The International Journal of Cardiovascular Imaging (2019) 35:2049–2056
https://doi.org/10.1007/s10554-019-01666-x

ORIGINAL PAPER

# Left atrial enlargement as a maker of significant high-risk patent foramen ovale

**Gianluca Rigatelli[1] · Marco Zuin[2] · Alessandro Adami[3] · Silvio Aggio[4] · Daniela Lanza[4] · Katia d'Elia[4] · Gabriele Braggion[5] · Monia Russo[6] · Alberto Mazza[7] · Loris Roncon[4]**

Received: 24 April 2019 / Accepted: 11 July 2019 / Published online: 19 July 2019


## Abstract

Left atrial (LA) enlargement is a marker of LA cardiopathy and, in patients with patent foramen ovale (PFO), is associated with an increased risk of ischemic stroke. The primary study outcome was the comparison of LA diameter between patients undergoing percutaneous PFO closure versus those treated conservatively. The secondary endpoints were the association of LA diameter with the Risk of Paradoxical Emboli (ROPE) score and the presence of Atrial septal aneurysm (ASA) and Right-To-Left Shunt (RLS). Retrospective analysis of clinical and instrumental data of 1040 subjects referred to a single tertiary center for PFO evaluation and treatment. Seven hundred and nineteen patients were enrolled: 495 patients (closure group, mean RoPE score $7.6 \pm 0.8$) underwent PFO closure while 224 patients (control group, mean RoPE score $4.1 \pm 0.9$. $p < 0.001$) were left to medical therapy. Preoperative LA diameter was significantly larger in closure group and reduced from $44.3 \pm 9.1$ to $37.3 \pm 4.1$ mm ($p = 0.01$) 1 year after the procedure to the size of controls. A larger LA diameter was associated with permanent RLS, RLS curtain pattern, ASA presence and multiple ischemic brain lesions pattern at neuroimaging. A LA diameter $\geq 43$ mm was a predictor a RoPEscore $> 7$. In our patients' cohort, LA diameter was associated with the clinic severity of PFO and RLS. The reversal of LA enlargement after PFO closure suggests a role for RLS to induce LA cardiopathy. LA enlargement has the potential to be considered per se as an indication to transcatheter PFO repair.

**Keywords** PFO · ASA · left atrium · Echocardiography

## Introduction

Paradoxical embolism through patent foramen ovale (PFO) represents the foremost proposed pathophysiological mechanism for cryptogenic stroke. Some previous investigation [1–3] have evidenced that in PFO patients, the presence of left atrial (LA) electrical or structural dysfunctions simulate some features observed in subjects with atrial fibrillation (AF) [4]. Moreover, it has been already demonstrated that a LA enlargement is associated with cortical infarction in PFO subjects [5] while LA enlargement, per se, is correlated with higher risk of adverse cardiovascular events, as stroke [6].

Thus, LA size evaluation could improve the individual risk stratification and the management of PFO patients. The severity of Right-To-Left Shunt (RLS) might be involved in the development of a so-called PFO-associated LA cardiopathy. In such a case, PFO closure might lead to the reversal of LA enlargement. To investigate this issue, we compared LA size before and after PFO closure in a large dataset of consecutive patients. We hypothesized the existence of an

✉ Gianluca Rigatelli
jackyheart@libero.it

1 Section of Adult Congenital and Adult Heart Disease, Cardiovascular Diagnosis and Endoluminal Interventions, Rovigo General Hospital, Via WA Mozart, 9, Rovigo, 37040 Legnago, Verona, Italy

2 Section of Internal and Cardiopulmonary Medicine, Department of Medical Science, University of Ferrara, Ferrara, Italy

3 Stroke Center, Istituto Don Calabria, IRCCS, Sacro Cuore Hospital, Negrar, Italy

4 Division of Cardiology, Echocardiography Lab, Rovigo General Hospital, Rovigo, Italy

5 Division of Cardiology, Adria General Hospital, Echocardiography lab, Adria (Rovigo), Italy

6 Department of Neuroscience, Rovigo General Hospital, Rovigo, Italy

7 Department of Internal Medicine, Rovigo General Hospital, Rovigo, Italy

association between LA size and the clinical severity of PFO as well as a subsequent reduction of LA size after the interatrial defect closure.

## Methods

### Hospital setting, population and protocols

We retrospectively analysed the clinical and instrumental records of 1040 consecutive patients referred to our tertiary center between March 2003 and March 2018, for PFO management and transcatheter closure. To avoid potential bias in the assessment and real LA size, patients with a previous history of untreated arterial hypertension (defined as systolic blood pressure greater than or equal to 140 mmHg and diastolic blood pressure greater than or equal to 90 mmHg in non diabetic patients while as > 135/85 mmHg [7]), and mild or severe mitral valve regurgitation or having a mitral transvalvular mean gradient > 5 mmHg were excluded from the analysis. The Hospital Editorial Board approved the study and all the procedure were performed accordingly the current international guidelines. Per our Institutional protocol, all PFO patients were assessed by a multidisciplinary team composed by skilled cardiologists and neurologists. In all cases, the following instrumental and laboratory investigations were performed: brain Magnetic Resonance Imaging (MRI), prothrombotic defects screening, 7-day electrocardiographic Holter monitoring, Transthoracic (TTE) and contrast Transoesophageal Echocardiography (cTEE) and Trans-Cranial Doppler (TCD) skilled cardiologists and neurologists.

### Criteria for PFO transcatheter closure

The following criteria for transcatheter closure [8] were used:

– previous neurologically confirmed Stroke/Transient Ischemic Attack (TIA)in the absence of alternative causes rather thank the PFO;

or

– positive brain MRI, 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 manoeuvre

and

– medium or large PFO on cTEE.

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

### Echocardiographic protocols

TTE and cTEE were performed using a GE Vivid 7 (General Electric Corp., Norfolk, VA, USA). Both LA function and diameter, as well as RLS degree, assessed by contrast injection during Valsalva manoeuvre, were recorded [9, 10]. ASA was graduated as previously proposed by Olivares et al. [11]. LA antero-posterior diameter was measured in parasternal long-axis view at the level of the aortic valve according to a leading edge–to–leading edge convention (Fig. 1a, b) accordingly to Lang et al. [9]. Baseline and follow-up echocardiographic images and measures were evaluated by two independent cardiologists with and inter-observer agreement of 99.4%.

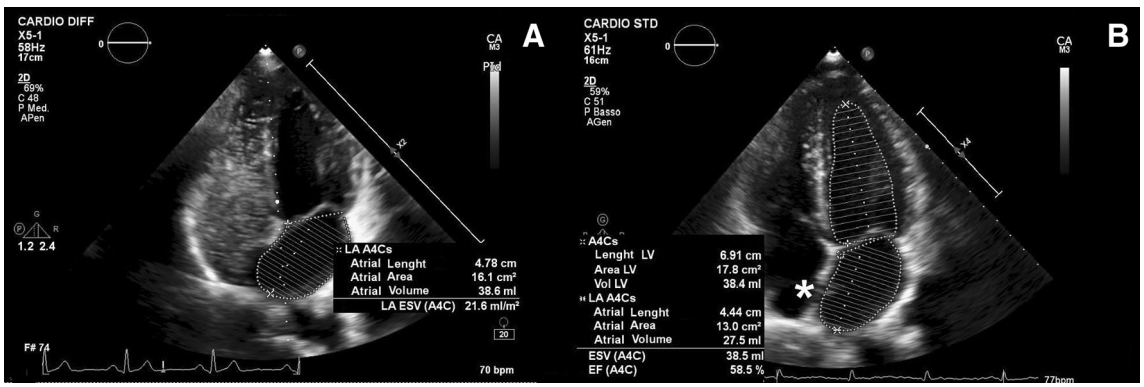


**Fig. 1** Left atrial anteroposterior diameter echocardiographic measurement in parasternal long-axis view before and 1 year after transcatheter closure of patent foramen ovale using a Gore Cardioform 25 mm

### Transcranial Doppler protocol

TCD was performed using intravenous bubble venous injection according to current recommendations [12] 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 cc of saline solution with 2–3 cc of Emagel. As we previously reported, RSL severity was evaluated counting the number of signals in MCA within 7 s from the injection [13].

### 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, CA, USA). The ICE study was conducted by performing a manual pull-back from the superior vena cava to the inferior vena cava through five sectional planes [14]. 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, MN, US), the Premere Occlusion system (St Jude Medical, Plymouth, MN, US) or the Gore Cardioform (WL Gore & Associates, INC, Flagstaff, Arizona, US) were implanted depending on presence /absence of > 2 Olivares et al., ASA, tunnel length > 10 mm, hypertrophy of the rim as well as the mean diameter of the fossa ovalis [15]. Aspirin 100 mg daily or clopidogrel 75 mg daily were given for 6 months after PFO closure. To assess the effect of closure, the 12-month echocardiographic control was chosen and analysed.

### Follow-up protocol

Our follow-up protocol included:cTEE after 1 month from PFO closure (in the presence of an even small residual shunt, cTEE was repeated at 6 months); TTE at 1, 6, and 12 months and every two years; TCD at 1 month; Holter monitoring at 1 month at any point if AF was suspected; clinical evaluation at 1, 6, 12 months and every two years after the first 12 months were also performed. Residual shunt was always assessed by contrast TEE and TCD.

## Statistical analysis

Continues variables were expressed as mean ± standard deviation (SD) and were compared by Student' *T* test if the data had normal distribution, otherwise by Wilcoxon-Mann–Whitney U test. Categorical variables, presented as percentage, were compared by the Pearson's $\chi 2$ test. Pearson's correlation was used to compare left atrial diameter and ejection fraction in different sub-group analyses. To identify the optimal thresholds value of LA diameter as a predictor of a RoPE > 7, a ROC curve analysis was performed. The relationships between the RoPE score and both LA diameter were calculated for independent variables by multivariate logistic regression analysis. Statistical significance was defined as $p < 0.05$. Statistical analyses were performed using SPSS package version 20.0 (SPSS, Chicago, IL, USA).

## Results

### Population findings

Over the study period, 719 patients (mean age 43.7 ± 9.6 years) were included in the analysis (Fig. 2). As expected, the closure group patients were characterized by a more severe ROPE score (7.6 ± 0.8 vs. 4.1 ± 0.9. $p < 0.001$) and had increased prevalence of male gender, stroke, TIA, brain lesions, migraine with aura and MTHFR mutations with hyperomocysteinemia then controls, but similar BMI and body surface (Table 1). The severity of RLS was also greater in the same group.

### Left atrium diameter

Preoperative LA diameter was larger in the closure group than controls (44.3 ± 9 vs. 38.2 ± 6.6 mm < 0.0001, Table 1). However, at 1-year follow-up after closure LA diameter reduced to 37.3 ± 4.1 mm ($p = 0.01$) without difference with controls (38.1 ± 5.3 mm $p = 0.28$, Fig. 3).

A receiver operating characteristics (ROC) curve was used to find the optimal cut-off value of LA diameter as a predictor of RoPE score > 7. Specifically, a LA diameter ≥ 43 mm appeared to be highly specific for the proposed outcome (AUC 0.91, 95% CI 0.81–0.96, $p < 0.0001$, Fig. 4), with a sensitivity, specificity, positive (PPV) and negative (NPV) predictive values of 96.5, 77.8%, 84% and 94%, respectively.

LA diameter was associated with RLS, ASA presence and with the multiple ischemic brain lesions pattern (Table 2): the multivariate analysis identified LA diameter > 43 mm as a predictor of curtain pattern of RLS and of a RoPE score > 7 (Table 3).

## Discussion

In a large cohort of PFO patients, we observed an association between an enlarged LA and the clinical severity of PFO and, foremost, the reversal of this enlargement after PFO closure. LA size was associated to RLS magnitude and

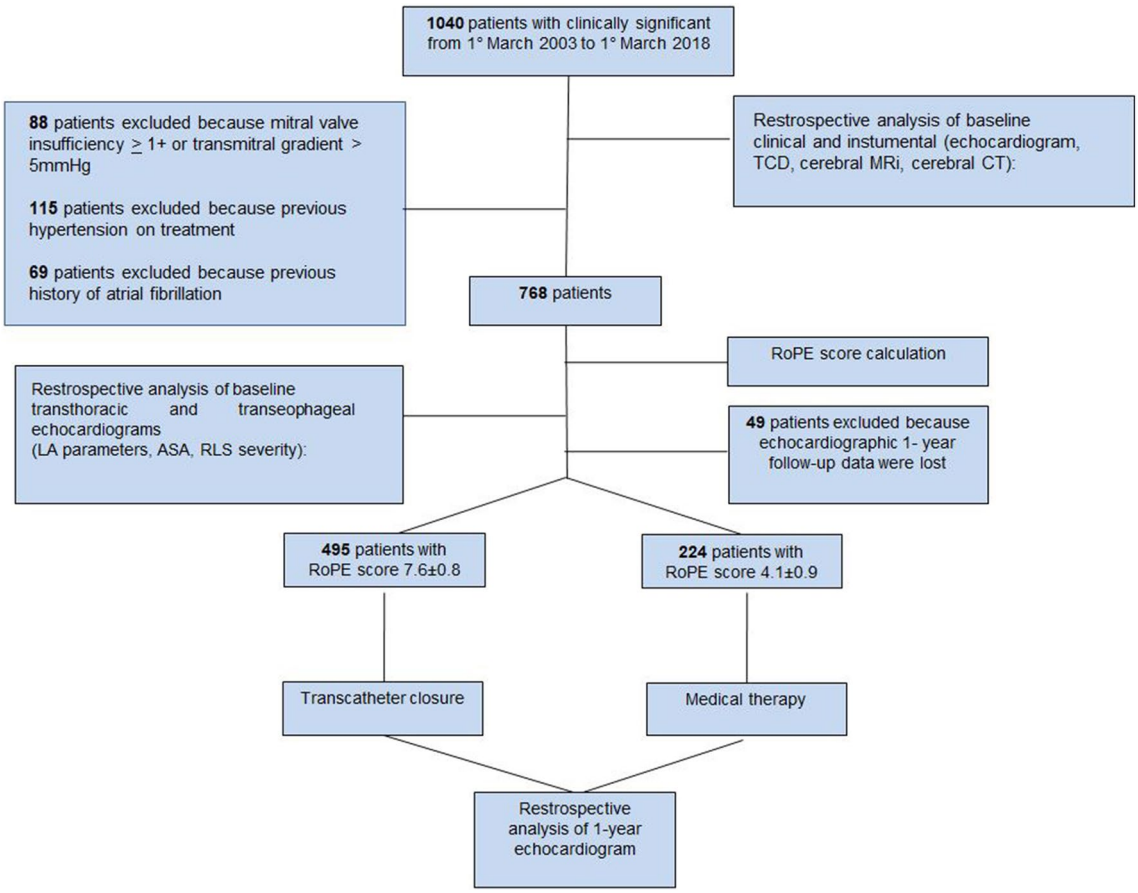


**Fig. 2** Study flow chart

pattern and the presence of ASA. A LA diameter ≥ 43 mm was predictive of a RoPE score > 7 independently from RLS and ASA.

Recently, attention has been posed in LA abnormalities associated to PFO as their potential role in contributing to PFO related ischemic stroke risk. In fact, LA enlargement has been extensively correlated with chronically increased left ventricular filling pressure and left ventricular diastolic dysfunction and found to be associated to unfavorable cardiovascular events including stroke [16–18]. Mahfouz et al. [18] found that LA desynchrony and stiffness are risk markers for PFO-related stroke. Our group and others shown that all the functional parameters of the LA including conduit, reservoir, active and passive emptying are altered in PFO patients with permanent RLS [2, 19].

Lee et al. [4] first demonstrated that in PFO patient an increased LA size was associated with ischemic stroke. Although our patients were characterized by a more severe RoPE score and a larger LA size, our results confirm their findings. Opposite to the study of Lee et al., we investigated the LA diameter than the more complex LA volume index. LA diameter has been demonstrated to correlate well with LA volume in previous analyses [20], its use is more suitable for clinical practice and it has been already used in large cohorts of patients for determining the risk of first clinical cardiovascular events [18] and stroke [21]. The reversal of LA enlargement at 12-month after PFO closure seems to confirm that a significant RLS per se induces LA cardiopathy. In this subject, we recently demonstrated that permanent RLS is associated to a lower blood flow vorticity magnitude in LA and speculated this might contribute to both LA enlargement and potential in situ thrombosis [4]. In the study of Lee, authors failed to find a correlation between LA size and RLS but, differently from our study, they investigated with TCD less than 20% of patients to determine RLS and in the study group the mean LA diameter was less than 37 mm, this not enabling any correlation between RLS and LA size. A complete analysis of LA function has been already provided by our group elsewhere [1]. However, in daily clinical practice, a simpler maker, able to identify as a first step-line those PFO patients at higher risk, as the LA diameter, may be helpful in daily clinical practice.

**Table 1** Demographics, clinical and echocardiographic characteristics of the study and control population

| Demographics and anthropometrics | Closure group N = 495 | Controls N = 224 | p |
|---|---|---|---|
| Age (years) | 44.3 ± 15.8 | 42.0 ± 11.4 | 0.50 |
| RoPE score | 7.6 ± 0.8 | 4.1 ± 0.9 | < 0.001 |
| Male, n (%) | 274 (55.3) | 106 (47.3) | 0.04 |
| Body surface | 1.79 ± 0.04 | 1.78 ± 0.12 | 0.77 |
| BMI (Kg/m$^2$) | 25.2 ± 12.8 | 24.6 ± 10.8 | 0.78 |
| Clinical variables | | | |
| SBP (mmHg) | 127.1 ± 15.4 | 125.1 ± 16.1 | 0.54 |
| DBP (mmHg) | 78.5 ± 11.4 | 74.9 ± 12.6 | < 0.0001 |
| HR (beats per minute) | 73.0 ± 12.2 | 70.1 ± 11.4 | 0.03 |
| PP (mmHg) | 48.6 ± 16.8 | 50.3 ± 10.9 | 0.16 |
| HT, n (%) | 108 (21.8) | 59 (26.3) | 0.18 |
| Diabetes mellitus, n (%) | 115 (23.2) | 51 (22.7) | 0.88 |
| Dyslipidaemia, n (%) | 75 (15.2) | 39 (17.4) | 0.44 |
| Active smokers, n (%) | 90 (18.2) | 41 (18.3) | 0.97 |
| Previous smokers, n (%) | 72 (14.5) | 15 (6.6) | 0.02 |
| TIA, N (%) | 146 (29.4) | 8 (3.5) | < 0.0001 |
| Stroke, n (%) | 126 (25.5) | 3 (1.4) | < 0.0001 |
| Migraine with aura, n (%) | 171 (34.5) | 21 (9.3) | < 0.0001 |
| Migraine without aura, n (%) | 90 (18.2) | 36(16.0) | 0.46 |
| Thrombophilia | | | |
| ATIII, n (%) | 24 (4.8) | 10 (4.4) | 0.81 |
| PRS, n (%) | 45 (9.1) | 19 (8.4) | 0.76 |
| PRC, n (%) | 72 (14.5) | 30 (13.2) | 0.66 |
| FV Leiden Homozigosis, n (%) | 0 (0) | 7 (3.1) | 0.001 |
| Hyperhomocysteinemia, n (%) | 153 (30.9) | 22 (9.8) | < 0.0001 |
| Mutation MTHFR 677 T, n (%) | 120 (24.2) | 16 (7.1) | < 0.0001 |
| Mutation MTHFR 1298 AC, n (%) | 99 (20.0) | 13 (5.8) | < 0.0001 |
| Auto-antibodies | | | |
| Antiphospholipid, n (%) | 0 (0) | 9 (4.0) | 0.001 |
| Anticardiolipin, n (%) | 54 (10.9) | 15 (5.3) | 0.01 |
| Shunt, TDC and cerebral lesions | | | |
| Continues shunt without Valsalva, n (%) | 188 (37.9) | 18 (8.0) | < 0.0001 |
| TDC curtain pattern, n (%) | 315 (63.6) | 16 (7.1) | < 0.0001 |
| TDC shower pattern, n (%) 9 | 180 (36.3) | 208 (92.8) | < 0.0001 |
| Number of brain lesion at MRI | 1.6 ± 1.5 | 0.3 ± 0.5 | < 0.0001 |
| At least 1 brain lesion at MRI/CT | 297 (60.0) | 188 (84.0) | < 0.0001 |
| > 1 brain lesion at cerebral CT scan, n (%) | 198 (40.0) | 36 (16.0) | < 0.0001 |
| Echocardiography parameters | | | |
| LA AP diameter (mm) | 44.3 ± 9.1 [21.1–69.4] | 38.2 ± 6.6 [18.2–46.1] | < 0.0001 |
| LA 4C area (cm$^2$) | 35.7 ± 5.8 | 16.7 ± 3.8 | < 0.0001 |
| LA 2C area (cm$^2$) | 34.2 ± 5.1 | 15.1 ± 4.0 | < 0.0001 |
| LA Ejection fraction (%) | 0.53 ± 0.8 [0.31–0.77] | 0.59 ± 0.3 [0.48–0.61] | 0.27 |
| LA maximal volume (ml) | 98.5 ± 16.3 | 99.4 ± 21.6 | 0.29 |
| LA minimal volume (ml) | 45.8 ± 20.1 | 44.7 ± 19.8 | 0.31 |
| LAA peak flow velocity (cm/s) | 48.1 ± 21.0 | 49.8 ± 23.2 | 0.18 |
| ASA (number of patients/%) | 315 (63.6%) | 46 (20.5%) | < 0.0001 |
| Left ventricle VTD (ml) | 68.9 ± 15.4 [38.7–110.4] | 66.6 ± 12.8 [42.1–90.6] | 0.05 |
| Left ventricle VTS (ml) | 22.8 ± 10.3 [11.8–61.9] | 20.1 ± 0.8 [9.27–51.4] | 0.001 |
| Left ventricle EF (%) | 0.67 ± 0.8 [0.43–0.80] | 0.71 ± 0.9 [0.46–0.81] | 0.55 |

*ASA* atrial septal aneurysm, *BMI* Body mass index, *DBP* Diastolic blood pressure, *HR* Heart rate, *HT* Arterial hypertension, *LA* left atrium, *LAA* left atrium appendage, *LVEF* left ventricular ejection fraction, *PP* Pulse pressure, *RoPE* Risk of paradoxical embolism score, *SBP* Systolic blood pressure, *TIA* Transient ischemic attack, *VTDi* tele-diastolic volume, *VTS* tele-systolic volume

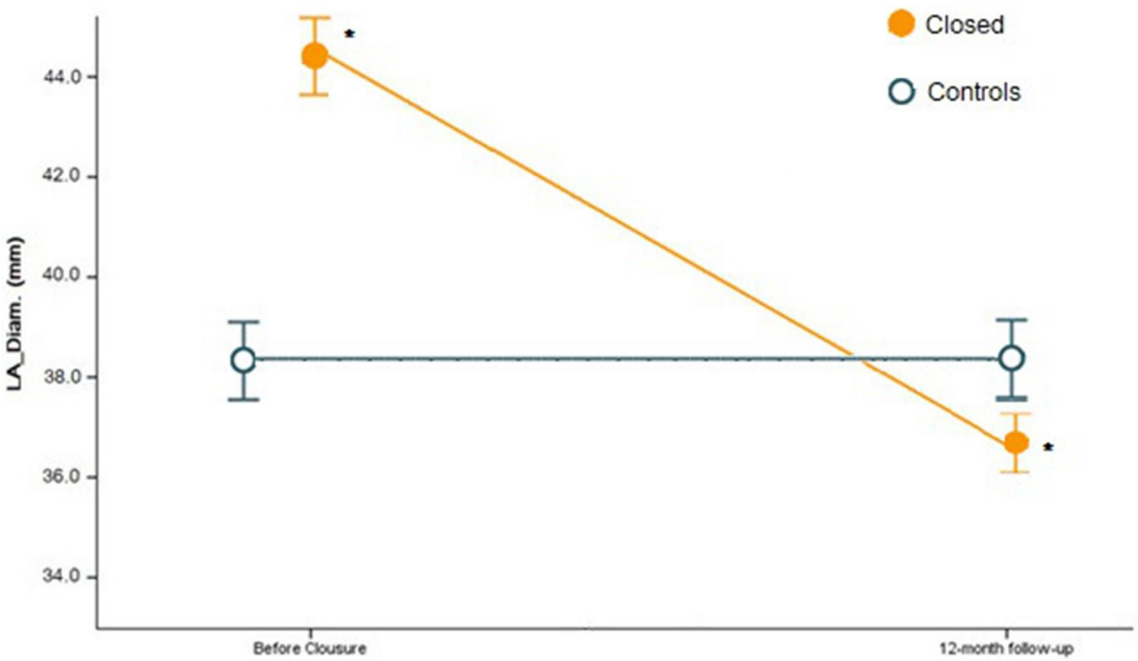


**Fig. 3** Graphic representation of decrease and normalization of the Left atrium diameter after closure at 12-months follow up. 1-year follow up window has been selected to avoid potential interferences by other factors than closure procedure. *p = 0.01

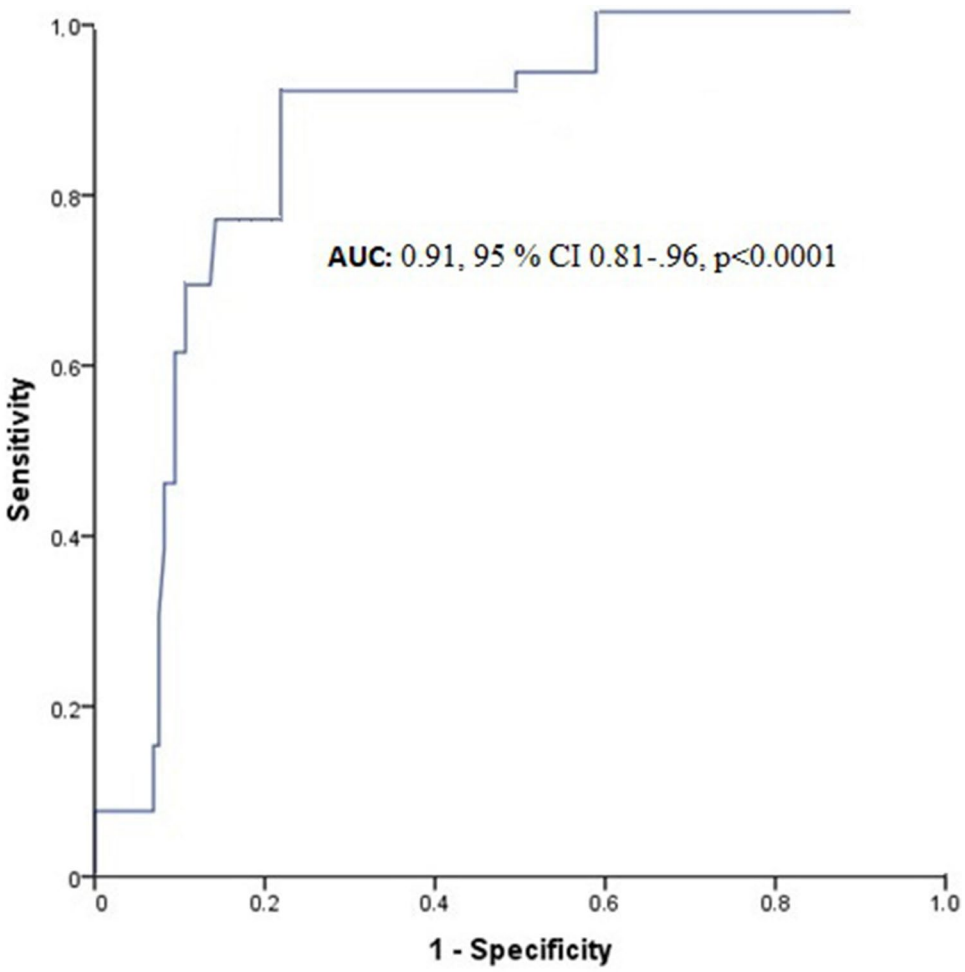


**Fig. 4** ROC curve analysis: 43 mm resulted the best cut off value

**Table 2** Correlations between left atrial diameter ASA, RLS and MRI pattern

| Clinical variables | LA diameter (mean ± SD) | p |
|---|---|---|
| RLS | | |
| Curtain | 46.2 ± 3.4 | 0.001 |
| Shower | 44.3 ± 3.6 | |
| Valsalva | 41.8 ± 3.3 | < 0.0001 |
| Permanent | 47.5 ± 4.9 | |
| ASA | | |
| Yes | 47.3 ± 2.6 | < 0.0001 |
| No | 42.2 ± 3.3 | |
| Brain RMi | | |
| Multiple lesion | 49.4 ± 2.2 | < 0.0001 |
| No lesion | 41.3 ± 2.9 | |

*ASA* atrial septal aneurysm, *LA* left atrium, *MRI* magnetic resonance imaging, *RLS* right-to-left shunting, *SD* standard deviation

**Table 3** Multivariate analysis for RoPE score > 7 and Curtain versus shower pattern of RLS

| | β | Wald | Sig | OR | 95% CI |
|---|---|---|---|---|---|
| Outcome: RoPE score > 7 | | | | | |
| Valsalva RLS | 1.80 | 12.7 | < 0.0001 | 3.02 | 2.84–3.51 |
| Permanent RLS | 1.77 | 40.10 | < 0.0001 | 3.26 | 3.02–4.34 |
| ASA[a] | 1.69 | 27.33 | 0.001 | 5.04 | 2.64–6.28 |
| LA diameter > 43[b] | 0.71 | 6.69 | < 0.0001 | 2.78 | 2.46–3.06 |
| Outcome: curtain versus Shower RL | | | | | |
| RoPE > 7 | 1.94 | 24.3 | < 0.0001 | 4.21 | 3.54–4.92 |
| ASA[a] | 1.77 | 10.1 | 0.001 | 2.16 | 1.92–3.26 |
| LA diameter > 43 | 1.96 | 25.9 | < 0.0001 | 4.52 | 4.11–4.98 |

[a]Atrial septal aneurysm more than 2RL or 2LR following Olivares et al. [11]

[b]LA diameter < 43 mm versus > 43 mm. Adding gender did not modify both models

## Limitations

Our study suffers from a number of limitations including firstly its retrospective nature and the non -randomized fashion: nevertheless, the size of the sample and amount of data are significant, and we believe that these two factors may mitigate the aforementioned limits. The use of LA diameter as the only parameter to investigate LA cardiopathy may limit the study conclusions. On the other side, this parameter has been widely used in literature to analyse the risk of stroke in different cardiac conditions and it is easier to be obtained in common clinical practice.

## Conclusions

A LA diameter ≥ 43 mm is associated with permanent/curtain pattern of RLS, ASA and brain damage severity in patients with symptomatic PFO. LA Size reverses after PFO closure, this suggesting a severe RLS may induce LA cardiopathy. LA enlargement has the potential to be considered per se an indication to transcatheter PFO repair.

### Compliance with ethical standards

**Conflict of interest** The authors declare that they have no conflict of interest.

**Ethical approval** The study was approved by the local board.

**Informed consent** Informed consent was obtained from all individual participants included in the study.

## References


1. Rigatelli G, Aggio S, Cardaioli P, Braggion G, Giordan M, Dell'avvocata F, Chinaglia M, Rigatelli G, Roncon L, Chen JP (2009) Left atrial dysfunction in patients with patent foramen ovale and atrial septal aneurysm: an alternative concurrent mechanism for arterial embolism? JACC Cardiovasc Interv 2:655–662.
2. Rigatelli G, Dell'Avvocata F, Cardaioli P, Giordan M, Braggion G, Aggio S, Chinaglia M, Mandapaka S, Kuruvilla J, Chen JP, Nanjundappa A (2011) Permanent right-to-left shunt is the key factor in managing patent foramen ovale. J Am Coll Cardiol 58:2257–2261
3. Cotter PE, Martin PJ, Pugh PJ, Warburton EA, Cheriyan J, Belham M (2011) Increased incidence of interatrial block in younger adults with cryptogenic stroke and patent foramen ovale. Cerebrovasc Dis Extra 1:36–43
4. Rigatelli G, Fong A, Nguyen T (2018) Computational flow dynamic analysis of right and left atrial in patent foramen ovale: potential links with atrial fibrillation. J AtrFibr 10:1–4
5. Kim TW, Jung SW, Song IU, Koo J, Choi HS, Lee KS, Park JW, Park HJ, Kim JS (2015) Left atrial dilatation is associated with severe ischemic stroke in men with non-valvular atrialfibrillation. J Neurol Sci 354:97–102
6. Lee MJ, Park SJ, Yoon CH, Hwang JW, Ryoo S, Kim SJ, Kim GM, Chung CS, Lee KH, Bang OY (2016) Association of left atrial enlargement with cortical infarction in subjects with patent foramen ovale. J Stroke 18:304–311
7. Williams B, Mancia G, Spiering W, Agabiti Rosei E, Azizi M, Burnier M, Clement DL, Coca A, de Simone G, Dominiczak A, Kahan T, Mahfoud F, Redon J, Ruilope L, Zanchetti A, Kerins M, Kjeldsen SE, Kreutz R, Laurent S, Lip GYH, McManus R, Narkiewicz K, Ruschitzka F, Schmieder RE, Shlyakhto E, Tsioufis C, Aboyans V, Desormais I; ESC Scientific Document Group (2018) 2018 ESC/ESH Guidelines for the management of arterial hypertension. Eur Heart J 39:3021–3104
8. Pristipino C, Anzola GP, Ballerini L, Bartorelli A, Cecconi M, Chessa M, Donti A, Gaspardone A, Neri G, Onorato E, Palareti G, Rakar S, Rigatelli G, Santoro G, Toni D, Ussia GP, Violini R, Italian Society of Invasive Cardiology (SICI-GISE); Italian Stroke

Association (ISA-AIS); Italian Association of Hospital Neurologists, Neuroradiologists, Neurosurgeons (SNO); Congenital Heart Disease Study Group of Italian Society Of Cardiology; Italian Association Of Hospital Cardiologists (ANMCO); Italian Society Of Pediatric Cardiology (SICP); Italian Society of Cardiovascular Echography (SIEC); Italian Society of Hemostasis and Thrombosis (SISET) (2013) Management of patients with patent foramen ovale and cryptogenic stroke: a collaborative, multidisciplinary, position paper: executive summary. Catheter Cardiovasc Interv 82:122–129

9. Lang RM, Badano LP, Mor-Avi V, Afilalo J, Armstrong A, Ernande L et al (2015) Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European Association of cardiovascular imaging. J Am Soc Echocardiogr 28:1–39
10. Silvestry FE, Cohen MS, Armsby LB, Burkule NJ, Fleishman CE, Hijazi ZM, Lang RM, Rome JJ, Wang Y; American Society of Echocardiography; Society for Cardiac Angiography and Interventions (2015) Guidelines for the echocardiographic assessment of atrial septal defect and patent foramen ovale: from the American Society of echocardiography and Society for cardiac angiography and interventions. J Am Soc Echocardiogr 28:910–958
11. Olivares-Reyes A, Chan S, Lazar EJ, Bandlamudi K, Narla V, Ong K (1997) Atrial septal aneurysm: a new classification in two hundred five adults. J Am Soc Echocardiogr 10:644–656
12. American College of Radiology. ACR-SPR-SRU practice parameter for performing and interpreting diagnostic ultrasound examinations 2017. https://www.acr.org/-/media/ACR/Files/Practice-Parameters/US-Transcranial.pdf
13. Homma S, Messe SR, Rundek T et al (2016) Patent foramen ovale. Nat Rev Dis Prim 2:15086
14. Rigatelli G, Hijazi ZM (2006) Intracardiac echocardiography in cardiovascular catheter-based interventions: different devices for different purposes. J Invasive Cardiol 18:225–233.
15. Rigatelli G, Pedon L, Zecchel R, Dell'Avvocata F, Carrozza A, Zennaro M, Mazza A, Zuin M, Russo M, Zanchetta M (2016) Long-term outcomes and complications of intracardiac echocardiography-assisted patent foramen ovale closure in 1,000 consecutive patients. J Interv Cardiol 290:530–538
16. Mancusi C, Canciello G, Izzo R, Damiano S, Grimaldi MG, de Luca N, de Simone G, Trimarco B, Losi MA (2018) Left atrial dilatation: A target organ damage in young to middle-age hypertensive patients. The Campania Salute Network. Int J Cardiol 265:229–233
17. Sardana M, Lessard D, Tsao CW, Parikh NI, Barton BA, Nah G, Thomas RC, Cheng S, Schiller NB, Aragam JR, Mitchell GF, Vaze A, Benjamin EJ, Vasan RS, McManus DD (2018) Association of left atrial function index with atrial fibrillation and cardiovascular disease: the framingham offspring study. J Am Heart Assoc 7:e008435
18. Kizer JR, Bella JN, Palmieri V, Liu JE, Best LG, Lee ET, Roman MJ, Devereux RB (2006) Left atrial diameter as an independent predictor of first clinical cardiovascular events in middle-aged and elderly adults: the Strong Heart Study (SHS). Am Heart J 151:412–418
19. Goch A, Banach M, Piotrowski G, Szadkowska I, Goch JH (2007) Echocardiographic evaluation of the left atrium and left atrial appendage function in patients with atrial septum aneurysm: implications for thromboembolic complications. Thorac Cardiovasc Surg 55:365–370.
20. Canciello G, de Simone G, Izzo R, Giamundo A, Pacelli F, Mancusi C, Galderisi M, Trimarco B, Losi MA (2017) Validation of left atrial volume estimation by left atrial diameter from the parasternal long-axis view. J Am Soc Echocardiogr 30:262–269
21. Yaghi S, Moon YP, Mora-McLaughlin C, Willey JZ, Cheung K, Di Tullio MR, Homma S, Kamel H, Sacco RL, Elkind MS (2015) Left atrial enlargement and stroke recurrence: the Northern Manhattan Stroke Study. Stroke 46:1488–1493