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Atrial fibrillation screening on systematic ambulatory electrocardiogram monitoring after percutaneous patent foramen ovale closure: A prospective study

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ABSTRACT

Background: Increased risk of new-onset atrial fibrillation (AF) after patent foramen ovale (PFO) closure was observed in randomized trials without however systematic AF screening. We aimed to evaluate the incidence of AF within 6-month following PFO closure with serial 24-hour ambulatory electrocardiogram (AECG) monitoring.
Methods: All patients undergoing PFO closure were prospectively included in 2 centers. AF was defined as irregular rhythm without discernible P waves > 30 s on AECG at day 0, 1-month and 6-month follow-up. Primary endpoint was the incidence of AF within the study period. Secondary endpoints evaluated clinical outcomes within 6-month follow-up.
Results: Between February 2018 and March 2019, 62 patients underwent PFO closure including 40 male (64.5%) with a mean age of 48 ± 9.5. Atrial septal aneurysm was observed in 37 patients (64.9%), 57 patients (91.9%) received an Amplatzer Occluder device (Abbott Vascular) and 5 (8.1%) an Occlutech device (Occlutech). After a mean follow-up of 7.7 ± 2.8 months, new-onset AF occurred in 3 patients (4.8%), all within the first month following PFO closure, including one per-procedural, all were asymptomatic and paroxysmal. Two patients with AF (3.2%) required chronic oral anticoagulant therapy. No adverse outcomes occurred at follow-up. No predictive factors of AF were highlighted. A total of 16 patients (25.8%) reported palpitations without AF on the AECGs.
Conclusion: In highly selected patients, incidence of AF, evaluated with 3 systematic 24-hour AECG within 6-month following PFO closure, was low (<5%). Always paroxysmal, AF occurred within the first month after the procedure and was not associated with adverse outcomes.

1. Introduction

Recent randomized trials demonstrated that percutaneous patent foramen ovale (PFO) closure in patients < 60 years with history of cryptogenic acute ischemic stroke (AIS), significantly decreases recurrence of AIS in comparison with antithrombotic therapy alone [1–4]. Specific advantages have been particularly demonstrated in high-risk PFO defined by large right to left shunt and/or associated with inter-

Abbreviations: AECG, ambulatory electrocardiogram; AF, atrial fibrillation; AIS, acute ischemic stroke; ASA, atrial septum aneurysm; DSC, decompression sickness; PFO, patent foramen ovale; TEE, transesophageal echocardiography; TIA, transient ischemic attack; TTE, transthoracic echocardiography.

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atrial septum aneurysm [1–4]. A recent *meta*-analysis including 3560 patients from 6 randomized clinical trials showed a lower incidence of AIS recurrence in the group with percutaneous PFO closure compared to the group with antithrombotic therapy only (1.96% versus 4.6 % respectively, $p = 0.01$) [5]. Importantly, PFO closure was well tolerated, with a low rate of serious adverse events, similar to the rate observed in patients receiving antithrombotic therapy [5]. However, the incidence of new onset supra-ventricular arrhythmia, mainly atrial fibrillation (AF) was significantly higher in the PFO closure group, suggesting that the procedure itself may induce AF. Recent *meta*-analysis confirmed a 4-fold increase of newly diagnosed AF after PFO closure compared with control [5–8]. Moreover, while randomized studies did not systematically assess occurrence of supra-ventricular arrhythmia after PFO closure, the incidence of this event after PFO closure may be underestimated. In addition, both evolution and adverse events associated with these arrhythmias, especially the risk of stroke from AF associated with PFO closure, remain unknown.

We aimed to assess the incidence of AF secondary to PFO closure using systematic 24-hour serial ambulatory ECG (AECG) monitoring within 6-month following the procedure.

2. Methods

2.1. Study population

This study was an observational prospective, multicentric study conducted in Montpellier and Nîmes University Hospitals between February 2018 and March 2019. All consecutive patients admitted to the cardiology department for percutaneous PFO closure after cryptogenic AIS or after decompression sickness (DSC) during scuba diving were included. The indication for PFO closure was systematically validated by a multidisciplinary team involving stroke neurologists and cardiologists.

Cryptogenic AIS was defined as AIS not attributable to a defined cause of stroke: (1) source of definite cardioembolism other than PFO or atrial septum aneurysm (ASA), (2) large artery atherosclerosis (stenosis $>$ 50% in the arterial territory or aortic arch atheroma $\geq$ 4 mm), (3) small artery disease (small deep infarct associated with other smell deep infarct and/or diabetes or hypertension), (4) other definite causes (vasculitis, prothrombotic disorders…) according to TOAST classification [9]. Systematic etiological workup was performed to rule out alternative causes of AIS: (1) non-invasive arterial imaging with intracranial and extracranial investigations (computed-tomography angiography (CTA) and/or contrast-enhanced magnetic resonance angiography (MRA)); (2) cardiac investigations : transthoracic (TTE) and transesophageal echocardiography (TEE), cardiac monitoring at the acute phase of AIS, admission 12-lead ECG, 24-hour to 72-hour ECG monitoring; (3) biological workup comprising antiphospholipid antibodies; (4) any other examination necessary to confirm a cause suspected on clinical date and/or the initial etiological work up (ie arteriography) [10,11]. A TEE was performed in all patients to confirm the diagnosis of PFO, to quantify the right to left shunt thanks to a contrast test potentiated by a Valsalva maneuver and to assess the presence or not of an associated ASA. Patients with large shunt (>30 bubbles) or ASA regardless PFO size were included. Interatrial defect with left to right shunt was an exclusion criterion. All patients were given full study information and written consent was obtained. The protocol was approved by an independent ethics committee (Comité de Protection des Personnes Sud Méditerranée, Montpellier, France), the institutional regulatory authorities (Institute Review Board (IRB) of Montpellier University Hospital (ID RCB: IRB-MPT_2020_02_202000380) and was conducted according to the principals of the Declaration of Helsinki. The study was registered with ClinicalTrials.gov (NCT04290052). Data that support the findings of this study are available from the corresponding author upon reasonable request.

2.2. PFO closure procedure

Percutaneous PFO closure was performed under local or general anesthesia, according to physician decision and patient convenience. The interatrial defect was calibrated before the procedure by TTE and TEE to allow prosthesis size and type selection. The procedure was performed through femoral venous route after ultra-sounded guided puncture. Prosthesis was positioned under fluoroscopic control and TTE in case of local anesthesia or TEE in case of general anesthesia. Two types of prosthesis were implanted: the Amplatzer PFO Occluder or Cribriform device (Abbott Vascular, United States of America) and the Occlutech PFO Occluder (Occlutech, Sweden). An Amplatzer Multi-Fenestrated Septal Occluder "Cribriform" prosthesis was preferred in case of large ASA. Intravenous injection of unfractionated heparin (5000 international unit) and 250 mg of Aspirin associated with antibiotic prophylaxis were administered before the procedure. After the procedure, all patients received anticoagulation during 24 h with 2 subcutaneous injections of low molecular weight heparin (Enoxaparin) adapted to the weight. In the absence of contraindication, a dual antiplatelet therapy including aspirin (between 75 and 160 mg) and clopidogrel 75 mg was introduced for 3 months followed by long-term aspirin. TTE was performed the next day to check the positioning of the prosthesis and the absence of complication. The hospital discharge was anticipated at day 1.

2.3. Follow-up

All patients had a 24-hour AECG monitoring immediately after the procedure (day 0), at 1-month ($\pm$10 days) and 6 months ($\pm$10 days) after the procedure (Fig. 1). TTE and cardiac follow-up were performed at discharge and at 6-month follow-up. TTE data included left ventricle ejection fraction, prosthesis position, left atrium surface and volume and residual right-to-left shunt assessed by contrast test performed at 6-month follow-up. Patients had systematic neurological follow-up, to detect recurrence of transient ischemic attack (TIA) or AIS, with brain imaging (MRI or CT scan) confirmation when required.

2.4. Study endpoints

The primary endpoint was the incidence of AF after PFO closure defined as irregular rhythm without discernible P waves $>$ 30 s on AECG monitoring within a 6-month follow-up period [11]. Characteristics of AF were assessed (time to occurrence, duration, recurrent nature, symptoms). The occurrence and characterization of AF was determined using the SYNESCOPE® software.

The secondary endpoints evaluated adverse events defined as prolongation of hospitalization for cardiac events, incidence of curative anticoagulation, need for cardioversion and occurrence of recurrent ischemic neurological events (TIA, AIS, confirmed by a stroke neurologist and cerebral imaging) within 6-month. Predictive factors for AF occurrence were evaluated.

2.5. Statistical analysis

Descriptive analyses used a Shapiro-Wilk test to assess normality of the distributions, and the quantitative variables were expressed as mean $\pm$ standard deviation and median (interquartile range) whereas categorical variables were expressed as number of subjects (percentage). Descriptive analysis was performed for the total population, the AF patients and the no AF patients. Student *t* test and Mann-Whitney test were performed to compare continuous variables between two groups (AF and no-AF groups). All tests were 2-sided with a significance level fixed at 5%. Statistical tests were performed with R 3.1.1 (The R Foundation for Statistical Computing) and SAS 9.2 (SAS Institute Inc., Cary, NC).

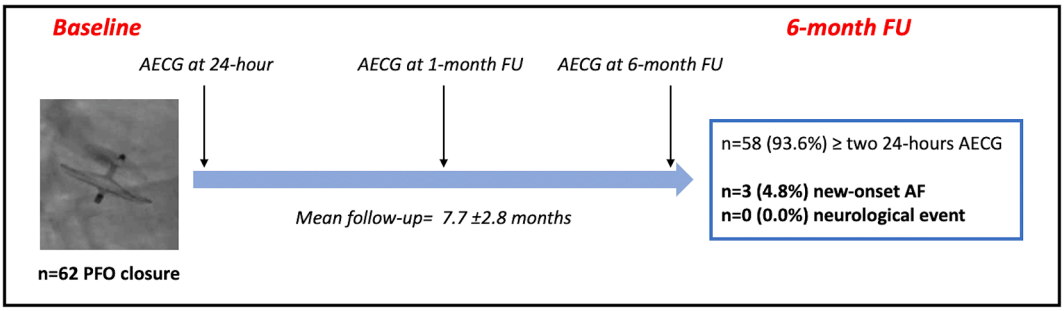

Fig. 1. Study design and incidence of new-onset atrial fibrillation and neurological events at 6-month follow-up. AECG: ambulatory electrocardiogram; AF: atrial fibrillation.

3. Results

3.1. Patients and procedural characteristics

Within the study period, 62 patients underwent percutaneous PFO closure with a mean age of 48 ± 9.5 and 64.5% of male (n = 40). A total of 59 patients (95.2%) had cryptogenic AIS including mainly carotid territory infarct (n = 40; 68%) and 3 (4.8%) had DSC. ASA was associated with PFO in most cases (n = 37, 64.9%). Patients' baseline characteristics are summarized in Table 1.

PFO closure procedure were performed mainly under local anesthesia (n = 54; 87.1%). Mean fluoroscopy time during the procedure was 4.8 ± 1.3 min. Regarding the type of prosthesis, 57 patients (91.9%) received an Amplatzer device including 15 cribriform prosthesis and 5 patients (8.1%) an Occlutech device. Median prosthesis diameter was 28.2 mm (IQR 25–35 mm) (Table 1). PFO closure procedure was successful with correct prosthesis positioning and absence of procedural complication in all patients.

3.2. Incidence of AF following PFO closure

Following PFO closure procedure, all patients underwent at least one AECG monitoring during follow-up and at least two AECG monitoring were performed in 58 patients (93.6%). After a mean follow-up of 7.7 ± 2.8 months, AF occurred in 3 patients, representing a cumulative incidence for AF of 4.8% within 6-month follow-up (Fig. 1). All AF episodes were recorded within the first month including one per procedural with a duration of 30 min. No other type of supraventricular arrhythmia (atrial flutter or atrial tachycardia) was observed. All AF episodes were paroxysmal (lasting between 30 min to 24 h) and asymptomatic. Details for patients with new onset AF are provided in Tables 1 and 2. Among patients with AF, 2 of them had associated ASA with PFO. All these 3 patients had a single episode of AF not requiring antiarrhythmic therapy, without any recurrence during follow-up. Two of the 3 patients with AF were considered as requiring curative anticoagulation with direct oral anticoagulants therapy and one of them did not require long-term anticoagulation as AF was considered to be induced by the procedure itself (Table 2).

Table 1
Baseline and procedural characteristics for the total population, for AF and no-AF patients.

	Total population n = 62	AF (n = 3)	No AF (n = 59)
Age (years)	48.0 ± 9.5	58.0	47.5
Sex, male	40 (64.5)	3 (100)	37 (62.7)
BMI (kg/m^2)	25.1 ± 4.0	24.5 ± 1.0	25.3 ± 4.2
Hypertension	11 (17.7)	1 (33.3)	10 (17.0)
Diabetes mellitus	1 (1.6)	0 (0)	1 (1.7)
Current smoker	25 (40.3)	1 (33.3)	24 (40.7)
Previous CAD	1 (1.6)	1 (33.3)	0 (0)
Sleep apnea syndrome	4 (6.5)	1 (33.3)	3 (5.1)
Cryptogenic AIS	59 (95.2)	3 (100)	56 (94.9)
DSC	3 (4.8)	0 (0)	3 (5.1)
LA size (cm^2)	18.3 ± 2.5	17.3 ± 1.2	18.2 ± 2.6
Septal anatomy			
- large PFO	25 (40.3)	1 (33.3)	24 (40.7)
- Associated ASA	37 (59.7)	2 (66.7)	35 (59.3)
Amplatzer prosthesis	57 (91.9)	3 (100)	54
Prosthesis size (mm)	28.2 ± 3.7	30.0 ± 5.0	28.1 ± 3.6

Values are mean ± SD or n (%)
AIS : acute ischemic stroke; ASA : atrial septal aneurysm; BMI: Body mass index; CAD = coronary artery disease; DSC : decompression sickness; LA = left atrium ; PFO: patent foramen ovale.

3.3. Secondary endpoints

No neurological event or hospitalization for cardiovascular event occurred within follow-up. Only one patient on antiplatelet therapy with low dose aspirin (in whom no arrhythmia was observed) had a spontaneous thigh hematoma with spontaneous favorable evolution. Regarding symptoms, 16 patients (25.8%) reported palpitations during the first days (Day 0 to day 3) following the procedure, but only isolated atrial ectopic beats were recorded in these patients with no AF observed on AECG in any patient. One patient with atrial ectopic beats (1.7%) required flecainide therapy for 1 month due to discomfort palpitations.

3.4. Predictive factors for AF and follow-up

No predictive factor for AF after PFO closure was highlighted. Older patients tended to have a greater risk for arrhythmia during follow-up, but this trend was not statistically significant (p = 0.3). Male sex (p = 0.6) left atria (LA) size (p = 0.5), ASA (p = 0.5) and device type (p = 1.0) were not associated with occurrence of AF. TTE at 6-month follow-up

Table 2
characteristics of patients with new onset AF.

	Patient 1	Patient 2	Patient 3
Age (years)	58	54	62
Sex	Male	Male	Male
Hypertension	No	Yes	No
ASA at baseline	yes	yes	no
Left atrium surface (cm^2)	18	16	18
Indication	AIS	AIS	AIS
CHADS-vasc score	2	3	2
Associated ASA	no	yes	yes
Local anesthesia	Yes	Yes	Yes
Prosthesis type	Amplatzer	Amplatzer	Amplatzer
Prosthesis size (mm)	30	35	25
Onset of AF (days)	40	periprocedural	24
AF duration	24 h	30 min	40 min
Long-term treatment	DOA	AAT	DOA

AAT: antiplatelet therapy; AF: atrial fibrillation; ASA: atrial septum aneurysm; DOA: Direct oral anticoagulant therapy.

showed optimal positioning of the device in all cases. A contrast test was performed in 34 patients (54.8%) and 14 of them (41.2%) had a persistent residual but low shunt (<10 bubbles) in all cases, and none of them had new-onset AF.

4. Discussion

In this prospective study, we aimed to assess incidence, clinical impact and predictive factors of AF up to 6-month following PFO closure using serial AECG at day 0, 1-month and 6-month follow-up.

4.1. Incidence and mechanism of AF following PFO closure

In the recent randomized controlled trials comparing PFO closure versus antithrombotic therapy following cryptogenic AIS, the risk for arrhythmia was higher in the PFO closure group compared to medical therapy with an increased risk by over 2–5 times, suggesting an association between the PFO closure procedure and AF [1–8]. However, none of these studies provided specific rhythm monitoring to detect arrhythmia following PFO closure, thus, underestimation of incidence of arrhythmia could be considered. In our contemporary population of patients selected according to current indications for PFO closure for cryptogenic shock and DSC, incidence of AF was low, occurring in less than 5% of patients, within the first month for all of them and without subsequent recurrence up to 6 months follow-up. Importantly, our study using systematic detection of arrhythmia by 24-hour serial AECG monitoring reported similar incidence of arrhythmia than those observed in the literature [1–8]. Several hypotheses were suggested to explain occurrence of atrial arrhythmia following PFO closure. First, a potential atrial irritation secondary to prosthesis positioning that may induce local inflammation, acting as a trigger for supra-ventricular arrhythmias [12]. In addition, the device could create an electrical obstacle and could be the source of new atrial re-entry circuits [13]. Lastly, intrinsic factors related to the patient, such as age, associated ASA or LA size, could also predispose to new-onset AF. Interestingly, in our study ASA and LA size were not related to AF suggesting that arrhythmia was induced by the procedure rather than related to patient characteristics. The difficulty of distinguishing the occurrence of AF secondary to the procedure from newly diagnosed AF during follow-up, which may be the potential etiology of stroke or TIA, remains a major concern. Main randomized trials [1–3] did not perform a prolonged cardiac monitoring to rule-out paroxysmal AF before including patients. In the present study, all patients had an exhaustive assessment to rule-out any paroxysmal arrhythmia with AECG monitoring for 24 to 72 h according to current European guidelines [11]. However, whether AF was related to the procedure rather than previous undiagnosed spontaneous AF remains unclear.

4.2. Clinical impact and predictive factors of AF following PFO closure

Whether induced arrhythmia is associated with a risk for recurrent AIS remains unknown but probably unlikely regarding their transient nature probably related to the procedure and not to the patient. Among the 3 patients in our study detected as having AF, 2 of them were considered for long-term anticoagulant therapy regarding the delayed AF episode occurring at 1-month following the procedure. No neurological event was observed in our study within a 6-month follow-up. Interestingly, all AF were asymptomatic in our study, as highlighted in recent *meta*-analysis [6–8]. We did not identify statistically significant clinical or anatomical predictors of AF in our population despite a trend for older patients. Association between elderly and AF following PFO closure was previously highlighted in numerous studies [14]. Anatomical factors as residual shunt, left atrium size, PFO size and ASA were suggested as associated with AF following PFO closure in the literature but with contradictory results [6–8]. In our study, the residual shunt was assessed in a limited number of patients at follow-up not allowing to analyse this parameter as a predictive factor of AF. A prospective study showed that patients with arrhythmia had a more dilated left atrium with the identification of a 40 mm anteroposterior diameter threshold above which the risk of arrhythmia significantly increased [15]. In our study, both patients with and without new-onset AF had similar LA size. Finally, in the study of Bonvini *et al.*[16], including 92 patients benefiting from PFO closure, PFO size was associated with the risk for arrhythmia. In our study, the prosthesis size was higher in patients with AF suggesting a larger PFO, without reaching significance. Based on these data, we could argue to use rhythmic monitoring for the oldest subjects (≥55 years) with largest left atrium and largest PFO after percutaneous PFO closure. In our study, symptomatic ectopic atrial heart beats occurred in one fourth of patients following PFO closure but were not associated with subsequent risk of AF. Moreover, these symptoms (palpitations) were always transient (within the first days after PFO closure) with spontaneous resolution in all patients. In an interesting way, this supraventricular non sustained arrhythmia did not correlate with further risk of AF which is an important data in current medical practice.

4.3. Study limitations

The first limitation of the study is related to the small size of the population (n = 62) although our results regarding incidence of AF correlate to those of large prospective studies. Secondarily, our study population is young with low burden of AF risk factors, which may have underestimated incidence of AF. Regarding predictive factors of arrhythmia, only half of patients had contrast TTE assessing residual shunt during follow up and no predictive factor of AF could be highlighted, which may also be explained by our small sample size. Despite systematic 24-hours AECG in our study, some transient AF could have been missed and more prolonged Holter monitoring or implantable Holter could be considered. Finally, our study was not designed to test for the association between PFO closure and new AF onset, as there was no control group without PFO closure.

5. Conclusion

In this prospective study including highly selected patients, incidence of AF, assessed by 3 systematic 24-hour AECG screening within 6-month following PFO closure, was relatively low (<5%). AF occurred early, was always paroxysmal, asymptomatic, not associated with traditional AF risk factors, and was not associated with recurrent stroke. Whereas symptomatic atrial ectopic beats occurred in numerous patients after PFO closure, they resolved spontaneously in most patients and were not associated with subsequent occurrence of AF.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper: [F. Leclercq received research grants from Edwards, Medtronic, Boehringer; consultant fees from Boehringer; and lecture fees from Astra Zeneca and Bayer. B. Lattuca received research grants from ACTION Study group, Biotronik, Boston Scientific, Daiichi-Sankyo, Fédération Française de Cardiologie and Institute of CardioMetabolism and Nutrition; consultant fees from Daiichi-Sankyo and Eli Lilly; and lecture fees from AstraZeneca and Novartis. G Cayla received research grants/consultant fees/lectures fees from Amgen, AstraZeneca, Bayer, Boehringer-Ingelheim, Boston, Biotronik, Bristol-Myers Squibb, Daiichi-Sankyo, Eli-Lilly, Europa, Fédération Française de Cardiologie, Fondation Cœur & Recherche, Medtronic, MSD, Pfizer, Sanofi-Aventis. M. Akodad received research grants from Fédération Française de Cardiologie, MUSE-Explore, Biotronik and Medtronic.].

References

[1] J.-L. Mas, G. Derumeaux, B. Guillon, et al., Patent Foramen Ovale Closure or Anticoagulation vs. Antiplatelets after Stroke, N. Engl. J. Med. 377 (2017) 1011–1021.

[2] L. Søndergaard, S.E. Kasner, J.F. Rhodes, et al., Patent Foramen Ovale Closure or Antiplatelet Therapy for Cryptogenic Stroke, N. Engl. J. Med. 377 (11) (2017) 1033–1042.

[3] J.L. Saver, J.D. Carroll, D.E. Thaler, et al., Long-Term Outcomes of Patent Foramen Ovale Closure or Medical Therapy after Stroke, N. Engl. J. Med. 377 (11) (2017) 1022–1032.

[4] P.H. Lee, J.-K. Song, J.S. Kim, et al., Cryptogenic Stroke and High-Risk Patent Foramen Ovale: The DEFENSE-PFO Trial, J. Am. Coll. Cardiol. 71 (20) (2018) 2335–2342.

[5] A.Y. Elgendy, I.Y. Elgendy, M.K. Mojadidi, et al., New-onset atrial fibrillation following percutaneous patent foramen ovale closure: a systematic review and meta-analysis of randomised trials, EuroIntervention. 14 (17) (2019) 1788–1790.

[6] L. Varotto, G. Bregolin, M. Paccanaro, A. De Boni, C. Bonanno, F. Perini, Network meta-analysis on patent foramen ovale: is a stroke or atrial fibrillation worse? Neurol. Sci. 42 (1) (2021) 101–109.

[7] L. Oliva, E. Huszti, M. Barker, C. Frankfurter, R. Hall, E. Horlick, L. Abrahamyan, New-onset atrial fibrillation following percutaneous closure of patent foramen ovale: a systematic review and meta-analysis, J. Interv. Card Electrophysiol. 60 (2) (2021) 165–174.

[8] B. Qiu, Y. Cai, D. Wang, J. Lin, Y. Fan, Closure versus Medical Therapy for Patent Foramen Ovale in Patients with Cryptogenic Stroke: An Updated Meta-Analysis of Randomized Controlled Trials, J. Stroke Cerebrovasc. Dis. 27 (12) (2018) 3463–3472.

[9] H.P. Adams, B.H. Bendixen, L.J. Kappelle, J. Biller, B.B. Love, D.L. Gordon, E. E. Marsh, Classification of subtype of acute ischemic stroke. Definitions for use in a multicenter clinical trial. TOAST. Trial of Org 10172 in Acute Stroke Treatment, Stroke 24 (1) (1993) 35–41.

[10] G.W. Albers, R.A. Bernstein, J. Brachmann, et al., Heart Rhythm Monitoring Strategies for Cryptogenic Stroke: 2015 Diagnostics and Monitoring Stroke Focus Group Report, J. Am. Heart Assoc. 5 (3) (2016), https://doi.org/10.1161/JAHA.115.002944.

[11] P. Kirchhof, S. Benussi, D. Kotecha, et al., 2016 ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS, Eur. Heart J. 37 (38) (2016) 2893–2962.

[12] B. Maesen, J. Nijs, J. Maessen, M. Allessie, U. Schotten, Post-operative atrial fibrillation: a maze of mechanisms, Europace 14 (2) (2012) 159–174.

[13] J.W. Waks, M.E. Josephson, Mechanisms of Atrial Fibrillation – Reentry, Rotors and Reality, Arrhythm Electrophysiol. Rev. 3 (2014) 90–100.

[14] S. Staubach, D.H. Steinberg, W. Zimmermann, N. Wawra, N. Wilson, N. Wunderlich, H. Sievert, New onset atrial fibrillation after patent foramen ovale closure, Catheter Cardiovasc. Interv. 74 (6) (2009) 889–895.

[15] K. Berthet, T. Lavergne, A. Cohen, L. Guize, M.-G. Bousser, J.-Y. Le Heuzey, P. Amarenco, Significant association of atrial vulnerability with atrial septal abnormalities in young patients with ischemic stroke of unknown cause, Stroke 31 (2) (2000) 398–403.

[16] R.F. Bonvini, R. Sztajzel, P.-A. Dorsaz, M. Righini, C. Bonvin, J. Alibegovic, U. Sigwart, E. Camenzind, V. Verin, J. Sztajzel, Incidence of atrial fibrillation after percutaneous closure of patent foramen ovale and small atrial septal defects in patients presenting with cryptogenic stroke, Int. J. Stroke 5 (1) (2010) 4–9.