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CLINICAL RESEARCH

STRUCTURAL

Risk of Cerebrovascular Events in Patients With Patent Foramen Ovale and Intracardiac Devices

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ABSTRACT

OBJECTIVES This study investigated whether patients with patent foramen ovale (PFO) have an increased risk of stroke due to permanent pacemaker (PPM)/implantable cardioverter-defibrillator (ICD) implantation.

BACKGROUND Data are lacking on the risk of stroke in patients with PFO and implantable intracardiac devices, either a PPM or an ICD. We investigated whether patients with PFO have increased risk of stroke due to PPM/ICD implantation.

METHODS Between 2001 and 2008, 2,921 consecutive patients with PFO (67.5 ± 16.4 years of age, 52.2% male) were identified from our echocardiography database. These patients were divided into a device group (patients had PPM/ICD implantation for any reason after receiving a diagnosis of PFO) and a no device group (patients did not have PPM or ICD implantation). Patients who had PFO closure during follow-up were excluded. Both groups were matched for baseline characteristics and medications. The incidence of ischemic stroke was assessed in each group after propensity score matching (case:control ratio of 1:1 yielding 231 pairs). All patients completed at least 4 years of follow-up until May 2012.

RESULTS There were 2,690 patients in the n device group (67.3 ± 16.4 years of age, 51.6% male) and 231 patients in the device group (75.4 ± 14.6 years of age, 59.3% male). Six patients (2.6%) in the no device group and 6 (2.6%) in the device group had a stroke during the follow-up period. No difference in the rate of stroke, transient ischemic stroke, or stroke/transient ischemic stroke was observed between the 2 groups.

CONCLUSIONS The risk of stroke in patients with PFO and an implantable intracardiac device is similar to those without an intracardiac device. In patients with PFO, without a history of stroke, device implantation might not be considered a risk factor for future stroke occurrence. (J Am Coll Cardiol Intv 2014;7:1221–6) © 2014 by the American College of Cardiology Foundation.

Implantation of permanent pacemakers (PPMs) and intracardiac defibrillators (ICDs) has steadily increased over the past 2 decades (1). Despite the benefits associated with device implantation, the risk of thrombus formation on intracardiac devices is a potential concern (2,3). Investigators have reported the occurrence of complications such as pulmonary embolism in patients with pacemaker lead thrombus (4).

This may also assume significance in patients who have an interatrial shunt, such as patent foramen ovale (PFO), with the possible association of such shunts with a higher risk of neurological events (5–15). Certain factors including PFO tunnel length

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ABBREVIATIONS AND ACRONYMS

ICD = implantable cardioverter-defibrillator

PFO = patent foramen ovale

PPM = permanent pacemaker

TIA = transient ischemic attack

and/or the presence of an associated atrial septal aneurysm have been associated with an increased risk of stroke in patients with PFO (16). Similarly, DeSimone et al. (17) reported their experience with 3 patients who presented with lead thrombus, PFO, and stroke, presumably due to paradoxical embolism.

Although the risk of cryptogenic stroke in patients with lead thrombosis and PFO is physiologically plausible, to our knowledge, there has been no systematic evaluation to study the effect of device implantation on stroke outcomes in a population consisting of only PFO patients. We compared the incidence of ischemic stroke in PFO patients with or without device implantation from our large institutional database.

METHODS

In this retrospective study, we identified patients with a diagnosis of PFO at the Cleveland Clinic either by transesophageal echocardiography (TEE), transthoracic echocardiography, or both between 2001 and 2008. Patients were then stratified by the presence or absence of PPM or ICD. The date of PFO diagnosis was considered the entry date for each patient in the study. Patients who had a history of stroke or transient ischemic attack (TIA) were excluded. Patients who had closure of PFO during the follow-up period were excluded from the study, unless they experienced a stroke/TIA before the closure procedure. We used electronic medical records to collect demographic information, baseline clinical characteristics, medical history, medications, and laboratory test results.

Patients were followed until the end of 2012 or until the primary endpoint, whichever occurred earlier. The primary endpoint was any ischemic stroke event during the follow-up period. Ischemic stroke was defined as the sudden onset of focal neurological deficit lasting >24 h with evidence of infarct documented on radiological investigation. Transient neurological dysfunction lasting <24 h and without evidence of infarction on radiological investigation was identified as a TIA. Any suspected cerebrovascular event was investigated using TEE along with computed tomography/magnetic resonance imaging; Doppler and color duplex examination of the extracranial carotid, vertebral, and basal intracranial arteries; echocardiography and Holter echocardiography; contrast transthoracic echocardiography and TEE; and necessary laboratory investigation. Permission for the study was obtained from the institutional review board.

STATISTICAL ANALYSIS. Statistical analyses were performed using SPSS 20.0 statistical package for Windows (IBM, Chicago, Illinois). Continuous data are expressed as mean ± SD, whereas categorical data are presented as a percentage. The chi-square test was used for comparison of categorical variables, and an independent *t* test was used to compare continuous variables. A p value <0.05 was considered significant for all statistical purposes.

Considering device implantation as the dependent variable, a propensity score was generated for each patient through a regression model using variables listed in Table 1. Each patient in the device group was matched to a patient in the no device group based on the closest propensity score. The method yielded 2 matched groups with 231 patients each (Figure 1). A time-to-event model was used to analyze the stroke outcome, and time of device implantation was considered as the time-varying covariate. The identification of PFO was considered as time zero for all the patients. Ischemic stroke, TIA, and the combined outcome were compared between the 2 groups using the chi-square test.

RESULTS

A total of 2,921 patients were included; 231 patients who received a PPM or ICD during the follow-up period were included in the device group and 2,690 patients who did not receive a PPM or ICD were included in the no device group. Propensity score matching yielded 1:1 matched groups from the total population.

Before propensity score matching, patients in the device group were older and were more often male (Table 1). Atrial fibrillation (58.9% vs. 28.7%, $p<0.001$), mitral regurgitation (23.4% vs. 13.9%, $p<0.001$), and heart failure (HF) (55.4% vs. 17.5%, $p<0.001$) were more common in the device group, and the average ejection fraction was lower in device group (40.41% vs. 52.47%, $p<0.001$). There were also significant differences in medication use, with patients in the device group receiving more medications compared with patients in the no device group (Table 1). After propensity score matching, the 2 groups ($n=231$ patients each) were identical with equivalent baseline characteristics and medications.

Ischemic stroke occurred in 6 patients in each group (Table 2). The primary outcome was not different between the 2 groups (2.6% vs. 2.6%, $p=1.0$). The event rate for stroke was 3.03 events/1,000 patient-years in the no device group and 2.82 events/1,000 patient-years in the device group. The time-to-event analysis showed that there was no

TABLE 1 Baseline Characteristics Between the 2 Groups

	Before Propensity Score Matching			After Propensity Score Matching		
	Device Group (n = 231)	No Device Group (n = 2,690)	p Value	Device Group (n = 231)	No Device Group (n = 231)	p Value
Age, yrs	75.39 ± 14.58	67.27 ± 16.36	<0.001	75.39 ± 14.58	76.87 ± 12.86	0.25
Male	137 (59.3)	1389 (51.6)	0.03	137 (59.3)	134 (58.0)	0.85
Atrial fibrillation	136 (58.9)	771 (28.7)	<0.001	136 (58.9)	128 (55.4)	0.51
Hypertension	107 (46.3)	1,103 (41.0)	0.13	107 (46.3)	111 (48.1)	0.78
Diabetes	91 (39.4)	654 (24.3)	<0.001	91 (39.4)	84 (36.4)	0.57
Smoking history	99 (42.9)	995 (37.0)	0.09	99 (42.9)	107 (46.3)	0.51
Dyslipidemia	86 (37.7)	919 (34.2)	0.35	86 (37.7)	74 (32.0)	0.28
COPD	21 (9.1)	227 (8.4)	0.71	21 (9.1)	22 (9.5)	1.00
Migraine	5 (2.2)	135 (5.0)	0.05	5 (2.2)	5 (2.2)	1.00
Atrial septal aneurysm	18 (7.8)	272 (10.1)	0.30	18 (7.8)	13 (5.6)	0.46
Heart failure	128 (55.4)	47 (17.5)	<0.001	128 (55.4)	122 (52.8)	0.64
Ejection fraction	40.41 ± 16.94	52.47 ± 11.46	<0.001	40.41 ± 16.94	40.13 ± 15.80	0.85
Creatinine	1.21 ± 0.62	1.13 ± 1.03	0.27	1.21 ± 0.62	1.21 ± 0.62	0.66
Aortic stenosis	5 (2.2)	22 (0.8)	0.06	5 (2.2)	7 (3.0)	0.77
Mitral regurgitation	54 (23.4)	374 (13.9)	<0.001	54 (23.4)	51 (22.1)	0.82
Aspirin	155 (67.1)	1,581 (58.8)	0.01	155 (67.1)	151 (65.4)	0.77
Clopidogrel	43 (18.6)	430 (16.0)	0.31	43 (18.6)	48 (20.8)	0.64
Beta-blockers	172 (74.5)	1,511 (56.2)	<0.001	172 (74.5)	175 (75.8)	0.83
ACE inhibitor	166 (71.9)	1,256 (46.7)	<0.001	166 (71.9)	171 (74.0)	0.68
Insulin	57 (24.7)	385 (14.3)	<0.001	57 (24.7)	47 (20.3)	0.32
Warfarin	146 (63.2)	1,112 (41.3)	<0.001	146 (63.2)	144 (62.3)	0.92
Statin	132 (57.1)	1,187 (44.1)	<0.001	132 (57.1)	124 (53.7)	0.51

Values are mean ± SD or n (%).
ACE = angiotensin-converting enzyme; COPD = chronic obstructive pulmonary disease.

difference in stroke outcome between the 2 groups (p = 0.748; odds ratio: 0.342; 95% confidence interval: 0.003 to 3.833). In patients who had a stroke (12 patients), the annual event rate was 0.33 events/year in the no device group, whereas it was 0.20 events/year for patients in the device group.

Further analysis in the matched cohort showed that of 22 events (stroke and TIA), 19 occurred in patients with atrial fibrillation. Subgroup analysis in patients with atrial fibrillation revealed that 10 patients in the device group experienced a neurological event compared with 9 patients in the no device group (7.4% vs. 7.0%, p = 1.00). In patients who did not have atrial fibrillation, no ischemic stroke event occurred after device implantation, whereas the event rate in the no device group was found to be 2.22 events/1,000 patient-years.

DISCUSSION

In our study, we found that implantation of an electrical cardiac device with an electrode in the right ventricle was not related to an increase in the incidence of stroke. PPM and ICD implantation has increased steadily, with >350,000 devices placed per year in the United States alone (18). As mentioned previously, device implantation can be complicated by thrombus formation on the lead, due to either thrombogenic properties associated with the lead or local vascular stenosis predisposing to thrombus formation at the site (19). PFO may be considered as an additional risk in the presence of an implanted device. Although PFO has been associated with cryptogenic stroke, data concerning the association of PFO with stroke is conflicting (5,6,10,12,13,20). Nevertheless, given the frequency of PFO in the general population and the substantial number of patients undergoing cardiac device implantation, the theoretical risk of lead thrombus formation leading to paradoxical embolism and stroke is not insignificant. The current literature in this regard is limited to a few case reports (21). We therefore believe that our retrospective analysis of a large group of patients undergoing device implantation, demonstrating that the presence of PFO did not increase the risk of stroke, is an important contribution.

DeSimone et al. (22) performed a retrospective study of 6,075 patients with an implanted device (364 PFO vs. 5,711 non-PFO patients). They concluded that patients

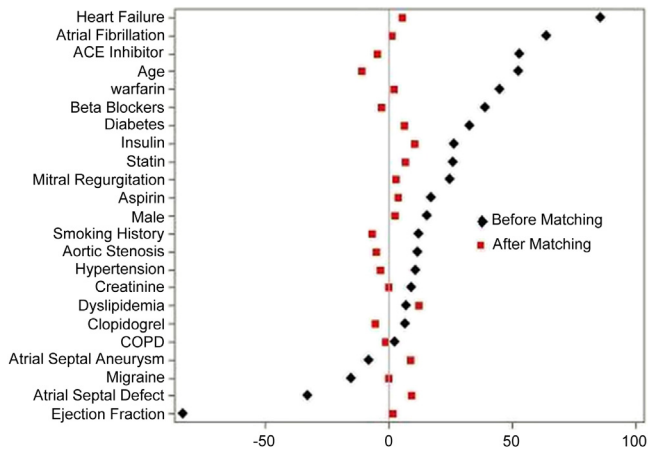

FIGURE 1 Standardized Difference of Baseline Characteristics and Discharge Medication Between the 2 Groups Before and After Propensity Score Matching

Using device implantation as the dependent variable, a propensity score was generated for each patient through a regression model using variables listed in Table 1. Each patient in the device group was matched to a patient in the no device group based on the closest propensity score. The method yielded 1:1 matched groups from the total population.

with PFO have a significantly higher stroke/TIA incidence compared with patients without PFO (8.2% vs. 2.0%, $p < 0.0001$). Our study differs from theirs in few important ways. First, our patient population consists of PFO patients only, as we want to specifically study whether device implantation has any impact on stroke outcome in patients with the defect. Second, they included patients with previous stroke/TIA, whereas we did not because previous stroke itself is an important predictor of future stroke (23).

We also considered many other baseline variables, including medications in our study. We believe that this detailed information is imperative because medications taken by patients are certainly important with regard to stroke outcomes. The role of statin therapy in the prevention of stroke has been widely studied (24). Also, meta-analysis done to compare the stroke outcome between medical therapy and PFO closure have not shown medical therapy to offer greater benefits as compared to closure (25–29). One study even showed medical therapy to be comparably efficacious to PFO closure (30). Overall, it can be said that the difference in medications between the 2 groups may affect the stroke outcomes. However, the medications taken by patients in our study group were identical, and the results of our study may also be attributed to comparable medical treatment between the 2 matched groups.

TABLE 2 Results

Outcomes	Device Group (n = 231)	No Device Group (n = 231)	p Value
Ischemic stroke	6 (2.6)	6 (2.6)	1.00
TIA/ischemic stroke	10 (4.3)	12 (5.2)	0.83

Values are n (%).
TIA = transient ischemic attack.

Interestingly, of a total of 22 cerebrovascular ischemic events in our population, 19 occurred in patients with atrial fibrillation. The association of atrial fibrillation with stroke is well established. Also, investigators have demonstrated the presence of undetected intermittent atrial fibrillation in patients with stroke (31–35). Hence, atrial fibrillation, and not device implantation, seems to be the most probable reason for a stroke event in our patient population. The incidence of atrial fibrillation and the use of anticoagulant medication were identical in our matched groups. This is an important message for operators evaluating patients for PFO closure in the setting of stroke and reminds clinicians of the need for a thorough evaluation for causes of stroke and appropriate medication therapy for patients with PFO.

The overall incidence of the primary outcome measure was fairly low in our study. Among patients with PFO and previous stroke, other investigators have demonstrated a stroke/TIA recurrence rate of as high as 19% at 4 years, which is 2 to 3 times the risk of patients without PFO (12,36). Because we included only those patients who did not have a previous stroke/TIA, there is a possibility that the ischemic event rate in our population was too low to detect a difference between patients with and without an implantable cardiac device. Further studies need to be performed to draw a definitive conclusion.

STUDY LIMITATIONS. The limitations associated with any retrospective study apply to this analysis, including selection bias and differences in unadjusted baseline characteristics. Correction for these factors using propensity score matching was performed, but is not equivalent to a true randomization. It is important to note that, before propensity matching, patients in the device group were receiving more aggressive antithrombotic therapy and other medications (warfarin, aspirin, statin). This difference is a limitation when comparing the risk of thromboembolic complications. Worse clinical characteristics (e.g., atrial fibrillation, age, heart failure, low ejection fraction) and medication use are likely to be associated with patients who require a device implantation. However, propensity score matching

yielded 2 groups with identical baseline and medication characteristics.

Second, we excluded the patients who had an implanted device but also underwent PFO closure during the follow-up period, apart from those who had any stroke/TIA before the closure. It is possible that high-risk patients may have benefited from closure to offset the risk of any event. To minimize the same, we included only those patients who had no history of a neurological event. The inclusion of patients who had an event before the closure was done to minimize possible selection bias. Overall, our study was mainly limited to only those PFO patients who were receiving medical therapy, and it needs to be viewed accordingly.

Another limitation of our study is the low event rate. Our strict exclusion criteria may well have accounted for low number of events in our study group. We limited our study to the majority of patients who may not be considered high risk and thus presents a dilemma for interventionalists concerning the decision to close the PFO. In the presence of these limitations, further studies from larger centers, collaborative studies, or possibly a randomized trial may produce more definite answers.

CONCLUSIONS

In patients with PFO and no previous episode of an ischemic neurological event, implantation of a PPM or ICD is not associated with an increased risk of an ischemic stroke event in the subsequent 4 years. Evaluation for other stroke risk factors, including atrial fibrillation, is imperative to reduce the risk of neurological events.

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