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ORIGINAL INVESTIGATION

Implications of detection of foramen ovale patent after cryptogenic ischemic stroke

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Abstract

Background Therapeutic uncertainty is inherent in decisions in patients with patent foramen ovale (PFO) and cryptogenic stroke. We aimed to determine clinical implications of PFO identification in transesophageal echocardiography (TEE) after a cryptogenic ischemic stroke.

Methods Consecutive TEE done between 2011 and 2015 in patients with previous cryptogenic stroke was evaluated. Clinical implications of PFO identification (closure and/or medical therapy) were retrieved from the medical records and discharge summaries. Adverse events related to therapy, stroke recurrence and death were analyzed during follow-up.

Results Three-hundred one patients (mean age 59 ± 11 years; 61% male) underwent a TEE, of which 77 (26%) patients had a diagnosis of PFO. Patients with PFO were younger (56 ± 13 versus 60 ± 14, $p = 0.03$). Of those with PFO, 23 (30%) underwent percutaneous closure of PFO and these patients had more frequently complex or large PFO ($p < 0.001$ and $p = 0.004$, respectively). The remaining 54 (70%) were treated with medical therapy: 30 (39%) with antiplatelet therapy and 24 (31%) with oral anticoagulation. During follow-up (44 ± 17 months), only two patients had another stroke (both referred for PFO closure, while they were waiting for the procedure) and two patients, on whom PFO closure was not performed, died (not for cardiovascular causes).

Conclusion PFO's (size and complexity) and patients' characteristics influenced clinical decision when PFO was detected on TEE. The risk for recurrent stroke was not increased in patients who did not undergo PFO closure; although two patients waiting for PFO closure had recurrent stroke, demonstrating its importance.

Keywords Cryptogenic stroke · Patent foramen ovale · Percutaneous closure · Transesophageal echocardiography

Abbreviations

AF	Atrial fibrillation
ASA	Atrial septal aneurysm
ECG	Electrocardiogram
h	Hour
LA	Left atrium
OAC	Oral anticoagulation
PFO	Patent foramen ovale
RA	Right atrium
TEE	Transesophageal echocardiography
TTE	Transthoracic echocardiography

Introduction

There is no uniform management for patients presenting with cryptogenic stroke and a patent foramen ovale (PFO) given that the role of closure of PFO in preventing stroke recurrence remains uncertain [1]. Although it is plausible that closure of the defect could reduce the risk of recurrent stroke, several randomized trials have not shown the superiority of PFO closure over medical therapy [2–4]. However, a systematic review and meta-analysis of existing randomized controlled trials suggest that in patients with cryptogenic stroke, PFO closure may be beneficial in reducing the risk of recurrent vascular events when compared with medical treatment and the benefit may be greater in patients with a substantial shunt [5]. Also recent trials (CLOSE [6] and Gore-REDUCE [7]) demonstrated that in highly selected patients, PFO closure was associated with a lower rate of stroke recurrence. Furthermore, the choice of medical

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therapy in those who did not undergo closure of PFO [antiplatelet therapy or oral anticoagulation (OAC)] is also still a controversial issue.

The aim of our work was to determine clinical implications of PFO identification in transesophageal echocardiography (TEE) after a cryptogenic ischemic stroke, since currently, there is no standardized methodology in what concerns clinical workup and treatment of the majority of findings.

Materials and methods

Patients

Between January 2011 and December 2015, consecutive patients with previous cryptogenic stroke referred to our Echocardiography Laboratory for undergoing a TEE were included in the study.

Study design

Of the patients who underwent a TEE after a cryptogenic stroke, we collected demographic data, cardiovascular risk factors, blood tests (including a hypercoagulability panel with tests for protein C, protein S, antithrombin 3, factor V Leiden, anti-cardiolipin antibodies, and antiphospholipid antibodies), brain and carotid imaging, electrocardiogram (ECG), transthoracic echocardiography (TTE), 24-h Holter monitoring and medications. All patients had been evaluated by a neurologist who requested TEE.

An ischemic stroke was defined as an acute focal neurologic deficit, presumably due to ischemia, that either resulted in clinical symptoms lasting 24 h or more or was associated with evidence of relevant infarction on computed tomography or magnetic resonance imaging of the brain. The stroke was defined as cryptogenic if satisfied criteria for cryptogenic embolism or other cryptogenic, according to SSS-TOAST system [8]. Hypertension was defined as resting systolic or diastolic blood pressure ≥ 140/90 mmHg on two occasions or prescription of anti-hypertensive drugs. Diabetes mellitus was defined as a serum fasting glucose ≥ 7.0 mmol/L or prescription of anti-diabetic medication. Smoking status was recorded as current smoker or non-smoker.

All TEE were retrospectively collected and reviewed by study personnel. The method of anesthesia was intravenous conscious sedation with midazolam (initial dose = 1.5–2.5 mg; if necessary, additional dose = 1 mg; maximum total dose = 3.5 mg) administered via upper extremity veins. Depth sedation during TEE did not occur. Sources of cardiac embolism were evaluated as well as implications of the findings. PFO is diagnosed if intravenous microbubbles (agitated infusion solution) passing from the right atrium (RA) into the left atrium (LA), either spontaneously or after a Valsalva maneuvre, are directly observed [9]. If passage through the PFO is not clearly visualized, only very early (within three heart cycles from appearance of contrast in the right atrium) LA-contrast bubble detection was counted as proof of PFO. A right-to-left or left-to-right shunt on color Doppler clearly originating from a passage between the two septa in the fossa ovalis is also diagnostic. Atrial septal aneurysm (ASA) was diagnosed if there is a fixed displacement or a mobile excursion of the fossa ovalis region of the atrial septum towards the right or left atrium, or both, exceeding 10 mm from the mid-line (a line from the basal part of the interventricular septum to the insertion of the septum secundum in the atrial wall). Complex PFO was defined as a PFO with an ASA, or with a tunnel length of ≥ 8 mm, or with multiple openings into the left atrium, or with septum primum deviation, or with additional multiple small defects on the fossa ovalis, or with the presence of a large bulky eustachian ridge [10]. Large shunt was defined by the appearance of more than 20 microbubbles in the LA within three cardiac cycles after opacification of the RA [11].

Implications of PFO detection in TEE, namely, PFO closure or medical therapy (antiplatelet therapy or OAC) were retrieved from the medical records and discharge summaries of our hospital as well as other institutions. Since PFO closure was not performed in our hospital; patients were referred to other centers, but all medical records concerning the procedure and follow-up in these institutions were collected. Device- and procedure-related adverse events were evaluated as well as new occurrence of atrial fibrillation (AF), documented by a standard 12-lead electrocardiogram (ECG) or a new 24-h Holter monitoring.

During follow-up, events of ischemic stroke, overall death and adverse events related to therapy were retrieved from the national patient registry and from medical records or discharge letters and were validated by reviewing patients' files. Patients who failed to have recent clinical records were contacted by phone. Ischemic stroke was defined as previously explained. Major hemorrhagic events were defined according to International Society on Thrombosis and Haemostasis (ISTH) as a fatal bleeding; and/or bleeding in a critical area or organ, such as intracranial, intraspinal, intraocular, retroperitoneal, intraarticular or pericardial, or intramuscular with compartment syndrome; and/or bleeding causing a fall in hemoglobin level of 20 g/L (1.24 mmol/L) or more, or leading to transfusion of two or more units of whole blood or red cells [12].

Ethics

All participants provided written informed consent. The Ethical Committee of Centro Hospitalar de Setubal approved the study. The study is in compliance with the Helsinki Declaration.

Statistical analysis

SPSS version 23 software (SPSS Inc., Chicago, Illinois) was used for statistical analysis. Data are expressed as mean ± standard deviation for continuous variables and as frequencies and percentages for categorical variables. Baseline characteristics and outcomes were compared using the Chi-square test for categorical variables and the Student's *t* test or the Mann–Whitney test for continuous variables. A value of $p < 0.05$ was considered statistically significant.

Results

Study population

Basal characteristics of patients with previous cryptogenic stroke who underwent TEE are shown in Table 1.

Potential sources of cardiac embolism detected on TEE

Of the 301 patients who underwent TEE, 124 (41%) had at least one potential source of cardiac embolism. Major and minor or unclear sources of embolism were classified according to the ESC recommendations [11]. Findings such as cardiac masses and endocarditis led to specific treatment such as OAC therapy or cardiac surgery, while the majority (88%) of patients with aortic arch atheromatous plaques had been treated with OAC. Minor findings as giant Lambl's excrescences and mitral annulus calcifications were not considered to have been associated with stroke event and no specific therapy other than antiplatelet therapy was given (Table 2). In total, 88 patients (29%) had other clinical management than antiplatelet therapy.

Table 1 Basal characteristics of patients who underwent transesophageal echocardiography

Basal characteristics of patients who underwent transesophageal echocardiography ($n = 301$)	
Demographic data	
Age (mean ± SD)	59 ± 11
Male gender, *n* (%)	184 (61)
Cardiovascular risk factors	
Hypertension, *n* (%)	116 (38)
Diabetes mellitus, *n* (%)	36 (12)
Dyslipidemia, *n* (%)	99 (33)
Smoke, *n* (%)	72 (24)
Cardiovascular history	
Acute myocardial infarction, *n* (%)	5 (2)
Previous stroke/transient ischemic attack, *n* (%)	8 (3)
Peripheral artery disease, *n* (%)	4 (1)

PFO detection

PFO was detected in 77 patients (26% of our population). Intravenous microbubbles (after agitated infusion solution) passing from the RA into the LA were directly observed in 21 patients (7 spontaneously and 14 after a Valsalva maneuvre) and very early (within three heart cycles from appearance of contrast in the right atrium) LA-contrast bubble was detected in 37 patients. A shunt on color Doppler clearly originating from a passage between the two septa in the fossa ovalis was present in 19 patients. Sixty-four patients had a simple PFO (number of microbubbles: mean 4.3 ± 3.0; minimum 1, maximum 15) and 13 complex PFO (8 patients with ASA; 2 patients with a tunnel length of ≥ 8 mm; 2 patients with multiple openings into the LA and 1 patient with additional multiple small defects on the fossa ovalis). Of these 13 patients, 7 had also a large shunt (Table 3). Figures regarding the representative cases are shown in Fig. 1. Of note, 10 patients were not able to perform Valsalva maneuvre after excluding PFO by other methods (shunt on color Doppler, spontaneously passage of microbubbles or detection of a complex PFO) due to stroke-induced incapacity. No patient with PFO had documented emboli in venous system which could be responsible for paradoxical embolism or any circumstance potentially leading to changes in intrathoracic pressure leading to right–left shunting to PFO. Patients with PFO were younger, but no other statistically significant differences were found between patients with and without PFO (Table 4).

Clinical implications of PFO detection

From the 77 patients with PFO, 23 patients (30%) underwent percutaneous closure of PFO [20 patients with Amplatzer PFO occluder (St Jude Medical, St Paul, MN, USA) and 3 patients with Atriasept Cardia (Cardiac Inc., Eagan, MN, USA)]. No patient underwent surgical closure. Patients were referred from our hospital to a tertiary hospital. The procedure was performed as soon as possible, within a maximum of 3 months. Patients who underwent PFO closure had more frequently complex or large PFO (Table 5).

The remaining 54 (70%) were treated with medical therapy: more than an half of them (56%, $n = 30$) with antiplatelet therapy and 44% ($n = 24$) with OAC (Fig. 2).

Table 2 Potential sources of cardiac embolism detected on transesophageal echocardiography ($n=301$)

Potential sources of cardiac embolism detected on TEE	*n* (%)	Clinical implications
Major risk sources		
Cardiac masses	14 (4.7%)	
Intracardiac thrombus	9 (3%)	OAC in all pts
Marantic vegetation	2 (0.7%)	Surgery in all pts
Papillary fibroelastoma	3 (1%)	Surgery in all pts
Endocarditis	4 (1.3%)	Surgery in all pts
Aortic arch atheromatous plaques	25 (8.3%)	OAC in 23 pts (88%)
Minor or unclear sources of embolism		
Patent foramen ovale*	77 (26%)	Percutaneous closure in 23 pts (30%); OAC in 24 pts (31%); antiplatelet therapy in the remaining 30 pts (39%)
Lambl's excrescences	2 (0.7%)	None
Mitral annulus calcification	1 (0.3%)	None
Total	124 (41%)	88 (29%)**

OAC oral anticoagulants, *Pts* patients, *TEE* transesophageal echocardiography

*8 patients had atrial septal aneurysm

**Clinical implications other than antiplatelet therapy

Table 3 Transesophageal echocardiography findings in patients with simple (left-hand) and complex (right-hand) PFO

Mode of detection			
Simple PFO ($n=64$)		Complex PFO ($n=13$)***	
Microbubbles passing spontaneously*	17	Atrial septal aneurysm	8
Microbubbles passing after Valsalva*	19	A tunnel length of ≥ 8 mm	2
Shunt on color Doppler **	28	Multiple openings into the LA	2
		Additional multiple small defects on the fossa ovalis	1

LA left atrium, *PFO* patent foramen ovale

*from the right atrium to the left atrium. **right-to-left or left-to-right shunt clearly originating from a passage between the two septa in the fossa ovalis. ***Seven of these 13 patients had large PFO

Among the patients under OAC, 21 (70%) received vitamin K antagonists and 9 (30%) received non-vitamin K antagonists.

Factors that influenced clinical decision in not performing PFO closure The main reason that influences clinical decision in what regards not closing PFO was PFO characteristics, namely, neither complex nor large PFO. Ten patients missed the schedule consult in tertiary center, but they were not lost; two patients were diagnosed with atrial fibrillation shorter after PFO detection and since OAC would be necessary, closure of PFO was not considered (Fig. 3).

Factors that influenced type of medical therapy The choice between antiplatelet and OAC in those who remained on medical therapy was based on individual circumstances, including, but not limited to hemorrhagic risk. No particular reasons were specified by physicians.

Safety

Complications of TEE

TEE was well tolerated, with no complications reported.

Related to percutaneous closure of PFO

There were no reported major procedure complications. PFO closure had not been successful in one patient. New-onset transient AF occurred in one patient within 1 month after the procedure.

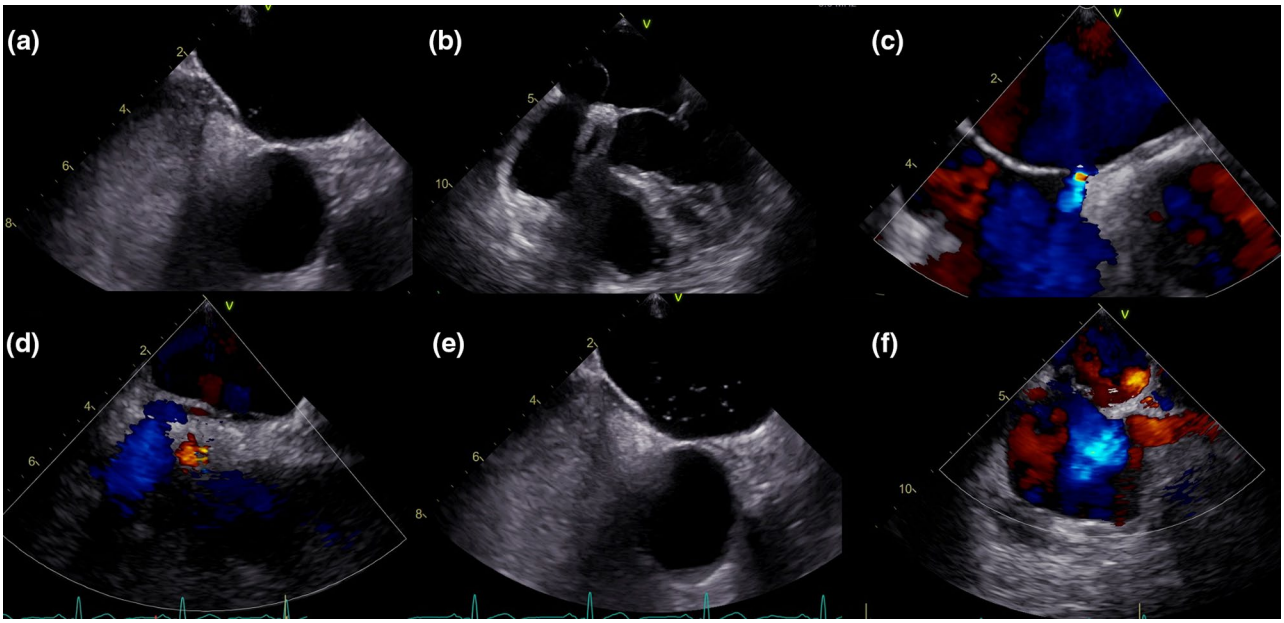

Fig. 1 Representative cases of patent foramen ovale (PFO) detection. **a** Intravenous microbubbles passing from the RA into the LA. **b** Atrial septal aneurysm. **c** and **d** shunt on color Doppler clearly originating from a passage between the two septa in the fossa ovalis. **e** A large shunt (more than 20 microbubbles observed). **f** Shunt on color Doppler with multiple openings

Table 4 Basal characteristics of patients with and without patent foramen ovale

Basal characteristics of patients with and without PFO			
	PFO ($n=77$)	No PFO ($n=224$)	p value
Demographic data			
Age (mean ± SD)	56 ± 13	60 ± 14	0.03
Male gender, *n* (%)	42 (54)	142 (63)	0.10
Cardiovascular risk factors			
Hypertension, *n* (%)	22 (29)	94 (42)	0.06
Diabetes mellitus, *n* (%)	7 (9)	29 (13)	0.22
Dyslipidemia, *n* (%)	21 (27)	78 (35)	0.25
Smoke, *n* (%)	15 (19)	57 (25)	0.36
Cardiovascular history			
Acute myocardial infarction, *n* (%)	1 (1)	4 (2)	0.94
Previous stroke/transient ischemic attack, *n* (%)	4 (5)	4 (2)	0.33
Peripheral artery disease, *n* (%)	1 (1)	3 (1)	0.51

PFO patent foramen ovale

Related to medical therapy

There were no major hemorrhagic events in patients under OAC or antiplatelet therapy during the follow-up period.

Recurrence of stroke event

During a mean follow-up of 44 ± 17 months, only two patients had a recurrent stroke, both referred for PFO closure since they have complex and large PFO, while they were waiting for the procedure and under OAC (one had multiple openings into the LA and the other had an atrial septal aneurysm). No recurrent stroke occurred in patients not referred to PFO closure ($p=0.57$).

AF

AF was diagnosed in four patients (7%), who underwent PFO closure during follow-up, while it occurred in

Table 5 Characteristics of patients who did and did not undergo patent foramen ovale closure

	PFO closure ($n=23$)	Medical therapy ($n=54$)	p value
Demographic data			
Age (mean ± SD)	56 ± 7	57 ± 11	0.69
Male gender, *n* (%)	11 (48)	31 (57)	0.63
Cardiovascular risk factors			
Hypertension, *n* (%)	5 (22)	17 (31)	0.60
Diabetes mellitus, *n* (%)	1 (4)	6 (11)	0.58
Dyslipidemia, *n* (%)	6 (26)	15 (28)	0.92
Smoke, *n* (%)	5 (22)	10 (19)	0.99
Cardiovascular history			
Acute myocardial infarction, *n* (%)	0 (0)	1 (2)	0.71
Previous stroke/transient ischemic attack, *n* (%)	2 (9)	2 (4)	0.74
Peripheral artery disease, *n* (%)	0 (0)	1 (2)	0.71
PFO characteristics			
Complex PFO	12 (52)	1 (2)	< 0.001
Large PFO	6 (26)	1 (2)	0.004

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one patient after PFO closure, as previously explained (Sect. 3.4.2) ($p=0.98$).

Death

Two patients who underwent PFO closure died (but not for cardiovascular causes and while under antiplatelet therapy). There were no deaths in patients who underwent PFO closure ($p=0.72$).

Discussion

Cardiac embolism accounts for approximately one-third of all cases of ischemic stroke and paradoxical embolism and embolism from the thoracic aorta, especially, if its atheroma contents are responsible for additional cases of stroke and systemic embolism [13]. Indeed, in patients with cryptogenic stroke, the exclusion of these potential sources of embolization into the cerebrovascular system is essential in choosing adequate secondary prevention. TEE is frequently used as a diagnostic method after ischemic stroke although it is unclear if its routine use in patients with cryptogenic stroke should be recommended. Its primary role is to establish the existence of a source of embolism, determine the likelihood that such a source is a plausible cause of stroke or systemic embolism, and guide therapy in an individual patient [11, 13]. However, the variability in the frequency

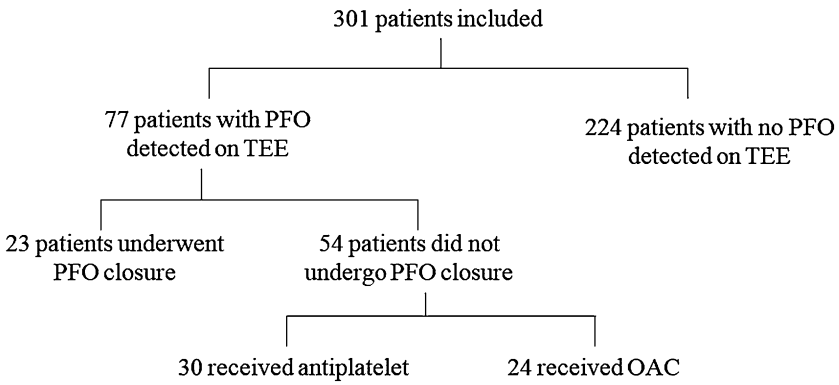

Fig. 2 Clinical implications of patent foramen ovale (PFO) detection on transesophageal echocardiography (TEE)

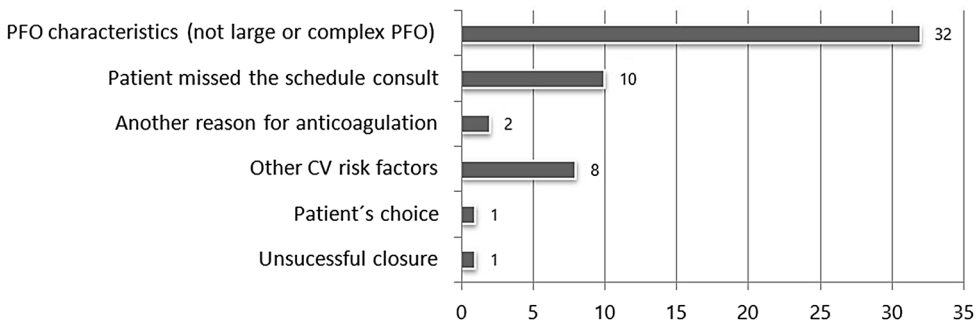

Fig. 3 Main reasons for not performing patent foramen ovale closure ($n=54$)

of cardiac findings between studies of similar populations and the lack of correlation between cardiac abnormalities thought to be associated with cryptogenic stroke are responsible for its controversial routine use. For this reason, major and minor/unclear sources of embolism are distinguished in guidelines [11], demonstrating that some potential sources of embolism are questionable.

In our study, TEE was useful in detecting a potential cardioembolic stroke. Forty-one percent of patients with previous cryptogenic stroke had a potential cardiac source of embolism after undergoing this exam and almost one-third had other clinical management than antiplatelet therapy due to its findings. Similar results were published by McGrath et al. (2014) in a meta-analysis [14]. However, only 14% of our patients had a major cardiac source of embolism as stated in guidelines. This difference is related with PFO detection since 61% of these patients had other clinical management than antiplatelet therapy (PFO closure or OAC therapy) although it is considered a minor source of embolism.

Nevertheless, PFO detection was less frequent in our study than in previously published ones. According to the literature, the foramen ovale remains open in about one-fourth of the general population and the prevalence increases among patients with cryptogenic stroke [15]. However, the prevalence of PFO in patients with cryptogenic stroke was highly variable between individual studies (ranges from 4 to 59% [14]) due to differences in age population, definitions for PFO and/or protocols used in TEE. For example, false-negative rates of up to 20% for PFO detection have been reported when the Valsalva maneuver is not used [16] while polygelatine is reported to be more sensitive than agitated saline for PFO detection [17]. Furthermore, older patients had less frequent PFO. Mean age in our population was 59 ± 11 years, which represents an older population comparing with other studies. We found than patients with PFO was indeed younger than those without it and an aging population can be the reason for a smaller proportion of patients with PFO in our study.

Since the way to implement secondary prevention for patients who present with a cryptogenic stroke and have a PFO is not clear, it was expected that PFO closure was not carried out in the majority of patients. Instead, individual evaluation was done and only patients with specific characteristics were sent to a tertiary center. Although results from CLOSE [6] and Gore-REDUCE [7] were not available at the time of clinical decision in our study, decision was based on similar findings to those of these studies. The majority (59%) of patients who did not undergo PFO closure had no complex or large PFO (similar to the concept applied in CLOSE trial [6]) and 15% of them had other cardiovascular risk factors that physicians considered important enough to have been the responsible for the stroke event (similar to the selection of patients in Gore-REDUCE [7]).

At present, there are no completed randomized controlled trials comparing OAC to antiplatelet therapy for PFO. Given the low anticipated event rates, randomized controlled trials of OAC versus antiplatelet therapy for this indication would require large sample sizes. In the CLOSE trial [6], besides PFO closure group, there were also two groups under OAC or antiplatelet therapy, but statistical significant differences were not analyzed because the study was not adequately powered to compare outcomes in these two groups. As such, it was expected that this difference was also not detected in our study. However, we showed that there were a considerable number of physicians who considered OAC effective in secondary prevention of stroke in patients with PFO.

Our study highlights the amount of possibilities to treat patients with cryptogenic stroke and PFO due to the uncertainty inherent to this issue. In our point of view, several questions need to be answered. First off all, a specific definition for what is a PFO with a high embolic potential is necessary. PFO is not all the same and probably "complex and large PFO" as defined in our study should be considered a "major" source of embolism. Although not statistical significant, two patients had a recurrent stroke while waiting for PFO closure, proving its high embolic potential. We admitted that this definition is not free from discussion since other studies used different definitions, but still it is primordial to allow a clinical management as universal as possible in our daily practice. For instance, in recent trials, slightly different concepts were applied: associated ASA or large interatrial shunt defined by the appearance of more than 30 microbubbles in the LA were eligible criteria in CLOSE trial [6], while in Gore-REDUCE trial no specified characteristics of PFO were considered, but 81% of patients had moderate (6–25 microbubbles in the LA) or large (> 25 microbubbles) shunts and ASA was not evaluated [7]. Second, once this question is clarified, undergoing TEE in selected patients with cryptogenic stroke should be recommended as a routine. As such, defining "selected patients" is also essential. We believe that young patients (defined as patients with less than 60 years) with no major cardiovascular risk factors that could justify the stroke event, should undergo TEE if their stroke was otherwise considered cryptogenic. Third, for those in whom individual circumstances led to not performing PFO closure, the best medical therapy should be studied in large trials. Logically, if in these patients PFO was not the responsible for stroke event, then OAC would not be necessary to prevent a second event. However, in Gore-REDUCE trial [7], there was a benefit of PFO closure in preventing recurrent stroke in opposition to previous studies [2–4] and one of the main reasons cited is the lack of a group with OAC (medical therapy group was all treated with antiplatelet therapy and no OAC).

Study limitations

It was retrospective and single-center study although it reflects the real world management of patients with cryptogenic stroke and PFO. Since PFO closure was not executed in our centre, patients were referred to tertiary centers and some patients missed the schedule consultation while others waited too long for the procedure. Prolonged ECG monitoring (noninvasive ECG monitoring during 30 days [18] or an insertable cardiac monitor [19]) was not used to exclude AF and undetectable AF might affect the overall results of this study. Time of follow-up and low number of patients were responsible for the low incidence of recurrent stroke and death, not allowing the detection of differences between the groups.

Conclusion

In our study, TEE findings led to other clinical management than antiplatelet therapy in almost one-third of patients with cryptogenic stroke. Because it is very common, PFO detection was responsible for more than an half of these cases, although it was not considered clinically relevant in other patients. PFO's and patients' characteristics influenced clinical decision when PFO was detected on TEE.

Compliance with ethical standards

Conflict of interest Rita Marinheiro, Leonor Parreira, Pedro Amador, Isabel Silvestre, Carla Antunes and Rui Caria declare that they have no conflict of interest.

Human rights statements and informed consent All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1964 and later revisions. Informed consent was obtained from all patients for being included in the study.

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