug concentration.[2] In the context of the present cohort, patients with LAAT who had higher albumin levels and were predominantly anticoagulated with warfarin may therefore have been receiving relatively insufficient anticoagulant exposure for their protein-binding capacity—a pharmacokinetic mechanism distinct from, and perhaps complementary to, the inadequate time-in-therapeutic-range (TTR) explanation the authors correctly raise as a limitation. The absence of TTR data precludes definitive conclusions, but this mechanistic pathway reinforces the call for prospective studies incorporating detailed anticoagulation quality metrics.

A second consideration concerns the temporal stability of MAPH score components in a chronically anticoagulated AF population. The MAPH score was originally validated in patients with ST-segment elevation myocardial infarction (STEMI), where laboratory values reflect an acute thromboinflammatory state at a clearly defined moment.[1] In contrast, hematocrit and mean platelet volume (MPV) are dynamic biomarkers subject to chronic modification in AF patients receiving long-term oral anticoagulation. Occult gastrointestinal blood loss—a well-recognized complication of anticoagulant therapy—progressively lowers hematocrit over time, independently of the thrombogenic milieu the score was designed to capture.[5] Similarly, MPV is influenced by antiplatelet co-medication, inflammatory comorbidities, and renal function—all prevalent in the AF population. Because blood sampling in the present study was performed 24–48 hours prior to TEE as a single time point, a chronically depressed hematocrit resulting from subclinical bleeding, rather than a genuinely elevated thrombogenic viscosity, could

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artificially elevate the MAPH score. This raises the possibility that the score is partly capturing anticoagulation-related hematological side effects rather than intrinsic thrombus-promoting physiology in this population. Longitudinal MAPH assessment, or at minimum correction for chronic anemia at baseline, would strengthen the mechanistic inference.

In conclusion, the albumin-LAAT association in this cohort likely reflects a pharmacokinetic disadvantage of warfarin under conditions of higher protein-binding capacity rather than a direct prothrombotic effect of albumin itself. Furthermore, the dynamic nature of hematocrit and MPV under chronic anticoagulation warrants careful consideration before the MAPH score is applied as a cross-sectional screening tool in this population. I concur with the authors that prospective validation studies are warranted, and I particularly emphasize that such studies should include TTR data for warfarin users, parallel direct oral anticoagulant (DOAC) subgroups with their more predictable pharmacokinetic profiles, and longitudinal MAPH assessments to disentangle the thrombogenic signal from anticoagulation-related hematological noise.

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Reply to the Letter to the Editor: "Albumin as a Pharmacokinetic Confound and the Temporal Validity of the MAPH Score in Atrial Fibrillation"

Editöre Mektup Yanıtı: "Atriyal Fibrilasyonda Farmakokinetik Bir Karıştırıcı Faktör Olarak Albümin ve MAPH Skorunun Zamansal Geçerliliği"

LETTER TO THE EDITOR REPLY
EDİTÖRE MEKTUP YANITI

To the Editor,

We express our gratitude to the author[1] for their insightful comments and for highlighting key aspects of our research.[2]

As previously observed, the correlation between elevated serum albumin levels and the presence of left atrial appendage thrombus (LAAT) should not be construed as indicating a direct prothrombotic effect. Instead, this observation likely reflects interactions between anticoagulation strategies and pharmacokinetic variability, particularly within a cohort predominantly using warfarin and lacking time-in-therapeutic-range (TTR) data. We agree that the proposed pharmacokinetic mechanism is biologically plausible and warrants further investigation through studies that comprehensively assess anticoagulation efficacy.

Concerning the temporal validity of the MAPH score components, our research was structured to assess contemporaneous laboratory parameters in relation to the presence of thrombus observed via transesophageal echocardiography, rather than to develop a longitudinal risk assessment model. Hematocrit and mean platelet volume are dynamic variables affected by chronic anticoagulation therapy and comorbidities. We consider this a general limitation inherent to cross-sectional analyses, rather than a restriction specific to our investigation.

We thank the author for expanding the interpretation of our findings and agree that, particularly in well-characterized populations, including patients treated with direct oral anticoagulants, longitudinal validation is crucial to further elucidate the clinical utility of the MAPH score.

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Addressing the Survival Paradox, Procedural Learning Curve, and Pharmacological Confounding in Patients with Left Ventricular Systolic Dysfunction Undergoing Transcatheter Aortic Valve Replacement

Transkateter Aort Kapak Değişimi Uygulanan Sol Ventrikül Sistolik Disfonksiyonlu Hastalarda Hayatta Kalma Paradoksu, Prosedürel Öğrenme Eğrisi ve Farmakolojik Karıştırıcı Etkenlerin Ele Alınması

LETTER TO THE EDITOR
EDİTÖRE MEKTUP

To the Editor,

I read with great interest the article by Keskin et al.[1] comparing balloon-expandable valves (BEV) and self-expanding valves (SEV) in patients with left ventricular systolic dysfunction (LVSD) undergoing transcatheter aortic valve replacement (TAVR). While the authors provide valuable real-world evidence in this fragile population, several methodological considerations warrant further discussion.

First, the discrepancy between the higher crude long-term mortality in the BEV group and the non-significant Kaplan–Meier analysis deserves attention. While baseline risks (older age and higher European System for Cardiac Operative Risk Evaluation II [EuroSCORE II] in the BEV group) are primary drivers,[2] the numerically longer median follow-up in the BEV cohort (1,160 vs. 962 days; P = 0.09) represents an equally important confounder. In high-mortality cohorts, an additional 200 days of observation naturally accumulates more events independent of device performance. This temporal imbalance explains why the crude mortality difference disappears once appropriately accounted for in survival analyses.

Second, the "procedural learning curve" may have disproportionately affected the BEV cohort. As early procedures in the study program were predominantly BEV-based, the higher in-hospital mortality (12.5% vs. 6.0%) may reflect institutional maturation rather than intrinsic device-related risk. Center experience is a well-documented predictor of periprocedural outcomes;[3] therefore, adjusting for the era effect would allow for a more nuanced comparison.

Finally, a major underappreciated confounder is the threefold higher prevalence of sodium–glucose cotransporter-2 inhibitor (SGLT-2i) use in the SEV group (34.0% vs. 12.5%; P < 0.001). Although SGLT-2i use was non-significant in the multivariable Cox model, this finding may reflect limited statistical power. Recent data from Morel et al.[4] suggest that SGLT-2i therapy after TAVR is independently associated with reduced mortality and bioprosthetic valve failure. This pharmacological advantage in the SEV group—particularly relevant in LVSD patients who depend on myocardial recovery—represents a systematic bias. Sensitivity analyses restricted to SGLT-2i non-users could clarify whether this imbalance influenced the long-term outcomes.

In conclusion, the survival parity between BEV and SEV in this study is likely shaped by the convergence of baseline risk differences, follow-up duration, and the learning curve. These observations underscore the need for careful adjustment for pharmacological covariates in future prospective studies aimed at optimizing valve selection in patients with reduced ejection fraction.

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Reply to the Letter to the Editor: Addressing the Survival Paradox, Procedural Learning Curve, and Pharmacological Confounding in Patients with Left Ventricular Systolic Dysfunction Undergoing Transcatheter Aortic Valve Replacement

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LETTER TO THE EDITOR REPLY
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To the Editor,

We thank the authors.[1] for their thoughtful and insightful comments regarding our study evaluating balloon-expandable (BEV) and self-expanding valves (SEV) in patients with left ventricular systolic dysfunction (LVSD) undergoing transcatheter aortic valve replacement (TAVR).[2] We appreciate the opportunity to clarify several important methodological aspects.

First, we agree that the higher crude long-term mortality observed in the BEV group may be related, at least in part, to the longer follow-up duration. For this reason, we performed time-to-event analyses, including Kaplan–Meier survival analysis and Cox proportional hazards models, to assess the impact of valve type on long-term mortality. As consistently reported throughout the manuscript, valve type was not associated with long-term mortality in these analyses. Crude mortality rates were presented only to describe the study cohort and were not intended to imply a causal relationship between valve type and outcomes.

Second, we acknowledge that the procedural learning curve may have contributed to early differences in mortality between valve types. This issue was already discussed in detail in the Discussion section. However, the observed numerical difference in in-hospital mortality did not reach statistical significance and is unlikely to have confounded long-term outcomes. We also chose not to exclude early cases to avoid loss of statistical power due to a reduced sample size. Importantly, patients who experienced in-hospital mortality were excluded from long-term analyses, thereby minimizing any potential impact on survival results. In addition, procedural complication rates were comparable between groups, and Kaplan–Meier curves demonstrated overlapping survival patterns, particularly in the early follow-up period.

Finally, we agree that sodium–glucose cotransporter-2 inhibitors (SGLT2i) offer important therapeutic potential in patients with reduced left ventricular ejection fraction undergoing TAVR. Although several observational studies suggest a potential long-term survival benefit, robust evidence from randomized trials remains limited. The randomized DAPA-TAVI trial.[3] designed to evaluate the effects of SGLT2 inhibitors in this population, has thus far reported only 1-year outcomes and did not demonstrate a mortality benefit, although reductions in heart failure-related hospitalizations and urgent visits were observed. Given the retrospective and observational design of our study, it was not intended to evaluate the effects of SGLT2 inhibitors. The higher rate of SGLT2i use in the SEV group may reflect baseline differences, such as a higher prevalence of low-flow, low-gradient aortic stenosis and diabetes mellitus. Although SGLT2 inhibitor use was not associated with long-term mortality in univariate analysis, residual pharmacological confounding cannot be fully excluded.

In conclusion, our study was designed to provide real-world evidence on valve selection and outcomes in patients with LVSD undergoing TAVR. These findings should be interpreted with caution given the retrospective nature of the study and the potential for residual confounding. Importantly, this was not a mechanistic study aimed at establishing causality, but rather an observational analysis reflecting routine clinical practice. Prospective, multicenter studies are warranted to further evaluate and expand upon these findings.

We thank the authors again for their valuable comments, which have helped to further contextualize our findings.

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When Definitions Shape Outcomes: A Critical Appraisal of Atherogenic Index of Plasma in Non-ST-segment Elevation Myocardial Infarction

Tanımlar Sonuçları Şekillendirdiğinde: Non-ST-segment Elevasyonlu Miyokard Enfarktüsünde Aterojenik Plazma İndeksinin Eleştirel Değerlendirmesi

LETTER TO THE EDITOR
EDİTÖRE MEKTUP

To the Editor,

We read with great interest the recent article by Hekimsoy et al.,[1] which investigated the role of the atherogenic index of plasma (AIP) as a predictor of critical multivessel coronary artery disease (MVD) in patients with non–ST-segment elevation myocardial infarction (NSTEMI). The authors should be commended for analyzing a relatively large cohort and for addressing the clinically relevant need for simple, accessible, and cost-effective markers of atherogenic burden. Nevertheless, several methodological considerations warrant attention, particularly regarding the interpretation and clinical applicability of the findings.

First, MVD was defined using a notably strict criterion, namely the presence of critical stenosis in all three major epicardial coronary arteries. While this approach enhances specificity, it may substantially limit generalizability and reduce comparability with prior studies, in which MVD is more commonly defined as ≥2-vessel disease.[2] Furthermore, the study classified left main coronary artery (LMCA) stenosis as two-vessel disease regardless of concomitant LAD or LCx involvement. However, LMCA disease is widely recognized as anatomically and prognostically equivalent to, or even more severe than, three-vessel disease, with important implications for management decisions such as coronary artery bypass grafting.[3,4] Therefore, categorizing patients with LMCA stenosis within the "non-MVD" group may have introduced misclassification bias and potentially underestimated the true atherosclerotic burden in the study population.

Second, although AIP was identified as an independent predictor of MVD, its discriminative performance remained modest, with an area under the curve (AUC) of 0.689 and both sensitivity and specificity of 65.6%. As the authors also acknowledged, this indicates only moderate diagnostic accuracy. From a clinical perspective, such performance is insufficient for standalone risk stratification. According to the 2023 ESC Guidelines for acute coronary syndromes, clinical decision-making in NSTEMI, particularly regarding the timing of invasive strategies, is primarily guided by validated risk scores such as GRACE and TIMI.[4] Importantly, the present study did not compare AIP with these established risk models. In the absence of such comparative analyses, it remains unclear whether AIP offers incremental predictive value beyond existing, well-validated tools routinely used in clinical practice.

Third, the lipid parameters used in the study were derived from a single measurement obtained during the acute phase of NSTEMI. It is well established that acute myocardial infarction triggers a transient acute-phase response, leading to dynamic alterations in lipid levels, particularly reductions in LDL cholesterol and fluctuations in triglyceride concentrations.[5] As also emphasized in a recent expert consensus, this phenomenon may complicate the accurate interpretation of lipid profiles in the acute setting.[6] Moreover, the same guideline strongly recommends the immediate initiation of high-intensity statin therapy (atorvastatin 40–80 mg or rosuvastatin 20–40 mg) in all patients following acute coronary syndrome, with the addition of agents such as ezetimibe when indicated.[6] Such aggressive lipid-lowering strategies can rapidly modify

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lipid parameters, thereby directly influencing derived indices such as AIP and potentially altering their values over time. Taken together, both the acute-phase response and the early initiation of intensive lipid-lowering therapy introduce substantial uncertainty regarding the extent to which AIP calculated during the acute phase truly reflects a patient's baseline atherogenic burden and long-term cardiovascular risk.

Finally, previous studies have demonstrated strong associations between AIP and both obesity and metabolic syndrome.[7,8] Although diabetes and hypertension were included in the analysis, key anthropometric variables such as body mass index (BMI) were neither incorporated into the multivariable models nor reported in the baseline tables. The omission of major confounding factors that directly influence AIP, such as adiposity and fat distribution, may have limited the ability to fully isolate the independent effect of AIP on MVD. In addition, excluding patients receiving lipid-lowering therapy at admission may have introduced selection bias by omitting a clinically relevant high-risk subgroup.

In conclusion, although this study provides valuable insight into the relationship between AIP and severe coronary artery disease in NSTEMI, its findings should be interpreted with caution. Further prospective, multicenter studies incorporating standardized definitions of MVD, comparisons with established risk models, and adjustment for key metabolic confounders are warranted to better define the clinical utility of AIP as a risk stratification tool in this setting.

Conflict of Interest: The authors have no conflicts of interest to declare.

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Reply to the Letter to the Editor: When Definitions Shape Outcomes: A Critical Appraisal of Atherogenic Index of Plasma in NSTEMI

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LETTER TO THE EDITOR REPLY
EDİTÖRE MEKTUP YANITI

To the Editor,

We sincerely thank the authors for their thoughtful comments[1] on our recently published study and for their interest in our work.[2] We appreciate the opportunity to clarify several methodological points and further discuss the clinical implications of our findings.

First, regarding the definition of multivessel disease (MVD), we acknowledge that no universally accepted definition exists across studies. In many reports, MVD is defined as the involvement of ≥2 vessels;[3] however, our intention was to focus on the most advanced anatomical disease burden by requiring critical stenosis in all three major epicardial coronary arteries. We deliberately selected this stricter definition to identify a subgroup with extensive, clinically relevant coronary atherosclerosis. As stated in our manuscript,[2] this approach may reduce comparability with some previous studies, but it increases specificity for severe disease. Regarding left main coronary artery involvement, we agree that left main disease carries major prognostic importance. Its categorization in our study was for methodological consistency and should not be interpreted as excluding other clinically accepted approaches.

Second, we agree that the atherogenic index of plasma (AIP) had moderate discriminative performance, and we did not intend to propose AIP as a standalone risk-stratification tool. Rather, our conclusion was that AIP may serve as a simple, inexpensive, and widely available adjunctive biomarker reflecting atherogenic burden. We fully concur that established scores, such as GRACE and TIMI, remain the cornerstone of clinical decision-making in non-ST-elevation myocardial infarction (NSTEMI).[4] Because these scores primarily estimate ischemic risk and prognosis rather than anatomical coronary complexity, direct comparison was beyond the principal scope of our study. Nevertheless, future studies evaluating the incremental value of AIP alongside validated risk models would be highly valuable.

Third, the authors correctly note that lipid parameters may fluctuate during acute coronary syndromes. To minimize this effect, blood samples were obtained early after admission and, whenever possible, before initiating lipid-lowering therapy. However, as acknowledged in our limitations section, single-time-point lipid measurements cannot fully capture long-term metabolic exposure.

Finally, we agree that residual confounding is possible in any retrospective observational study. Variables such as body mass index, waist circumference, dietary habits, and physical activity were not consistently available in our database and, therefore, could not be included in the multivariable model. This should be taken into account when interpreting our findings.

In conclusion, we appreciate these constructive comments, which help contextualize our results. We believe our study provides preliminary evidence supporting an association between AIP and severe coronary artery disease in NSTEMI, while prospective multicenter studies are needed to confirm its clinical utility.

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