Heart and Vessels (2019) 34:1499–1508
https://doi.org/10.1007/s00380-019-01385-2

ORIGINAL ARTICLE

Atrial septal defect and patent foramen ovale: early and long-term effects on endothelial function after percutaneous occlusion procedure

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Received: 22 October 2018 / Accepted: 15 March 2019 / Published online: 20 March 2019

Abstract

Percutaneous closure of atrial septal defect (ASD)/patent foramen ovale (PFO) can influence systemic hemodynamics. The aim of this research was to evaluate the influence of the closure procedure on morphological and functional characteristics of systemic vascular walls. Fourteen ASD (mean age 40 ± 16 years) and 14 PFO (45 ± 8 years) patients were enrolled in this retrospective study. All underwent percutaneous closure procedure; physical, clinical and biochemical evaluations; echocardiography; carotid evaluation; and brachial artery flow-mediated vasodilatation (FMD). All the evaluations were performed at the time of enrollment, 24 h post-procedure, at 1–6–12-month follow-up. FMD at enrollment was higher in PFO patients as compared to ASD (8.5% [7.6–10.7%] versus 6.5% [5.6–7.6%], $p < 0.0001$). FMD values in ASD patients significantly increased during follow-up (enrollment: 6.5% [5.6–7.6%], 12-month follow-up: 8.8% [7.2–10.3%], $p < 0.01$). PFO patients showed reduced FMD values 24 h after the procedure (enrollment: 8.5% [7.6–10.7%], 24 h post-procedure: 7% [6.3–9%], $p < 0.001$), while recovering endothelial function during follow-up period to baseline values (FMD at 12-month follow-up: 8.2% [7.6–10.5%]). At one-year follow-up, FMD remained inversely related to systolic pulmonary arterial pressure and right and left atrial/ventricle chambers dimensions (RV proximal diameter efflux tract, right atrium [RA] longitudinal diameter, RA transverse diameter, RA area, left ventricle [LV] end-diastolic diameter, left atrium [LA] anteroposterior diameter, LA area; $p < 0.01$) in ASD patients. Endothelial function improved after percutaneous closure of ASD, while remaining stable after PFO closure. Therefore, ASD patients seem to improve their cardiovascular risk profile after percutaneous closure of their defect.

Keywords Atrial septal defect · Patent foramen ovale · Percutaneous closure procedure · Endothelial function

Introduction

Atherosclerosis is a systemic inflammatory disease involving the walls of the vascular tree and contributing to the highest degree in mortality rate in developed countries [1, 2].

Several well-established risk factors had been considered to be related to the development of atherosclerosis: hypertension, dyslipidemia, diabetes, smoke, age, etc. [3]. Nevertheless, many other pathological conditions can influence the development and progression of the atherosclerotic process, such as chronic systemic inflammatory diseases, chronic obstructive pulmonary diseases and bowel inflammatory diseases [4, 5].

Atrial septal defect (ASD) and patent foramen ovale (PFO) are two of the most prevalent congenital heart diseases: the former shows an incidence of about 56 per

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s00380-019-01385-2) contains supplementary material, which is available to authorized users.

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100,000 live births and prevalence equal to 6–10% in children and 30% in adults suffering from congenital heart defects; the latter a prevalence of 20–25% in the general population [6–9].

The alteration in systemic hemodynamics related to non-corrected defects can theoretically influence both the systemic and pulmonary vascular performance. The changes in vascular shear stress, the reduction in arterial compliance due to increased solicitation of biomechanical endothelial cells receptors and the consequences of the biochemical intracellular pathways can promote the development of endothelial dysfunction and morphological vascular wall alterations [10, 11]. Some studies [12] demonstrated amelioration in nitric oxide production in the vascular stream after percutaneous closure of cardiac defects. This reveals the theoretical influence of such procedure on endothelial function [13].

Recent work from Rodés-Cabau et al. [14] tried to evaluate the influence of PFO presence on the atherosclerotic burden of young patients suffering from a cryptogenic stroke, but they did not observe an increase in carotid intima-media thickness (C-IMT) or a decrease in endothelial function as compared to patients without PFO.

The aim of this research was to establish the systemic atherosclerotic burden derived from PFO/ASD presence and the possible influence of the closure procedure on morphological and functional vascular performances. A secondary endpoint was to confirm the literature in terms of amelioration of cardiac chamber remodeling after percutaneous PFO/ASD closure [15–21] and the possible relationship between such changes and endothelial function/morphology.

Materials and methods

Study population

This was a retrospective study. We consecutively enrolled 14 patients with ASD ostium secundum type (1 male, mean age 40 ± 16 years) and 14 patients with PFO (6 males, mean age 45 ± 8 years) who were admitted to the Invasive Cardiology Section, Department of Cardiac Surgery, Policlinic Hospital-University of Bari, Bari—Italy, in order to undergo percutaneous closure procedure. The study was performed in collaboration with the Angiology Section, Department of Cardiovascular Diseases, Policlinic Hospital-University of Bari, Italy.

Inclusion criteria ASD/PFO diagnosed by means of transthoracic (TTE) and transesophageal (TEE) echocardiography; indication to percutaneous closure of ASD in line with European Guidelines for the management of Grown-up Congenital Heart Disease (GUCH) [22]; indication to percutaneous closure of PFO in agreement with Italian Society of Cardiology and Neurology Guidelines [23].

Exclusion Criteria Patients suffering from any major cardiovascular risk factors (hypertension defined as systolic blood pressure > 140 and diastolic blood pressure > 90 mmHg or use of anti-hypertensive drugs; dyslipidemia defined as total cholesterol (TC) > 200 mg/dL; low-density lipoprotein cholesterol (LDL-C) > 130 mg/dL, high-density lipoprotein cholesterol (HDL-C) < 45 mg/dL, triglycerides > 150 mg/dL or use of lipid-lowering drugs; diabetes defined as fasting glycemia > 126 mg/dL or use of antidiabetic drugs; and smoking defined as at least 5 cigarettes/day consumption within the 3 months before hospital admission or smoking habit interruption within one years before study entry) [3]; history of cardiovascular diseases (peripheral artery diseases; previous myocardial infarction; previous myocardial revascularization; stable coronary artery diseases; any cardiomyopathies; heart valve diseases; acute/chronic heart failure, etc.); history of kidney/liver diseases; suspected or diagnosed neoplasm; acute and/or chronic systemic inflammatory diseases.

Informed consent was obtained from each patient before enrollment. The study was performed in agreement with the ethical guidelines of the Declaration of Helsinki and received the approval from the local ethics committee.

Clinical/anthropometric and biochemical evaluations

All the patients underwent physical and clinical evaluation. Biochemical evaluations were performed at 8.00 a.m.; the patients fast for at least 12 h. Blood samples were collected the day before percutaneous procedure (evaluation: complete blood count [CBC], fasting glycemia, blood urea nitrogen, creatinine, liver enzymes, total cholesterol [TC], low-density lipoprotein cholesterol [LDL-C], high-density lipoprotein cholesterol [HDL-C], triglycerides, C-reactive protein [CRP]), and the day after procedure, one month, six months and one year later (CBC and CRP). In particular, our laboratory considers "normal" CRP whose normal values were < 2.9 mg/L.

Echocardiographic evaluations

All the patients underwent TTE evaluation the day before the procedure, then the day after, at one-month, six-month and one-year follow-up visits. The ultrasound examinations were performed by means of GE Healthcare Vivid 7 machine, M4S probe. All the ultrasound examinations were performed by the same physician in order to avoid inter-observer variability.

The following echocardiographic parameters were measured in agreement with the American Society of

Echocardiography (ASE) and the European Association of Cardiovascular Imaging (EACVI) recommendations [24, 25]: anteroposterior (LAAP), longitudinal (LAL) and transverse (LAT) diameters of the left atrium; left atrium area (LAA), left ventricle end-diastolic diameter (LVEDD), left ventricle ejection fraction (LVEF), longitudinal (RAL) and transverse (RAT) diameters of the right atrium, right atrium area (RAA), proximal diameter of the right ventricle outflow tract (RVOT PD, parasternal view, short axis), diastolic basal diameter of the right ventricle inflow tract (RVIT DD), tricuspid annular plane systolic excursion (TAPSE), estimated systolic pulmonary arterial pressure (sPAP), pulmonary-to-systemic blood flow ratio (Q_p/Q_s ratio) in ASD patients.

Ultrasound carotid evaluation

Ultrasonographic echo-color Doppler studies of left and right common carotid arteries were performed bilaterally with a Philips Sonos 5500 using a 7.5-MHz high-resolution probe. All the ultrasound examinations were performed by the same physician in order to avoid inter-observer variability. Carotid evaluations were originally performed the day before the procedure and then repeated at follow-up. The patients were placed in supine position, with the neck extended and rotated contralaterally by 45°, and the common carotid arteries were examined on the sagittal axis with a lateral view. Carotid IMT was defined as a low-level echo gray band that does not project into the arterial lumen and was measured during end-diastole according to the method described by Pignoli [26]. The measurements were bilaterally taken 1 cm proximally to the carotid bulb, for three times, and mean C-IMT was calculated. C-IMT measurements were always taken in arterial segment devoid of atherosclerotic plaque, defined according to Mannheim carotid intima-media thickness consensus (2004–2006) as C-IMT greater than 1.5 mm or a focal structure encroaching into the arterial lumen of at least 0.5 mm or 50% of the surrounding C-IMT value [27].

Flow-mediated vasodilation of the brachial artery

Temperature, food, stress, drugs and sympathetic stimuli influence the FMD. The study was performed with the subjects fasting for at least 8–12 h, in a quiet air-conditioned room (22–24° C), early in the morning, the day before the procedure and then repeated at follow-up. The subjects were asked not to play exercise, or take exciting substances like coffee/tea, chocolate which could impair endothelial function and for at least 4–6 h before the examination. The right brachial artery was evaluated in a long-axis projection between 5 and 10 cm above the elbow using a 7.0-MHz or higher linear probe. The study was performed using a high-resolution ultrasonography (Philips Sonos 5500) connected to an image analysis system, certified by the CNR of Pisa (MVE II) [28]. All the ultrasound examinations were performed by the same physician in order to reduce bias. With the subject in supine position for at least 10 min, the arm was positioned comfortably in order to get good images of the brachial artery. A sphygmomanometer cuff was placed in the distal site to the artery, in cases of a humeral artery on the forearm. After 1 min of flow image baseline acquisition, the artery was occluded by inflating the cuff to a pressure of 200–220 mmHg for exactly 5 min. After cuff deflation, a high-flow condition (reactive hyperemia in the forearm microcirculation) develops. The resulting increased shear stress provides the stimulus for dilatation of the humeral artery. Within 15 s from the end of ischemia, the flow rate was measured and then the degree of hyperemia. The image of the artery was then recorded continuously for 2–3 min after ischemia. Reactive hyperemia was calculated as the ratio of the change in diameter (maximal dilatation after deflation-baseline) divided by the baseline value, which corresponds to the maximum FMD recovery value. FMD was analyzed as the percentage increase in brachial artery diameter after the application of a pressure stimulus [29].

Percutaneous closure procedure of ASD and PFO defects

All the patients underwent clopidogrel bolus (600 mg) the day before the procedure; 1 h before the procedure performance, an i.v. antibiotic was administered. Local regional anesthesia was bilaterally performed at the level of the inguinal region before the entering of the septal occluder device. This was positioned under fluoroscopic guide and intracardiac echocardiographic (ICE) monitoring which used an 8-F (Siemens) ACUSON AcuNav™ probe. The latter was introduced through the left femoral vein and finally positioned at right atrium level; a 10- or 12-F delivery catheter was used.

The measurement of the defect's diameter of ASD patients was taken both by ICE and through the distension of the defect borders by means of a pre-calibrated catheter balloon and the subsequent ultrasound evaluation of the absence of interatrial flow (stretched diameter). The septal device had a dimension equal to or inferior to 2 mm as compared to ASD stretched diameter.

The measurements of the fossa ovalis diameters and the whole interatrial septal length of PFO patients were obtained by means of ICE; the length of the PFO tunnel and the edge thickness were also measured. Atrial septal aneurysm (ASA) was classified according to Olivares' criteria [30]. The kind of device was chosen in relation to qualitative and quantitative data obtained from ICE evaluation, i.e., length of the edge, the presence of bidirectional ASA or atrial septal bulging.

After the selection of the most reliable device, this was pulled till left atrium and correctly positioned. After the positioning of the device, ICE and fluoroscopic evaluations were performed in order to evaluate the correct position of the device. During all the stages of the procedure, the activated clotting time (ACT) was measured and kept to a level of 200–300 s with repeated controls every 20–30 min. In cases where the ACT was less than 200 s, another injection of 25–50 unit/kg/dose of unfractionated heparin was allowed.

The patients received double antiplatelet drug therapy (aspirin 300 mg o.d. and clopidogrel 75 mg o.d.) during the next one month from the procedure; after one month, a single treatment with aspirin 300 mg o.d. (or clopidogrel 75 mg o.d. in case of aspirin intolerance) was maintained till one-year follow-up.

Statistical analysis

Categorical variables are given as frequencies. Nonparametric tests have been used for the small dimension of samples. Data are expressed as median and interquartile range (IQR). The differences between the groups were made by using the Mann–Whitney U test for two independent samples or the Wilcoxon test for dependent samples. Frequencies were compared using Chi-square or Fisher's exact test. Correlation analysis was performed with the Spearman rank-order correlation. In the multiple comparisons, Bonferroni correction was applied to p values to avoid statistical inferences. The statistical significance was set at p values < 0.05. All the statistical analyses were performed by means of SPSS Statistics 20. The intraobserver variability of ultrasound measurements was assessed by the intraclass correlation coefficient (ICC good if > 0.80 [31]). In particular, the evaluation of C-IMT shows excellent reproducibility with an ICC of 0.97 as well as FMD with an ICC of 0.96.

Results

Table 1 shows the main characteristics of the study population. ASD and PFO patients showed similar anthropometric, clinical and biochemical features, although the distribution of male and female was different between the two groups: most of ASD patients were female, while PFO patients

Table 1 Main characteristics of the population of the study

	ASD		PFO		p value
No. of patients	14		14		NS
Gender (M/F)	1/13		6/8		0.03
Clinical history (n)					
Stroke/TIA	7		14		
Exertional dyspnea	1		0		
Occasional diagnosis	6		0		
	Median	Interquartile range	Median	Interquartile range	
Age (years)	35	27.5–58.25	46	37.25–52.25	NS
Body mass index (kg/m^2)	25	21–30	24.5	22.6–25.9	NS
Systolic blood pressure (mmHg)	120	115–130	112.5	118.7–130	NS
Diastolic blood pressure (mmHg)	75	70–80	80	73.7–85	NS
Blood sample					
White blood cell count (10^3/uL)	6.3	5.3–8.7	7.4	6–7.9	NS
Fasting glycemia (mg/dL)	83	76.25–90.25	87.5	80–90	NS
Total cholesterol (mg/dL)	177.5	144–195.7	159.5	147.25–194.25	NS
LDL-C (mg/dL)	97	74–129	89	79.7–116	NS
HDL-C (mg/dL)	53.5	46.7–66.2	50	41.7–59	NS
Triglycerides (mg/dL)	80.5	50–100	89.5	62.5–131.25	NS
CRP (mg/L)	1.5	1.17–2.1	1.8	1.2–2.2	NS
Q_p/Q_s ratio	2.2	2.2–2.2	–	–	–
Baseline C-IMT (mm)	0.5	0.48–0.67	0.6	0.55–0.7	NS
Baseline FMD (%)	6.5	5.6–7.6	8.5	7.6–10.7	0.0002

Data are expressed as number or as mean ± standard deviation or median and interquartile range. *ASD* atrial septal defect, *C-IMT* carotid intima-media thickness, *CRP* C-reactive protein, *FMD* flow-mediated vasodilation, *HDL–C* high-density lipoprotein cholesterol, *LDL–C* low-density lipoprotein cholesterol, *PFO* patent foramen ovale, Q_p/Q_s *ratio* pulmonary-to-systemic blood flow ratio, *TIA* transient ischemic attack

showed an almost equal distribution between female and male. There were no cardiovascular adverse outcomes (death from any cause, death from cardiovascular diseases, stroke/transient ischemic attack, hospitalization due to cardio-/cerebrovascular events, etc.) during the entire duration of the follow-up period.

Baseline brachial artery FMD was higher in PFO patients than in ASD whose value was below the normal range (8.5% [7.6–10.7%] versus 6.5% [5.6–7.6%] in ASD patients, $p = 0.0002$) (Table 1). Beyond endothelial dysfunction, no vascular morphological alterations were between the two groups as they showed similar values of baseline carotid IMT (PFO: 0.6 mm [0.55–0.7 mm] versus ASD: 0.5 mm [0.48–0.67 mm], $p =$ ns).

Table 2 provides data about the variations in FMD values during follow-up periods. The FMD values recovered in ASD patients after percutaneous closure procedure. During the 12-month follow-up period, the values of FMD significantly increased in ASD patients as compared to enrollment phase, progressively transiting from 6.5% [5.6–7.6%] to 8.8% [7.2–10.3%] ($p < 0.01$, after Bonferroni's method correction). Inflammatory markers such as CRP and white blood cell count, despite a transient increase 24 h after the percutaneous procedure, turned to baseline values at 12-month follow-up, with no statistically significant differences with baseline values. Such variation in inflammatory biomarkers may reflect a direct effect of the closure procedure itself.

No differences were for FMD values in PFO patients when comparing enrollment values to 12-month follow-up evaluation (Table 2). Our results demonstrated a sudden, significant decrease in FMD values soon after the percutaneous procedure, as compared to the baseline levels (enrollment: 8.5% [7.6–10.7%]; 24 h after procedure: 7% [6.3–9%], $p < 0.001$, after Bonferroni's method correction). Nevertheless, a prompt recover was noticed during the next follow-up evaluations, till returning to baseline levels at 12-month follow-up (enrollment: 8.5% [7.6–10.7%]; 12 months: 8.2% [7.6–10.5%], $p <$ ns).

Supplementary Table 1 gathers the main findings related to the possible morphological and functional variations in the right ventricle and atrium characteristics after the percutaneous procedure both in ASD and in PFO patients. ASD patients effectively showed enlargements in both right atrium and ventricle geometrical indexes as compared to PFO patients. After percutaneous procedure, no differences in such parameters were for PFO patients. Nevertheless, ASD patients demonstrated right atrium and ventricle remodeling.

Supplementary Table 2 collects the main findings from left atrium and ventricle. ASD patients showed a statistically significant improvement in LVEF. Both left cardiac chambers increased their dimensions after ASD closure.

Table 2 Inflammatory markers, endothelial function and morphological vascular modifications before and during follow-up visits in ASD and PFO patients

	Enrollment		24 h after procedure		1-month follow-up		6-month follow-up		12-month follow-up	
	Median	Interquartile range	Median	Interquartile range	Median	Interquartile range	Median	Interquartile range	Median	Interquartile range
ASD ($n = 14$)										
WBC count (10^3/uL)	6.3	5.3–8.7	8.9*	7.2–9.8	$6.6^{\approx}$	5.3–8.3	$6.5^{\Diamond}$	5.2–8.4	$6.5^{\approx}$	5.3–7.8
CRP (mg/L)	1.5	1.17–2.1	$7.8^{\dagger}$	4.6–9.7	$2.8^{\dagger}$	1.9–3.3	$1.9^{\dagger\text{¤}}$	0.8–2.6	$1.3^{\dagger\sim}$	0.7–1.6
FMD (%)	$6.5^{\#\$}$	5.6–7.6	7*	6.4–8.4	$7.8^{\Diamond}$	4.6–9.7	$8.4^{\Diamond}$	7.4–9.7	$8.8^{\bullet\Diamond\text{¤}\$}$	7.2–10.3
PFO ($n = 14$)										
WBC count (10^3/uL)	7.4	6–7.9	7.8	6.7–9.2	6.9	5.8–8.3	6.4	5.8–7.7	$6.4^{\approx}$	5.8–7.7
CRP (mg/L)	1.8	1.2–2.2	$7^{\dagger}$	4.5–12.7	2	1.5–4.7	$1.6^{+\text{¤}}$	1.3–2.3	$1.5^{+\sim}$	1.2–2.1
FMD (%)	8.5	7.6–10.7	$7^{\dagger}$	6.3–9	7.7*	7–10	8.3^{+}	7.4–10.4	$8.2^{+\text{¤}}$	7.6–10.5

ASD atrial septal defect, *CRP* C-reactive protein, *FMD* flow-mediated vasodilatation, *PFO* patent foramen ovale, *WBC* white blood cell count

Statistical evaluations corrected by means of Bonferroni's method

*$p < 0.05$ versus enrollment; $^{\bullet}p < 0.01$ versus enrollment; $^{\dagger}p < 0.001$ versus enrollment

$^{\approx}p < 0.05$ versus 24 h post-procedure; $^{\Diamond}p < 0.01$ versus 24 h post-procedure; $^{+}p < 0.001$ versus 24 h post-procedure

$^{\sim}p < 0.01$ versus 1 month; $^{\text{¤}}p < 0.05$ versus 1 month; $^{\$}p < 0.05$ versus 6 months

$^{\#}p < 0.001$ versus PFO FMD enrollment, PFO FMD 6 months, PFO FMD 12 months; $^{\$}p < 0.01$ versus PFO FMD 1 month

There were no differences in morphological and functional parameters of left chambers in PFO patients. Percutaneous procedures did not significantly modify the geometric and functional characteristics of the left cardiac chambers in PFO patients.

Finally, we tried to evaluate the relationship between FMD and each echocardiographic parameter (Table 3). ASD patients showed an inverse, statistically significant ($p < 0.01$) relationship between FMD and right cardiac chamber parameters at each follow-up stage. The negative remodeling of right cardiac chambers seemed to be related to improvement in endothelial function even at longer follow-up (i.e., 1 year). Also, the remodeling of left cardiac chambers was related to FMD amelioration during the follow-up period (Table 3).

PFO patients showed similar results. In particular, data showed an inverse relationship between FMD values and PAPs, as well as FMD and right ventricle basal diameter (Table 3). Furthermore, PFO patients also demonstrated that FMD values showed an inverse relationship with left

Table 3 Correlation among cardiovascular parameters and flow-mediated vasodilation (FMD) in ASD and PFO patients

		sPAP	RV proximal diameter efflux tract (mm)	RV basal diameter in apical 4C view (mm)	TAPSE	RA longitudinal diameter (mm)	RA transverse diameter (mm)	RA Area (cm^2)
Baseline								
ASD ($n=14$)	FMD (%)	−0.843	−0.722	−0.807	NS	−0.696	−0.778	−0.696
PFO ($n=14$)	FMD (%)	NS	−0.666	−0.809	0.731	−0.667	NS	NS
24 h post-procedure								
ASD ($n=14$)	FMD (%)	−0.820	−0.726	−0.804	0.730	−0.776	−0.827	−0.818
PFO ($n=14$)	FMD (%)	NS	−0.676	−0.746	0.753	NS	NS	NS
1 month								
ASD ($n=14$)	FMD (%)	−0.888	−0.716	−0.739	NS	−0.797	−0.699	−0.741
PFO ($n=14$)	FMD (%)	−0.687	NS	−0.830	NS	−0.811	NS	−0.717
6 months								
ASD ($n=14$)	FMD (%)	−0.839	−0.730	−0.694	0.788	−0.806	−0.666	−0.827
PFO ($n=14$)	FMD (%)	NS	NS	NS	NS	NS	NS	NS
12 months								
ASD ($n=14$)	FMD (%)	−0.914	−0.869	NS	NS	−0.827	−0.852	−0.833
PFO ($n=14$)	FMD (%)	−0.805	NS	−0.837	NS	NS	NS	NS

		LVEDD (mm)	LV ejection Fraction (%)	LA APD (mm)	LA LD (mm)	LA TD (mm)	LA Area (cm^2)
Baseline							
ASD ($n=14$)	FMD (%)	NS	0.831	−0.696	−0.707	−0.704	−0.732
PFO ($n=14$)	FMD (%)	−0.807	NS	−0.699	NS	−0.730	−0.741
24 h post-procedure							
ASD ($n=14$)	FMD (%)	NS	0.693	−0.777	−0.717	−0.738	−0.715
PFO ($n=14$)	FMD (%)	−0.670	0.731	−0.724	−0.640	−0.662	NS
1 month							
ASD ($n=14$)	FMD (%)	NS	0.724	−0.754	−0.704	−0.770	−0.793
PFO ($n=14$)	FMD (%)	−0.805	NS	NS	−0.675	−0.676	−0.666
6 months							
ASD ($n=14$)	FMD (%)	−0.762	0.802	−0.669	−0.729	−0.795	−0.773
PFO ($n=14$)	FMD (%)	−0.817	NS	NS	−0.744	NS	−0.703
12 months							
ASD ($n=14$)	FMD (%)	−0.821	0.880	−0.770	−0.821	−0.857	−0.837
PFO ($n=14$)	FMD (%)	−0.790	−0.761	−0.807	−0.679	NS	NS

Spearman correlation analysis. The numbers are referred to the Spearman correlation coefficient. Significant correlation is intended at the 0.01 level (2-tailed)

ASD atrial septal defect, *FMD* flow-mediated vasodilatation, *LA* left atrium, *LA APD* LA anteroposterior diameter, *LA LD* LA longitudinal diameter, *LA TD* LA transverse diameter, *LV* left ventricle, *LVEDD* left ventricle end-diastolic diameter, *PFO* patent foramen ovale, *sPAP* systolic pulmonary arterial pressure, *RA* right atrium

ventricle end-diastolic diameter and anteroposterior left atrium diameter (Table 3).

Discussion

Our study demonstrated for the first time the influence of hemodynamics alterations due to ASD, and partially PFO, on systemic vascular endothelial function.

The main findings from our study lie on the identification of baseline lower FMD values in ASD patients as compared with PFO patients, despite similar, general characteristics of the two groups. Both groups showed similar cardiovascular risk factors (Table 1), while no alterations in vascular morphology could be detected (normal values of C-IMT and no detectable carotid plaques, as given in Table 1).

Literature provides controversial data as compared to our results. Rodés-Cabau et al. [14] tried to define the influence of atherosclerotic burden on the determination of cryptogenic stroke in PFO patients. They found a negative correlation between PFO presence and increased carotid IMT (the lower carotid IMT values were in PFO patients rather than in those without: 0.75 ± 0.20 mm versus 1.03 ± 0.31 mm, $p < 0.0001$) [14]. Furthermore, PFO patients showed better endothelial vascular function as compared to those without PFO ($7.16 \pm 4.09\%$ versus $5.04 \pm 3.39\%$; $p = 0.02$) [14]. Therefore, early signs of atherosclerotic vascular lesions were not usual in PFO patients. These results reflect those from Jaffre et al. [32]: Patients suffering from PFO had reduced incidence of non-obstructive carotid atherosclerosis as compared to their control counterpart. There are no data on the relationship between carotid IMT and ASD. Our population showed normal values of carotid IMT which were not divergent from those in PFO patients. In the end, both populations showed normal and comparable values of baseline carotid IMT.

Endothelial function is rather altered in ASD patients while demonstrating baseline normal values in PFO patients (Table 1). Nevertheless, the novelty is related to the direct improvement in FMD soon after percutaneous closure procedure of the ASD which persistently ameliorated at long-term follow-up (Table 2).

The influence of the presence of PFO on endothelial function is quite a matter of debate. Microbubbles, generated from diving or from medical therapies (hemodialysis and cardio-pulmonary bypass, for instance), can promote endothelial dysfunction in patients suffering from PFO [33]. Fok et al. [33] demonstrated the reduction in FMD after bubble injection in patients suffering from PFO; therefore, the closure procedure can reduce the risk of chronic impairment in vascular walls function. Nevertheless, no change in FMD values can be observed in the study by Lantz et al. [34]. Different results were in the literature for ASD patients. ASD patients seem to be at higher risk of developing endothelial dysfunction [12, 35–37].

The pathophysiologic reasons for these results are quite a matter of debate. Lin et al. [35] observed the occurrence of endothelial dysfunction in congenital heart diseases such as ASDs. Such impairment was determined by the generation of endothelial microparticles. Endothelial microparticles are membrane vesicles that are released by cell activation or apoptosis. They are able to promote vascular inflammation, alter the coagulation/fibrinolytic process favoring the coagulation process, and increase endothelial lesions [38]. In particular, they are able to directly impair endothelial function by negatively influencing the action of endothelial nitric oxide synthase [38]. Lin et al. demonstrated that patients suffering from ASD showed increased levels in circulating endothelial microparticles which seemed to promote endothelial dysfunction [35].

Humpl et al. [12] observed a reduction in exhaled nitric oxide levels in children suffering from ASD and still not a undergone percutaneous procedure as compared to post-procedure determinations. The measurement of the exhaled nitric oxide is a biomarker of endothelial function: the more the NO into the expired airflow, the better the function of the pulmonary endothelium [39]. It has been observed that NO production is inversely related to PAPs [39]. The ASD closure can mitigate the hemodynamics of the pulmonary vascular bed, and this can account for the amelioration in endothelial function. It is possible that the higher shear stress in pulmonary vascular bed in ASD patients can turn into oscillatory shear stress which is able to promote atherosclerosis and endothelial dysfunction [40, 41]. The ASD closure can reduce the oscillatory shear stress, thus promoting amelioration in pulmonary endothelial function. Meanwhile, the amelioration in the performances of left ventricle chambers is also able to improve systemic endothelial function. The exact pathogenetic mechanisms are not fully understood but evidence [42, 43] suggested that positive remodeling of the left ventricle can promote the amelioration in vascular performances.

Furthermore, the demonstrated increase in platelets activity in ASD can also be considered as a potential condition for vascular functional impairment, potentially reversible by percutaneous closure procedure [36], although dedicated studies should be provided for finally demonstrating such condition.

Our study further demonstrated the influence of transcatheter percutaneous vascular procedure on echocardiographic features of cardiac chambers. In particular, ASD patients showed enlargement in left cardiac chambers and amelioration in LVEF at 12-month follow-up; right chambers reduced their dimensions in ASD patients (Supplementary Tables 1 and 2). PFO patients showed substantially no significant remodeling of cardiac chambers at 12-month

follow-up (Supplementary Tables 1 and 2). These results were in line with the literature [16, 44–46]. We detected direct relationships between ASD/PFO closure and echocardiographic parameters (Table 3). In particular, the amelioration in endothelial function after percutaneous closure procedure was related to the reversal remodeling of the right cardiac chambers. Furthermore, a positive correlation was noticed between FMD and left ventricle ejection fraction, and negatives between FMD and reduction in the left atrium and ventricle dimensions (Table 3). The inverse remodeling in right ventricle after ASD closure can influence the left cardiac chambers by promoting their enlargement, and amelioration in LVEF may be due to Frank–Starling's law. It can be supposed a positive amelioration in the compliance of left cardiac chambers which translates in LVEF increase. This change in left chambers promotes improvement in systemic hemodynamics: The consequent increase in vascular shear stress may improve endothelial function. Such a theory can explain the correlation outlined in Table 3 between left cardiac chambers and FMD values. Nevertheless, further studies are needed to validate such considerations.

The remodeling of left chambers can influence the systemic performances of the endothelium [47, 48]. The release in NO can explain part of the mechanism related to the complex relationship between left chambers remodeling and systemic endothelial function [47–49].

Although there are no adequate data to support a definite correlation between endothelial function and cardiac chamber remodeling due to study limitations, we do speculate about such a possible correlation, hoping it could be demonstrated in further, larger, and randomized studies.

During follow-up, no patient showed adverse cardiovascular events. Major or minor cardiovascular events were not detectable during follow-up; thus, we cannot evaluate the real influence of FMD evaluation on cardiovascular outcomes of patients. Longer follow-up is needed in order to achieve such a goal.

Limitations

The small sample size and the retrospective nature of this study can be considered as limitations. The prevalence of female gender in ASD group can influence endothelial function due to estrogen levels.

Conclusions

Percutaneous closure procedure in ASD patients can promote early and long-term amelioration in peripheral endothelial function; thus, the overall cardiovascular risk profile of these individuals improved. PFO patients did not show amelioration in endothelial function after percutaneous closure procedure. The cardiac chamber remodeling was related to FMD amelioration, although further studies are needed in order to demonstrate such relationships.

Funding This research received no grant from any funding agency in the public, commercial or not-for-profit sectors.

Compliance with ethical standards

Conflict of interest The authors declare that there is no conflict of interest.

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