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Atrial Fibrillation following Device Closure of Patent Foramen Ovale

Annika Burow Markus Schwerzmann Dieter Wallmann Hildegard Tanner
Takao Sakata Stephan Windecker Bernhard Meier Etienne Delacrétaz

Swiss Cardiovascular Center Bern, University Hospital, Bern, Switzerland

Key Words
Patent foramen ovale · Paradoxical embolism · Cryptogenic stroke · Arrhythmias · Long-time ECG recording

Abstract
Objectives: Recurrent embolic events after device closure of patent foramen ovale (PFO) have been related to incomplete closure. Another cause could be atrial fibrillation (AF). The aim of this study was to determine the incidence of AF in stroke patients after PFO closure. ***Methods:*** Consecutive patients with device closure of a PFO after a stroke or transient ischemic attack and control patients with stroke underwent 7-day event loop recordings 3 and 6 months after PFO closure or stroke, respectively. ***Results:*** Forty patients treated by PFO device closure 96 ± 68 days after cryptogenic ischemic stroke and 70 control patients with ischemic stroke of other etiologies (known AF excluded) were compared. AF was identified in 6 patients (15%) of the treated group and in 12 control patients (17%, p = 0.77). In multivariate analysis, the presence of an occluder device was not an independent risk factor for AF. ***Conclusions:*** The incidence of AF is high after device closure of a PFO in stroke patients and similar to that in patients with stroke of non-PFO etiology and, hence, with no device. Further studies are required to determine the risk of thromboembolism and the optimal treatment in patients developing AF after device closure of a PFO.

Introduction

Patent foramen ovale (PFO) has been associated with otherwise unexplained stroke and hence has been termed cryptogenic stroke in young adults. Device closure of the PFO has emerged as a treatment option in recent years. Observational studies have reported recurrent thromboembolic event rates of 2–4% per year following percutaneous PFO closure [1–5]. Although recurrent thromboembolic events have been related to incomplete closure in some cases, other etiologies such as concomitant cerebrovascular disease or thromboembolic complications of atrial fibrillation (AF) may be present. The incidence of AF following device closure of the PFO ranges from less than 1 to 6% in short-term observational studies [6–8]. Most of the studies addressing this issue only included clinical endpoints (e.g. symptomatic AF) and short-term ECG monitoring. Moreover, none of the studies comprised control groups of patients without a device.

The aim of this study was to determine the incidence of AF in stroke patients following percutaneous PFO closure using long-term ECG monitoring. In addition, the incidence of AF in this patient population was compared to that in patients with stroke of other etiologies who did not undergo device closure.

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Fax +41 61 306 12 34
E-Mail karger@karger.ch
www.karger.com

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Prof. Etienne Delacrétaz, MD
FESC, Swiss Cardiovascular Center Bern, University Hospital
CH–3010 Bern (Switzerland)
Tel. +41 31 632 21 11, Fax +41 31 632 42 99
E-Mail etienne.delacretaz@insel.ch

Table 1. Patient characteristics

	PFO device (n = 40)	No device (n = 70)	p value
Age, years, mean ± SEM	50 ± 2	66 ± 1	<0.0001
Male sex	26 (65)	44 (63)	0.65
Coronary artery disease	7 (18)	11 (16)	0.81
Diabetes	1 (3)	14 (20)	0.01
Smokers	16 (40)	17 (24)	0.08
Dyslipidemia	21 (53)	41 (59)	0.54
Hypertension	15 (38)	58 (83)	<0.0001
Echocardiographic data			
Left atrial dimension, mm	37 ± 1	40 ± 1	0.03
LV mass index, g/m^2	91 ± 4	122 ± 6	0.0002
LV ejection fraction	64 ± 1	60 ± 1	0.04
Mitral valve regurgitation	12 (30)	39 (56)	0.009
Carotid artery stenosis	1 (4)	8 (13)	0.25
Vertebral artery stenosis	0 (0)	3 (5)	0.28

Figures in parentheses indicate percentages.

Patients and Methods

Patients with device closure of a PFO after a stroke or transient ischemic attack (TIA) and exclusion of etiologies other than PFO, and control patients with stroke or TIA attributed to non-PFO etiologies were prospectively studied. Patients with known AF were excluded. All patients underwent cardiac echocardiography, carotid artery imaging and magnetic resonance imaging of the brain. In addition, 7-day event loop recordings were performed 3 and 6 months after PFO closure, or 3 and 6 months after stroke (control patients), using an R-Test Evolution II device (Novacor, Rueil-Malmaison, France). This 2-lead device has a total recording time of 20 min and performs an event-triggered (e.g. onset of AF) or patient-triggered sampling of the ECG during the recording period. The event loop recording was programmed to store irregular RR-intervals that could correspond to AF paroxysms. Parameters for event-triggered recordings were as follows: 60 s for absolute pauses (RR interval >2.0 s); 60 s for relative pauses (RR interval >175% of the previous RR interval); 600 s for premature beats [RR interval < (85% × mean RR)]; 60 s for bradycardia (R frequency <50 min^{-1}); 360 s for runs [RR interval < (85% × mean RR) for ≥3 beats], and 60 s were devoted to patient-triggered recording. AF was identified by manual reviewing of the ECG recordings. Heart rate trend was stored throughout the period of use and variations in heart rate frequency were, therefore, recorded continuously. AF was defined as a documented episode of absolute arrhythmia of more than 30 s. The research protocol was approved by the local ethics committee and informed consent was obtained from all patients.

Statistical Analysis

Continuous values are presented as means (SD). The Mann-Whitney U test and the χ^2 test were used for comparisons between groups when appropriate. Backward stepwise multiple logistic regression analysis was performed to assess the relationship between PFO device and subsequent AF with adjustment for covariates. The assumption of proportional hazards for the Cox regression model was checked for the following factors: age (<65 vs. ≥65 years), hypertension, diabetes, the presence of left-atrial enlargement, left-ventricular (LV) hypertrophy and impaired LV function. A two-sided p value < 0.05 was considered significant. All statistical analyses were performed using Statview 4.5 (Abacus Concepts) and SPSS 10.0 for Windows.

Results

The study included 110 patients: 40 patients treated with percutaneous device closure of the PFO 96 ± 68 days after ischemic stroke and 70 control patients without a PFO occluder 92 ± 22 days after ischemic stroke. Amplatzer occluder devices were used (AGA Medical, Golden Valley, Minn., USA; 25-mm devices in 34 patients, 30-mm devices in 6 patients). The characteristics of both patient groups are shown in table 1. Patients with a device were younger and less often had arterial hypertension. Accordingly, left-atrial size was larger and LV mass index higher in control patients. In addition, mitral valve regurgitation was present more often in control patients. The prevalence of carotid and vertebral artery stenosis was low in both groups. Paroxysmal AF was identified in 6 patients (15%) after PFO closure and in 12 control patients (17%, p = 0.77; fig. 1). After adjustment for clinical covariates in a multiple logistic regression model, parox-

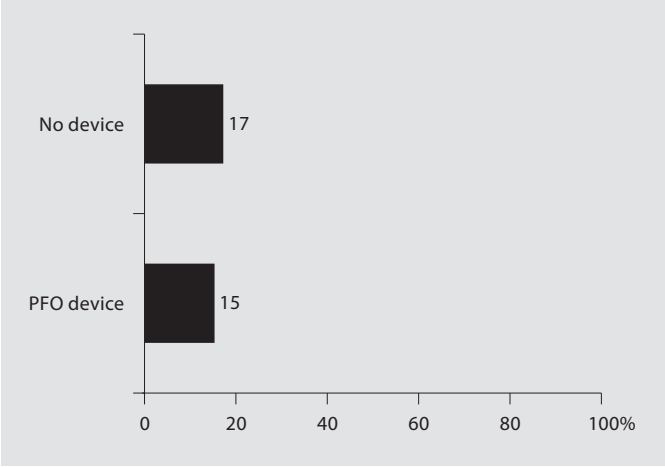

Fig. 1. Incidence of atrial fibrillation (percent of patients) using long-term ECG recording in stroke patients following percutaneous closure of foramen ovale (PFO device) and in control patients (no device). p = 0.77.

ysmal AF was associated with the age of the patients ($p < 0.001$) and the presence of diabetes ($p < 0.05$). Conversely, device closure of a PFO was not independently associated with intermittent AF.

Discussion

The findings of the present study indicate that AF occurs with similar relatively high frequency in stroke patients with or without device closure of a PFO when using long-term ECG recording. It remains to be determined whether asymptomatic AF in these patients is associated with an increased risk of recurrent thromboembolism.

Although lower rates of recurrent paradoxical embolism have been observed in stroke patients after exclusion of a stroke cause other than a PFO and treatment by percutaneous device closure of a PFO compared to similar patients undergoing medical treatment, recurrent thromboembolic events continue to occur at a rate of 2–4% [1–5]. While some recurrent events have been related to incomplete PFO closure, the present study suggests that some of the recurrences may be related to AF with possible thromboembolism from the left-atrial appendage.

The incidence of AF reached 16% in the present study, and AF was more frequent than in other reports on cryptogenic stroke patients after percutaneous PFO closure. Our patient group was on average older than the patients studied in some earlier series, and the high incidence of AF may be related to the fact that we included patients >55 years in the treated group. However, previous studies were based on clinical endpoints (i.e. symptomatic AF) with limited cardiac monitoring [6–8]. A number of AF episodes may be asymptomatic, and AF incidence is underestimated when only clinical endpoints are considered. Furthermore, the length of the monitoring period, e.g. from 1 day to 2 weeks, multiplies the yield of detecting asymptomatic AF.

All AF episodes lasting >30 s, defined as sustained AF, were taken into account in our study. Whereas short periods of AF, which were recorded in some of the patients, may not be sufficient to lead to thrombus formation, they are commonly associated with longer AF episodes and may be prone to a thromboembolic milieu, especially in patients with additional risk factors. Accordingly, 4 of 6 patients with AF and an occluder device received oral anticoagulation.

Both stroke patient groups differ regarding risk factors for thromboembolism and most patients with a PFO device have a low risk profile apart from the fact that they suffered a stroke, which is usually recognized as an indication for oral anticoagulation. However, in patients with ischemic stroke determined as cryptogenic before PFO documentation, stroke may result from paradoxical embolism and not represent a thromboembolic risk factor once the PFO is occluded. Further studies are required to determine the risk of thromboembolism and the optimal treatment in patients developing AF after device closure of a PFO.

Some studies have suggested that the occluder device itself may be arrhythmogenic [6–8]. In a study by Alaeddini et al. [8], sustained AF or atrial flutter appeared more frequently in patients with a larger occluding device. Using ambulatory ECG monitoring before and after percutaneous PFO closure, Hill et al. [6] detected a significant increase in the number of supraventricular premature beats and a trend towards a higher incidence of nonsustained atrial tachycardia after percutaneous PFO closure. However, this study only focused on arrhythmias occurring immediately after the intervention. When cardiac rhythm was analyzed 6–12 months after percutaneous PFO closure, there was no difference in atrial ectopy during 24-hour ECG recording [9]. Atrial ectopic beats and nonsustained atrial tachycardias may be due to mechanical interaction of the occluding device with the muscular part of the interatrial septum, especially if the position of the device is unstable. How-

ever, instability is unlikely to persist over time. In our study group, there was no systematic long-term ECG monitoring before PFO closure and we cannot analyze the arrhythmogenic effect of the device itself. In all patients together, the presence of an occluder device was not an independent risk factor for developing AF, and there was no difference in the incidence of AF between patients with and without an occluder device. However, we cannot rule out an arrhythmogenic effect of the occluder device, since our study group is small and the number of covariates important.

Conclusions

The incidence of AF is high after device closure of a PFO in stroke patients and similar to that in patients with stroke of non-PFO etiology and, hence, with no device. The question of the potential role of transient atrial arrhythmias in thrombus formation and stroke recurrence remains to be determined in these patient populations. Long-term ECG recordings may be considered in patients with thromboembolic risk factors to guide further therapy.

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