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Changing of Left Atrial Function Index in Symptomatic Patients with Patent Foramen Ovale After Device Closure

Patent Foramen Ovaleli Semptomatik Hastalarda Cihaz Kapatıldıktan Sonra Sol Atriyal Fonksiyon İndeksinin Değişmesi

ORIGINAL ARTICLE
KLİNİK ÇALIŞMA

ABSTRACT

Background: Left atrial function is impaired in patients with patent foramen ovale. This study aimed to evaluate the role of left atrial function index in monitoring the course of left atrial function in a patient with patent foramen ovale before and after percutaneous closure.

Methods: We retrospectively reviewed the findings of consecutive patients evaluated in our tertiary center for patent foramen ovale closure to identify those subjects with acute ischemic stroke, transient ischemic attack, or radiological evidence of cerebral ischemic events (index event) who performed a complete echocardiography evaluation reporting evidence of patent foramen ovale between September 2004 and September 2018. The left atrial function was evaluated at baseline and then yearly using the left atrial function index.

Results: The cohort of 448 consecutive patients (mean age 43.4 ± 10.4 years, 257 males) was divided into 2 groups according to the temporal window between the index event and patent foramen ovale closure, defined as <1-year (216 patients) and ≥1-year (232 patients). Patients treated within 1 year from the index event maintained similar parameters of left atrial function and left atrial function index over the time, also after the interventional procedure. Conversely, patients treated after 1 year demonstrated a significant reduction of left atrial emptying function and maximal left atrial volume ($P < .001$ for all) compared to the basal values. The same parameters slightly increased after the percutaneous closure during the second year without reaching the basal values.

Conclusions: Left atrial function index can be used as a non-invasive marker of atrial dysfunction severity in patients with patent foramen ovale before and after the interventional procedure.

Keywords: Patent foramen ovale, echocardiography, device, closure, left atrium

ÖZET

Amaç: Patent foramen ovaleli hastalarda sol atriyal fonksiyon bozulmuştur. Çalışmamızın amacı sol atriyal fonksiyon indeksinin patent foramen ovaleli hastalarda perkütan kapatma öncesi ve sonrası sol atriyal fonksiyonunun seyrinin izlenmesindeki rolünü değerlendirmektir.

Yöntemler: Akut iskemik inme, TIA veya serebral iskemik olayların radyolojik kanıtı (indeks olayı) olan, Eylül 2004 ve Eylül 2018 arasında patent foramen ovaleli kanıtlarını bildiren tam bir ekokardiyografi değerlendirmesi gerçekleştirilen hastaları belirlemek amacıyla, üçüncü basamak merkezimizde patent foramen ovaleli kapanması için değerlendirilen ardışık hastaların bulgularını geriye dönük olarak inceledik. Sol atriyal fonksiyonu başlangıçta ve ardından sol atriyal fonksiyon indeksi kullanılarak yıllık olarak değerlendirildi.

Bulgular: Ardışık 448 hastadan oluşan kohort (ortalama yaş 43,4 ± 10,4 yıl, 257 erkek), indeks olay ile patent foramen ovaleli kapanması arasındaki temporal pencereye göre, <1 yıl (216 hasta) ve ≥1 yıl (232 hasta) olarak tanımlanan iki gruba ayrıldı. İndeks olayından sonraki 1 yıl içinde tedavi edilen hastalar, girişimsel prosedürden sonra da zaman içinde benzer sol atriyal fonksiyonu ve sol atriyal fonksiyon indeksi parametrelerini korumuşlardır. Tersine, 1 yıl sonra tedavi edilen hastalar, bazal değerlere kıyasla sol atriyal boşaltma fonksiyonunda ve maksimum sol atriyal hacminde (tümü için $P < ,001$) önemli bir azalma gösterdiler. Aynı parametreler perkütan kapatmadan sonra ikinci yılda, bazal değerlere ulaşmadan hafifçe arttı.

Sonuç: Sol atriyal fonksiyon indeksi, girişimsel işlem öncesi ve sonrasında patent foramen ovaleli hastalarda atriyal disfonksiyon şiddetinin non-invaziv bir belirteci olarak kullanılabilir.

Anahtar kelimeler: Patent foramen ovale, ekokardiyografi, cihaz, kapatma, sol atriyum

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Over the latest years, the interest in the left atrial (LA) function in patients with patent foramen ovale (PFO) has increased.[1,2] Previous investigations have demonstrated that a LA enlargement was associated with cortical infarction in PFO subjects[3] and, per se, correlated with a higher risk of adverse cardiovascular events such as stroke.[4] Moreover, our group recently reported that the reversal of LA enlargement after PFO closure indirectly demonstrated the contribution of the right-to-left shunt (RLS) in generating a LA cardiopathy.[5] Several echocardiographic non-invasive parameters have been recently described for the evaluation of the LA function such as the LA function index (LAFI) which has been correlated with the risk of cardiovascular events.[6-7] The aim of this study is to evaluate the possible role LAFI in monitoring the course of LA function in a patient with PFO before and after percutaneous closure.

Methods

Population

We retrospectively reviewed the clinical and instrumental findings of consecutive patients evaluated in our tertiary center for PFO closure to identify those subjects with acute ischemic stroke on whom we performed transthoracic echocardiography (TTE) and contrast transoesophageal echocardiography (cTOE) and reported evidence of PFO between September 2004 and September 2018. Specifically, all patients, per institutional protocol, underwent TTE after the diagnosis of transient ischemic attack (TIA), stroke, or radiological findings of at least 1 cerebral ischemic lesion and then yearly. These events were defined in the study as event. Exclusion criteria were patients with a previous history of untreated arterial hypertension, mild or severe mitral valve regurgitation or having a mitral transvalvular mean gradient >5 mm Hg, patients with atrial fibrillation (AF), atrial flutter, supraventricular tachycardia, and bundle branch blocks, since these clinical conditions could represent a bias in the evaluation of LA function.[5] Moreover, patients were referred to our unit by the local neurological team after receiving a diagnosis of acute ischemic stroke or TIA and echocardiographic evidence of PFO.[8,9] Subsequently, all subjects were evaluated by a local multidisciplinary team composed of skilled cardiologists and neurologists to plan the most appropriate treatment and secondary prevention strategies.[10] The cohort was divided into 2 groups: patients who received the percutaneous PFO closure within (<1 year) and after (≥1 year) after the cerebral ischemic events and/or radiological diagnosis of cerebral ischemic lesion. According to our national laws, ethical approval was not required due to the retrospective design of the study.

Echocardiographic Protocols

Transthoracic echocardiography and contrast transoesophageal echocardiography were performed using a GE Vivid 7 (General Electric Corp., Norfolk, Va, USA). Two echocardiographers with 20 years of experience calculated the echocardiographic items with an agreement of 98.3%. Both LA function and diameter, as well as RLS degree assessed by contrast injection during Valsalva maneuver, were recorded.[11-12] Atrial septal aneurysm (ASA) was graduated as previously proposed by Olivares et al.[13]

Left atrial volumes were assessed at 2 time points: just before mitral valve opening and at mitral valve closure which have been defined as maximal (LAESV) and minimal LA volume (LAEDV). Specifically, LA volume have been measured from both 4- and 2-chamber views using the biplane method of discs.[6] Left atrial reservoir volume was defined as the difference between LAESV and LAEDV, while the LA emptying function (LAEF, %) was calculated with the formula: [((LAESV−LAEDV)/LAESV) × 100]. The LAESV was then normalized for the body surface area (m^2), using the Dubois and Dubois formula. Mitral inflow velocity (m/s) was obtained from a 4-chamber apical view by pulsed-wave Doppler examination, placing the sample volume at the tips of the mitral leaflets. Peak velocity of atrial contraction in diastole was calculated as an average of 3 beats. Moreover, velocity–time integral of a wave was assessed using planimetry.[14]

Left Atrial Function Index

The LAFI was calculated with the formula (1):

$$\frac{\text{LAEF} \times \text{LVOT-VTI}}{LAESVI} \quad (1),$$

where the velocity–time integral of the left ventricular outflow tract (LVOT-VTI) was measured in centimeter as an average of 3 beats. Specifically, LVOT-VTI was calculated by placing the pulsed Doppler sample volume in the outflow tract below the aortic valve and recording the velocity and then integrating with respect to time.[15]

Transcranial Doppler Protocol

Transcranial Doppler (TCD) was performed using intravenous bubble venous injection according to current recommendations[16] using a TCD monitoring device (DWL MultidopX, ScanMed Medical, UK). Middle cerebral arteries (MCA) were simultaneously monitored through the temporal bone window using 2 MHz probes. The contrast was obtained by mixing 100 cm^3 of saline solution with 2-3 cm^3 of Emagel. Right-to-left shunt (RSL) severity was evaluated by counting the number of signals in MCA within 7 seconds from the injection.[17]

Criteria for PFO Transcatheter Closure

The following criteria for transcatheter closure[18] were used:

- previous neurologically confirmed stroke/TIA in the absence of alternative causes rather than the PFO;

ABBREVIATIONS

AF	Atrial fibrillation
ASA	Atrial septal aneurysm
cTOE	Contrast transoesophageal echocardiography
CVD	Cardiovascular disease
ICE	Intracardiac echocardiographic
LA	Left atrium
LAFI	Left atrial function index
LVOT	Left ventricular outflow tract
MCA	Middle cerebral arteries
PFO	Patent foramen ovale
RLS	Right-to-left shunt
RoPE	Risk of paradoxical embolism
TCD	Transcranial Doppler
TIA	Transient ischemic attach
TTE	Transthoracic echocardiography

and/or
- positive brain magnetic resonance imaging, defined as single or multiple cortical ischemic lesions; periventricular and deep white matter hyperintensities were not considered as an infarction;
- permanent or shower or curtain RLS shunt pattern on TCD with Valsalva maneuver;
and
- medium or large PFO on cTEE.

Those patients not fulfilling these criteria or with extracranial arteries disease stenosis ≥ 50% or history of paroxysmal AF or permanent AF and need for long-term anticoagulant therapy were treated medically.

Transcatheter Closure and Intracardiac Echocardiography Protocol

All patients fulfilling the inclusion criteria underwent intracardiac echocardiographic (ICE)-guided transcatheter PFO closure using the mechanical 9F 9 MHz UltraICE catheter (EP Technologies, Boston Scientific Corporation, San Jose, Calif, USA). The ICE study was conducted by performing a manual pull-back from the superior vena cava to the inferior vena cava through 5 sectional planes.[19] Conversely, during the implantation procedure, ICE monitoring was conducted using the four-chamber plane. Across the years, the Amplatzer PFO Occluder or Cribriform Occluder (St Jude Medical, Plymouth, Minn, USA), the Premere Occlusion system (St Jude Medical, Plymouth, Minn, USA), or the Gore Cardioform (WL Gore & Associates, INC, Flagstaff, Ariz, USA) were implanted depending on the presence /absence of >2 ASA[12], tunnel length > 10 mm, hypertrophy of the rim as well as the mean diameter of the fossa ovalis.[20] Aspirin 100 mg daily or clopidogrel 75 mg daily was given for 6 months after PFO closure. To assess the effect of closure, the 12-month echocardiographic control was chosen and analyzed.

Statistical Analysis

Continues variables were expressed as mean ± standard deviation and were compared by Student's *t*-test if the data had normal distribution, otherwise by Wilcoxon–Mann–Whitney *U* test. Categorical variables were presented as proportions and compared by Pearson's χ^2 test. The longitudinal assessment of LAFI between groups was evaluated using mixed-effects repeated measures models of unstructured–variance–covariance matrix. The model was adjusted for age, gender, BSA, and risk of paradoxical embolism (RoPE) score. Statistical significance was defined as $P < .05$. Statistical analyses were performed using Statistical Package for the Social Sciences package version 20.0 (IBM Corp., Armonk, NY, USA).

Results

Population

Over the study period, 501 patients were retrospectively identified. Among these, 35 and 18 subjects were excluded because they had a previous history of AF and a moderate-severe mitral valve regurgitation, respectively. Finally, 448 consecutive patients (mean age 43.4 ± 10.4 years, 257 males) met the inclusion criteria and were analyzed (Figure 1). Of these, 216 received a percutaneous PFO closure within 1 year (8.3 ± 2.7 months) from the index event (<1-year group). Conversely, the remaining 232 patients underwent closure after 1 year but in all the other cases no later than the second year after the index event (16.4 ± 3.8 months, ≥1-year group). No significant differences were observed in demographical and clinical items among the 2 groups (Table 1). Procedural success was obtained in 100% of cases. Predischarge echocardiography demonstrated a complete occlusion in 193/212 (91.0%) of the <1 year versus 208/232 (89.6%) >1 year closure group (p).

LA Size and Baseline Function

Left atrial volumes, both in 4- and 2-chamber apical view, were not different among the 2 groups (36.3 ± 6.2 vs. 37.1 ± 9.5, $P=.29$ and 35.3 ± 6.4 vs. 35.9 ± 7.2, $P=.35$, respectively). Similarly, the terms included in the LAFI formulae were comparable among the 2 groups (Table 2).

LAFI Before and After Interventional Closure

Patients treated within 1 year from the index event maintained similar parameters of LA function and LAFI over the time, also after the interventional procedure. Conversely, patients treated after 1 year demonstrated a significant reduction of LAEF, LVOT-VTI, and LAESV ($P < .001$ for all) compared to the basal values. The same parameters slightly increased after the percutaneous

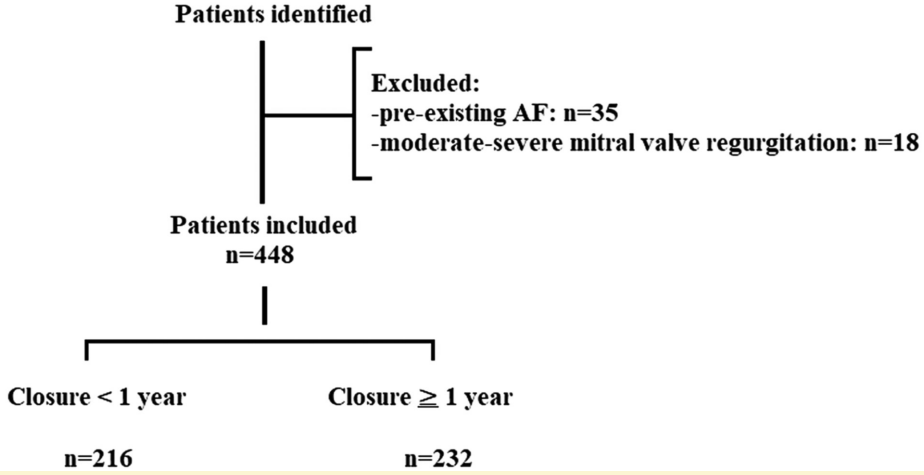

Figure 1. Study flowchart. AF, atrial fibrilliation.

Table 1. General Characteristics of the Population Enrolled

	Closure < 1 year n=216	Closure ≥ 1 year n=232	*P*
Age (years)	42.1 ± 12.7	44.8 ± 13.2	.063
RoPE score	7.4 ± 0.8	7.5 ± 0.7	.154
Males, n (%)	126 (58.3)	131 (56.4)	.579
BSA (m^2)°	1.77 ± 0.9	1.79 ± 0.3	.746
BMI (kg/m^2)	25.2 ± 10.3	25.6 ± 8.7	.655
SBP (mm Hg)	122.3 ± 10.4	123.1 ± 13.2	.472
DBP (mm Hg)	76.3 ± 7.8	75.2 ± 9.3	.172
HR (beats per minute)	78.2 ± 12.45	80.3 ± 14.3	.091
Arterial hypertension, n (%)	53 (24.5)	61 (26.2)	.680
Diabetes, n (%)	56 (25.9)	59 (25.4)	.900
Smokers, n (%)	35 (16.2)	39 (16.8)	.864
TIA, n (%)	101 (46.7)	109 (45.6)	.814
Stroke, n (%)	115 (53.2)	123 (53.0)	.965
At least 1 CT/MRI lesion, n (%)	47 (21.7)	49 (21.1)	.875
Migraine with aurea, n (%)	61 (28.2)	67 (28.8)	.884
Migraine without aurea, n (%)	30 (13.8)	32 (13.7)	.972
Thrombophilia, n (%)[b]	18 (8.3)	21 (9.0)	.794
TDC shunt curtain, n (%)	39 (16.6)	41 (17.6)	.772
TDC shunt shower, n (%)	64 (29.6)	69 (29.7)	-
Continuous shunt without Valsalva, n (%)	77 (35.6)	81 (34.9)	.872
ASA, n (%)	126 (58.3)	135 (58.1)	.972
Closure device type and size			
Amplatzer PFO occuder, 18 mm	22 (10.3)	23 (9.9)	.791
Amplatzer ASD cribriform, 25 mm	78 (36.7)[a]	80 (34.4)	.685
Amplatzer cribriform, 30 mm	34 (16)	35 (15)	.753
Gore cardioform, 20 mm	12 (5.6)	15 (6.5)	.702
Gore cardioform, 25 mm	24 (11.3)	25 (10.7)	.811
Gore cardioform, 30 mm	8 (3.7)	10 (4.3)	.657
Premere occlusion system, 25 mm	38 (17.9)	34 (14.6)	.620

[a]Calculated using the Dubois and Dubois formula.
[b]In the presence of at least one of the following: protein C resistance; protein S resistance; antithrombin III deficit; mutations of the factor V and/or II and/or VIII; hyperhomocysteinemia; methylenetetrahydrofolate reductase mutation; antiphospholipid syndrome.
BSA, body surface area; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; HR, heart rate; TIA, transient ischemic attach; CT, computed tomography; MRI, magnetic resonance imaging; TDC, transcranial Doppler; ASA, atrial septal aneurysm.

closure during the second year without reaching the basal values (Table 2). The baseline LAFI was comparable among the 2 groups (0.56 ± 0.16 vs. 0.58 ± 0.09, *P*=.10). However, after 1 and 2 years, patients treated earlier showed a significantly higher LAFI compared to those treated after 1 year from the index event (Figure 2).

Adverse Events After 1 Year from the Procedure

During the year after the PFO closure, patients treated after 1 year from the index event had a trend towards a higher rate of adverse events although that trend was not statistically significant (1.7% vs. 0.9%, *P*=.45) (Figure 3). In fact, 2 patients developed chronic AF, one had stroke, and one experienced a device thrombosis in the group treated after 1 year. Conversely, among patients receiving the interventional procedure within 1 year from the index event, device thrombosis and stroke were experienced in 2 cases (1 case of thrombosis and 1 of stroke, respectively).

Discussion

Our results demonstrated that the LAFI decreased over the time in patients requiring PFO closure treated after 1 year from the index event. Moreover, in these subjects, the LAFI subsequently improved after 1 year from the interventional procedure without reaching the baseline values. Conversely, patients

Table 2. Echocardiographic Parameters of Atrial Function Among the 2 Cohorts of Patients

	Closure < 1 year n=216	Closure ≥ 1 year n=232	*P*
Basal			
LAEF (%)	55.3 ± 4.5	56.2 ± 5.8	.061
LVOT-VTI (cm)	21.1 ± 2.2	20.9 ± 2.4	.352
LAESV (mL)	36.3 ± 12.4	35.6 ± 14.2	.588
1-year			
LAEF (%) (cm)	53.2 ± 4.8	42.1 ± 7.9	<.001
LVOT-VTI (cm)	20.9 ± 1.8	17.8 ± 3.9	<.001
LAESV (mL)	35.6 ± 13.6	21.1 ± 18.3	<.001
2-year			
LAEF (%)	54.2 ± 3.1[a]	47.3 ± 8.1	<.001
LVOT-VTI (cm)	21.2 ± 1.2[b]	18.6 ± 3.1	<.001
LAESV (mL)	35.9 ± 11.4[c]	45.4 ± 10.1	<.001

[a]Comparison between baseline and 2-year LAEF, $P < .001$; [b]Comparison between baseline and 2-year LVOT-VTI, $P < .001$; [c]Comparison between baseline and 2-year LAESV, $P < .001$.
LAEF, left atrial emptying fraction; LVOT-VTI, velocity time integral across the left ventricular outflow tract; LAESV, left atrial end systolic volume.

treated within the year maintain stable LAFI values over the time after closure.

Adverse LA remodeling is associated with increased risk of cardiovascular disease (CVD) and CVD-specific and all-cause mortality.[21,22] In fact, an increased LA volume and/or abnormality in phasic function have been reported to be independent predictors of incident or recurrent AF, heart failure, and cerebrovascular accident.[21,22] Moreover, a small decline in LA function, detected by impaired LA phasic function intended as atrial reservoir phase, passive atrial emptying, and atrial systole, has been associated with the incident and recurrent cardiovascular events.[23-26] Unfortunately, these echocardiographic measures are not routinely collected during an echocardiographic examination. Left atrial function index represents a composite measure of LA structure and function, combining data about atrial reservoir function as well as LA size, body surface, and left ventricular function, indirectly assessed using the LVOT-VTI.[27,28]

Intriguingly, the same parameters considered at the basis of LA enlargement and dysfunction represent risk markers for PFO-related stroke.[29] Left atrial conduit, reservoir, active, and passive emptying function are found to be altered in PFO patients with permanent RLS.[5,30,31] As demonstrated by our results, a delay in PFO closure can have a significant repercussion on the LA function as RLS leads to enlarging LA size causing LA dysfunction. The abolishment of RLS induced a rapid remodeling of the LA after closure in the late closure group. The impact of LA dysfunction in the late closure group can be also argued by the statistically insignificant trend toward a higher rate of adverse events in patients treated after 1 year. The absence of significant difference could be either because there is genuinely no difference or since there was a difference in the impact on LAFI that the number of events was too low to make a reliable comparison. The low event rate could be due to the fact that PFO closures were performed as secondary prevention and the patients received antiplatelet treatment until the index event.

Left atrial function index can be considered also as a marker of atrial dysfunction severity in patients with PFO. Indeed, when the closure occurred late after the stroke, LAFI tends to improve after closure but without complete recovery. Otherwise, in a patient with early closure after stroke, the parameter remained substantially unchanged but lower than that in patients with late closure. Our results seem to confirm our recent report showing that a significant enlargement of LA is associated with more severe neurological impairment and RoPE score and can be considered a marker of LA cardiopathy in patients with symptomatic PFO. These findings raise the question about the optimal timing of PFO closure suggesting that an early approach can result in a better outcome and conserved AF.

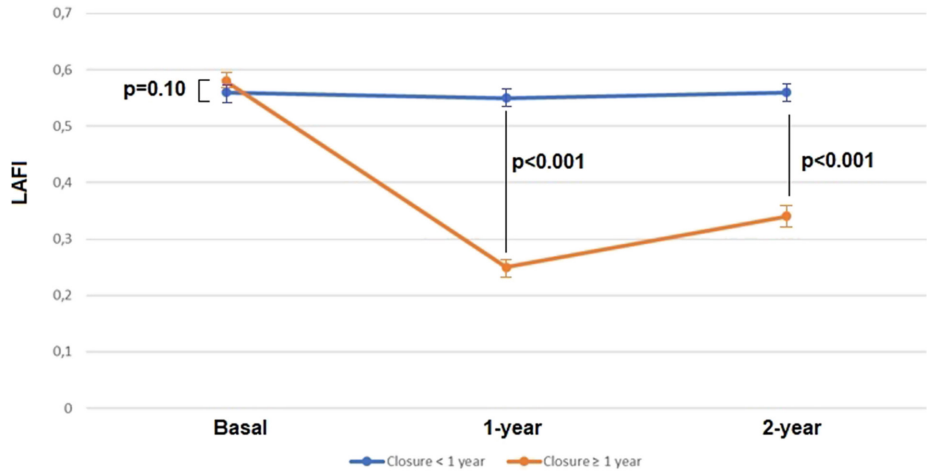

Figure 2. Temporal change in LAFI among the 2 groups. LAFI, left atrial function index.

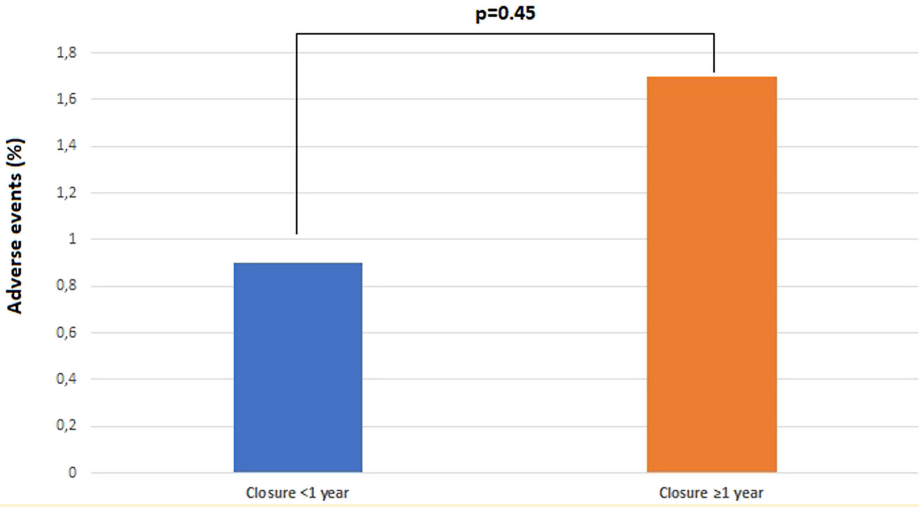

Figure 3. Comparison of adverse events between the 2 groups.

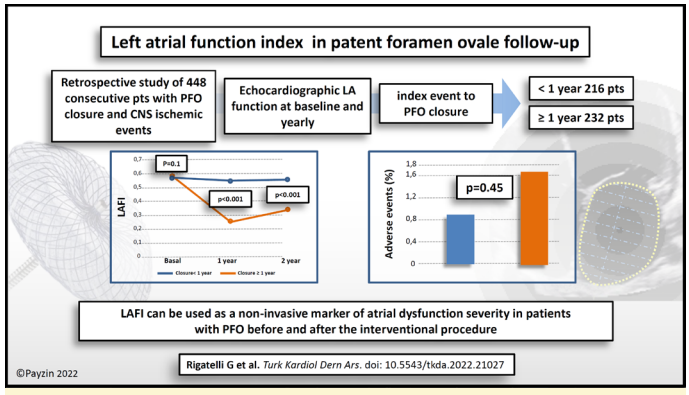

Figure 4. Visual summary of the article.

Limitations

Our investigation has some limitations due to the retrospective and monocentric design of the study as well as the non-randomized fashion. However, the size of the sample and amount of data are significant, reducing the impact of these limitations. Moreover, we did not perform a LA evaluation using the speckle tracking technique and strain and strain rate because the study encompassed 14 years and the early phased strain and strain rate analysis were not regularly used in PFO patients. Finally, the estimation of LA volumes was performed by means of 2-dimensional echocardiography leading to the underestimation of the actual volume values as compared with real-time 3-dimensional echocardiography or cardiac magnetic resonance, thus an overall underestimation of such volume cannot be excluded in our population. However, this potential bias should be considered minimized by the comparison of the 2 groups.

Conclusion

Left atrial function index can be used as a non-invasive marker of atrial dysfunction severity in patients with PFO before and after the interventional procedure. A delay in the PFO closure results in significant impairment of LA function. Indeed, this study, for the first time in literature, assessed the impact of PFO device-based closure on LA volume suggesting that a LA cardiopathy and underlying dysfunction can be associated with late closure (after 1 year) of PFO after the cerebral ischemic event.

Visual summary of the article can be seen in Figure 4.

Ethics Committee Approval: According to the national laws of the authors, ethical approval was not required due to the retrospective design of the study.

Informed Consent: Written informed consent was obtained from all participants who participated in this study.

Peer-Review: Externally peer-reviewed.

Author Contributions: Concept – G.R., M.Z.; Design – G.R., L.R.; Supervision – G.R., L.R.; Data Collection and/or Processing – D.L., G.B., S.A.; Analysis and/or Interpretation – G.R., M.Z.; Literature Search – D.A.; Writing – G.R.,M.Z.; Critical Revision – L.R., A.D.

Declaration of Interests: None of the authors have conflicts of interest to declare.

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