Stoke or Transient Ischemic Attack in Patients With Transvenous Pacemaker or Defibrillator and Echocardiographically Detected Patent Foramen Ovale

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Background—A patent foramen ovale (PFO) may permit arterial embolization of thrombi that accumulate on the leads of cardiac implantable electronic devices in the right-sided cardiac chambers. We sought to determine whether a PFO increases the risk of stroke/transient ischemic attack (TIA) in patients with endocardial leads.

Methods and Results—We retrospectively evaluated all patients who had endocardial leads implanted between January 1, 2000, and October 25, 2010, at Mayo Clinic Rochester. Echocardiography was used to establish definite PFO and non-PFO cohorts. The primary end point of stroke/TIA consistent with a cardioembolic etiology and the secondary end point of mortality during postimplantation follow-up were compared in PFO versus non-PFO patients with the use of Cox proportional hazards models. We analyzed 6075 patients (364 with PFO) followed for a mean 4.7±3.1 years. The primary end point of stroke/TIA was met in 30/364 (8.2%) PFO versus 117/5711 (2.0%) non-PFO patients (hazard ratio, 3.49; 95% confidence interval, 2.33–5.25; P<0.0001). The association of PFO with stroke/TIA remained significant after multivariable adjustment for age, sex, history of stroke/TIA, atrial fibrillation, and baseline aspirin/warfarin use (hazard ratio, 0.91; 95% confidence interval, 0.77–1.07; P=0.25). There was no significant difference in all-cause mortality between PFO and non-PFO patients (hazard ratio, 0.91; 95% confidence interval, 0.77–1.07; P=0.25).

Conclusions—In patients with endocardial leads, the presence of a PFO on routine echocardiography is associated with a substantially increased risk of embolic stroke/TIA. This finding suggests a role of screening for PFOs in patients who require cardiac implantable electronic devices; if a PFO is detected, PFO closure, anticoagulation, or nonvascular lead placement may be considered. (Circulation. 2013;128:1433-1441.)

Key Words: defibrillators ■ foramen ovale, patent ■ International Classification of Diseases ■ ischemic attack, transient ■ pacemaker, artificial ■ stroke

Transvenous cardiovascular implantable electronic devices (CIEDs) are widely used because of the effectiveness with which they treat cardiac arrhythmias and the relative ease and safety with which they are implanted.1,2 However, an endovascular lead within the right atrium or ventricle represents a foreign body that can promote the formation of mobile thrombi that may dislodge to the pulmonary circulation.3,4 Although symptomatic pulmonary embolism after pacemaker or defibrillator implantation is uncommon, asymptomatic emboli may be present far more frequently,5,6 and endovascular lead-related thrombi are likely underdetected. With the use of ventilation perfusion scanning,1 study showed asymptomatic pulmonary emboli in 15% of patients within 2 weeks of device implantation without heparin prophylaxis,8 and, at autopsy, pulmonary emboli were present in 21% of patients with CIEDs.6 A study using intracardiac echocardiography at the time of a planned electrophysiological procedure found mobile thrombi attached to leads in 30% of patients.9 These thrombi were rarely seen with the use of transthoracic echocardiography (TTE), reflecting their small size. Moreover, the presence of lead-related thrombi was associated with increased pulmonary artery systolic pressure, suggesting subclinical pulmonary embolic events.3 Elevated pulmonary artery pressures may in turn increase the likelihood of right-to-left shunting across a patent foramen ovale (PFO).

Clinical Perspective on p 1441

Transvenous cardiovascular implantable electronic devices (CIEDs) are widely used because of the effectiveness with which they treat cardiac arrhythmias and the relative ease and safety with which they are implanted.1,2 However, an endovascular lead within the right atrium or ventricle represents a foreign body that can promote the formation of mobile thrombi that may dislodge to the pulmonary circulation.3,4 Although symptomatic pulmonary embolism after pacemaker or defibrillator implantation is uncommon, asymptomatic emboli may be present far more frequently,5,6 and endovascular lead-related thrombi are likely underdetected. With the use of ventilation perfusion scanning,1 study showed asymptomatic pulmonary emboli in 15% of patients within 2 weeks of device implantation without heparin prophylaxis,8 and, at autopsy, pulmonary emboli were present in 21% of patients with CIEDs.6 A study using intracardiac echocardiography at the time of a planned electrophysiological procedure found mobile thrombi attached to leads in 30% of patients.9 These thrombi were rarely seen with the use of transthoracic echocardiography (TTE), reflecting their small size. Moreover, the presence of lead-related thrombi was associated with increased pulmonary artery systolic pressure, suggesting subclinical pulmonary embolic events.3 Elevated pulmonary artery pressures may in turn increase the likelihood of right-to-left shunting across a patent foramen ovale (PFO).
Up to 25% of the population may have a PFO detectable on autopsy, with persistence after the birth of a connection between the right and left atria. In patients with elevated right-sided pressures, flow through a PFO provides a mechanism of blood flow from the right heart to the left-sided circulation. In patients with a PFO, endovascular leads may pose a unique hazard, because the thrombi that develop on leads may shunt across the PFO to the systemic circulation, resulting in ischemic cerebrovascular events or other systemic thromboembolisms. We have previously published 2 case series on device lead–mediated paradoxical thromboembolism and the effective management of such high-risk CIED patients with PFO closure to prevent recurrent strokes. Transvenous pacing leads have also been associated with an increased risk of systemic thromboembolism in patients with intracardiac shunts. Presently, when an intracardiac shunt, such as an atrial or ventricular septal defect, is recognized, endocardial leads are not implanted, and patients are referred for either closure of the shunt or epicardial lead placement. However, whether the presence of a PFO in most CIED recipients increases the risk of clinical strokes or transient ischemic attacks (TIAs) is unknown. Therefore, screening for a PFO is not routinely performed at the time of CIED implantation, and the presence or absence of a PFO does not affect the implant decision or strategy in current clinical practice. To test the hypothesis that patients with PFO and right-sided CIED leads are at an increased risk for stroke or TIA, we performed a large retrospective study.

Methods

Patient Population
All patients who underwent transvenous implantation of an implantable cardioverter-defibrillator or pacemaker at Mayo Clinic, Rochester, Minnesota, between January 1, 2000, and October 25, 2010, were included in the study, and patients’ charts were reviewed between the last quarter of 2010 and the first quarter of 2011. All patients had authorized review of their medical records for research purposes. Data were deidentified to protect patient confidentiality. Patients were excluded from the analysis if they were identified as sustaining a possible neurological event during follow-up, but they lacked sufficient details in the electronic medical record regarding the symptoms and timing of stroke/TIA, or had an inadequate evaluation to establish a diagnosis and cause of the event. Patients were also excluded if PFO was suspected on echocardiography but not definitively confirmed, or if the diagnosis of PFO was made within 30 days after the occurrence of a stroke/TIA event.

Assessment of PFO and Clinical Characteristics
All patients receiving implanted devices with endocardial leads at our center routinely have comprehensive TTE performed. Data are prospectively entered into a clinical database with predefined variables, including the absence or presence of a PFO. PFO was detected as part of standard protocol for TTE and transesophageal echocardiography (TEE) at Mayo Clinic. This includes the routine use of 2-dimensional and color Doppler interrogation of the interatrial septum. We also attempt, in all TTEs, the measurement of right-sided pressures from the tricuspid regurgitant jet velocity. When necessary, the use of agitated saline to evaluate for right-to-left shunting is performed, typically, based on the size of the right atrial chambers and whether there are doubts on the structural integrity of the interatrial septum. If a shunt is visualized or diagnosed but cannot be easily seen at the usual place of a PFO or primum or atrial septal defect (primum or secundum), then a TEE to exclude a sinus venous-type atrial septal defect is done.

For all study participants, all echocardiogram reports (transesophageal and transesophageal) were reviewed for the presence of a PFO either by color-flow Doppler or an intravenous agitated saline bubble study. The study personnel reviewing echocardiography reports for PFO diagnoses were blinded to the clinical outcomes. This allowed for delineation of the study population into 2 groups, those with and those without a PFO. Some reports were coded as possible or probable PFO; in the absence of additional studies that definitely included or excluded PFO, these patients were excluded from the study population. The use of aspirin, warfarin, and clopidogrel was obtained from the electronic medical record in all study patients at 3 points in time: (1) the date of device implantation, (2) the date of the index echocardiogram (at which the absence or presence of PFO was determined), and (3) the date of stroke or TIA (in those patients who had neurological events). Clinical characteristics of the patient population including comorbidities and a history of atrial fibrillation (AF) were obtained from the diagnosis codes (International Classification of Diseases, Ninth Revision, Hospital International Classification of Disease Adaptation, and Berksom Mayo Clinic coding system) for clinical encounters until the time of index device implantation.

Assessment of Outcomes
Outcomes data were obtained from a centralized system that contained complete records of all patients treated and followed at Mayo Clinic and its hospitals. These records provide a detailed history and diagnosis for all outpatient encounters, emergency department visits, home and nursing home visits, and inpatient care. We used the diagnosis codes consistent with cerebrovascular events to identify patients with possible stroke or TIA. The electronic medical records were reviewed, and, in consultation with a board-certified vascular neurologist (A.A.R.), the absence or presence of a documented ischemic stroke or TIA consistent with a cardioembolic etiology was determined and the date of events confirmed. We excluded those events from our stroke/TIA definition in which a definite noncardioembolic cause for the stroke or TIA was documented, such as intracranial hemorrhage, proximal mobile aortic atheroma, severe ipsilateral carotid stenosis, radiologically proven small subcortical stroke with lacunar presentation, and severe intracranial stenosis in the relevant vessel. Mortality status and date of death were obtained from multiple sources including the Mayo Clinic registration database and Accurint (LexisNexis, Philadelphia, PA), an institutionally approved fee-based Internet research and location service.

Statistical Methods
Baseline patient demographics were compared between PFO and non-PFO groups by using χ² tests for discrete variables and t tests for continuous variables. The cumulative probabilities of stroke/TIA and of death following device implant among the 2 groups by PFO status were estimated by using the Kaplan–Meier method. Potential confounders that attribute risk of stroke/TIA or mortality were evaluated by using proportional hazards regression models. Univariate and multivariate-adjusted Cox proportional hazards models (adjusting for age, sex, previous history of stroke/TIA, and additionally adjusting for history of AF and the use of aspirin and warfarin at the time of implant) were used to determine differences in stroke/TIA and death between PFO and non-PFO patients during follow-up. Additional covariates were added to the Cox model by using stepwise selection. A 2-tailed α-level 0.05 was considered the threshold for statistical significance for all tests. SAS version 9.3 (Cary, NC) was used for statistical analysis.

The authors were entirely responsible for study hypothesis development, study design, data collection, data analysis, and manuscript preparation. The study was funded exclusively by the Mayo Clinic as part of an implantable device quality practice review. There was no support or input from industry. This study was approved by the Mayo Clinic Institutional Review Board (IRB #10–007582).
Results

Our study included 6075 patients receiving CIED implantations with endocardial leads. The average follow-up after device implantation was 4.7±3.1 years (range, 0–12.3 years). There were 364 patients with definite PFO and 5711 patients without PFO. TEE reports were available for 12.6% of patients, and 108/364 (29.7%) PFO diagnoses were based on TEEs. We excluded 74 patients with probable/possible PFO on echocardiography that was not confirmed with further tests, and excluded 11 patients who had a diagnosis of PFO made within 30 days after the index stroke/TIA event. Another 40 patients (5 in the PFO group and 35 in the non-PFO group) were excluded because of the lack of sufficient follow-up data to confirm or refute the diagnosis of stroke/TIA.

Baseline characteristics are presented in Table 1. There was no notable difference between PFO and non-PFO patients in terms of age, sex, history of stroke/TIA, diabetes mellitus, carotid artery disease, hyperlipidemia, hypertension, peripheral vascular disease, congestive heart failure, cerebral occlusion/stenosis, and CHA2DS2-VASc score. The PFO group was more likely to have a history of AF at baseline (49% in PFO versus 44% in non-PFO group; \(P=0.03\)). The 2 groups were evenly matched for the distribution of CHA2DS2-VASc scores (mean, 3.1±2.0; \(P=0.58\)). Aspirin was used less often at the time of CIED implantation among patients with PFO (42% in PFO versus 48% in non-PFO group; \(P=0.026\)), but warfarin use was similar (31% in PFO versus 32% in non-PFO group; \(P=0.65\)).

Among patients with PFO, a total of 30 (8.2%) met the combined primary end point of ischemic stroke/TIA consistent with a cardioembolic etiology during follow-up as opposed to a total 117 (2.0%) among those without PFO (\(P<0.0001\)). Of these, 20/30 (66.7%) in the PFO group and 80/117 (68.4%) in the non-PFO group were classified as strokes as opposed to TIs, thus an overall stroke rate of 5.2% versus 1.4% (\(P<0.0001\)). At 1 year postimplantation, the Kaplan–Meier cumulative incidence of stroke/TIA was higher in PFO patients (1.4%) versus non-PFO patients (0.6%). The cumulative difference progressed increasingly over time to 3.3% in PFO versus 1.0% in non-PFO patients at 2 years, and 7.9% in PFO versus 2.3% in non-PFO patients at 5 years (Figure 1).

On univariate time-to-event proportional hazards estimation, the hazard rate of stroke/TIA in PFO versus non-PFO patients was 3.49 (97% confidence interval [CI], 2.33–5.25; \(P<0.0001\)). This strong association between PFO and stroke in patients with endocardial leads remained significant after multivariable adjustment for age, sex, and history of previous stroke/TIA (hazard ratio, 3.30; 95% CI, 2.19–4.96; \(P<0.0001\)) and after additionally adjusting for a history of AF and the use of aspirin and warfarin at the time of index device implant (hazard ratio, 3.36; 95% CI, 2.23–5.07; \(P<0.0001\)). No other covariates reached the statistical level for inclusion in the stepwise selection model (Table 2).

We performed further exploratory analyses to delineate possible subgroups with a different effect of PFO on stroke or TIA in comparison with the overall population. We stratified the analysis based on age (dichotomized at 65 years), sex, previous history of stroke/TIA, baseline history of AF, baseline aspirin and warfarin use, and thromboembolic risk as measured by CHA2DS2-VASc score (0–2 versus 3 or more). The association between PFO and stroke/TIA was uniformly present in all subgroups as shown in the Kaplan–Meier curves in Figure 2.

There was no difference in unadjusted all-cause mortality among CIED patients with PFO (155/364; 46%) in comparison with patients without PFO (2200/5711; 39%), hazard ratio, 0.91 (95% CI, 0.77–1.07; \(P=0.25\); Figure 1). The absence of a difference in mortality between groups persisted after adjusting for age, sex, and history of stroke/TIA (hazard ratio, 0.90; 95% CI, 0.76–1.06; \(P=0.20\)), additional adjustment for history of AF and baseline aspirin and warfarin use (hazard ratio, 0.89; 95% CI, 0.75–1.05; \(P=0.15\)), and further adjustment by the use of stepwise selection of covariates (hazard ratio, 0.90; 95% CI, 0.77–1.07; \(P=0.23\); Table 2).

Discussion

In this large, retrospective analysis of endocardial pacemaker and defibrillator recipients, we found a >3-fold higher risk of stroke or TIA following device implantation in patients with a PFO in comparison with those without a PFO. This dramatically increased risk remained after adjustment for age, sex, previous stroke or TIA, history of AF, and baseline use of aspirin and warfarin. Moreover, the elevated risk persisted over the course of follow-up. This finding contrasts population-based observational studies of PFO and thromboembolism, which failed to find an association between PFO and thromboembolism.\(^{18,19}\) However, these studies did not specifically include patients with endovascular pacemakers and defibrillators. The fact that endovascular leads are a nidus for thrombus development\(^{16,20}\) and adopt an intracardiac course that frequently is in juxtaposition to the interatrial septum likely accounts for the strong association we observed between PFO and stroke/TIA in device recipients (Figure 3). This is the first systematic evaluation of the risk of systemic

\[\text{Table 1. Baseline Characteristics Among the Patent Foramen Ovale and Nonpatent Foramen Ovale Groups}\]

<table>
<thead>
<tr>
<th>Variable</th>
<th>PFO (n=364)</th>
<th>No PFO (n=5711)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>67.9±15.3</td>
<td>66.8±17.0</td>
<td>0.22</td>
</tr>
<tr>
<td>Male, n (%)</td>
<td>219 (60)</td>
<td>3672 (64)</td>
<td>0.11</td>
</tr>
<tr>
<td>Stroke/TIA, n (%)</td>
<td>53 (15)</td>
<td>857 (15)</td>
<td>0.82</td>
</tr>
<tr>
<td>Diabetes mellitus, n (%)</td>
<td>81 (22)</td>
<td>1327 (23)</td>
<td>0.67</td>
</tr>
<tr>
<td>Carotid artery disease, n (%)</td>
<td>26 (7)</td>
<td>402 (7)</td>
<td>0.94</td>
</tr>
<tr>
<td>Cerebral occlusion/stenosis, n (%)</td>
<td>15 (4)</td>
<td>188 (3)</td>
<td>0.39</td>
</tr>
<tr>
<td>Coronary artery disease, n (%)</td>
<td>175 (48)</td>
<td>2542 (45)</td>
<td>0.18</td>
</tr>
<tr>
<td>Hyperlipidemia, n (%)</td>
<td>191 (52)</td>
<td>2928 (51)</td>
<td>0.66</td>
</tr>
<tr>
<td>Hypertension, n (%)</td>
<td>221 (61)</td>
<td>3410 (60)</td>
<td>0.70</td>
</tr>
<tr>
<td>Atrial fibrillation, n (%)</td>
<td>180 (49)</td>
<td>2492 (44)</td>
<td>0.03</td>
</tr>
<tr>
<td>Peripheral vascular disease, n (%)</td>
<td>41 (11)</td>
<td>648 (11)</td>
<td>0.96</td>
</tr>
<tr>
<td>Congestive heart failure, n (%)</td>
<td>171 (47)</td>
<td>2640 (46)</td>
<td>0.78</td>
</tr>
<tr>
<td>CHA2DS2-VASc score</td>
<td>3.1±2.0</td>
<td>3.1±2.0</td>
<td>0.58</td>
</tr>
</tbody>
</table>

(Plus–minus values are means±standard deviation. PFO indicates patent foramen ovale; and TIA, transient ischemic attack.)
embolic events among patients with implanted endocardial pacemaker or defibrillator leads who have an incidentally identified PFO on echocardiography. In current practice, endocardial leads are avoided in patients with unclosed septal defects.14,15 Our findings suggest it may be reasonable to extend this strategy to patients with PFO, especially those with significant right-to-left shunt and easily identifiable on routine echocardiography.

PFO has long been postulated as a mechanism for cryptogenic stroke.20 Although numerous studies have suggested an association between cryptogenic stroke and PFO,20–25 an Olmsted county population–based study did not show an increased risk of stroke or TIA in comparison with age- and sex-matched controls.18 Similarly, the PFO in cryptogenic stroke study found no association between PFO and recurrent stroke among patients treated with aspirin or warfarin.19 The Closure I trial randomly assigned patients with cryptogenic stroke to PFO closure and antiplatelet therapy or to medical therapy alone and found no difference in the rate of recurrent stroke or TIA.26 Several observations likely account for the lack of benefit of PFO closure in Closure I as opposed to the strong association between stroke and PFO in our study. First, Closure I excluded patients with endovascular leads. PFO alone likely poses a significantly lower stroke risk without the concomitant presence of leads to seed thrombus formation in proximity to the interatrial septum. Second, the vast majority of patients with stroke or TIA after enrollment had mechanisms other than paradoxical embolism to account for the event, suggesting that, in the device-free cryptogenic stroke population, paradoxical embolus is a relatively uncommon stroke mechanism. Third, Closure I compared an interventional with a medical strategy for stroke prevention; the finding that these had similar efficacy does not exonerate PFO from culpability in systemic embolism. The role of PFO in stroke or TIA is supported by a prospective, observational study that used propensity score–matched comparison groups to show fewer recurrent ischemic events after device closure of PFO.27 Patient follow-up was longer (median of 10 years) than in the Closure I trial (2 years).

Additional observations support the mechanistic role of PFO in thromboembolism in patients with endovascular

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Stroke/TIA</th>
<th>Death</th>
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<tbody>
<tr>
<td></td>
<td>Hazard Ratio (95% Confidence Interval)</td>
<td>P Value*</td>
</tr>
<tr>
<td>Unadjusted</td>
<td>3.49 (2.33–5.25)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Adjusted for age, sex, and history of stroke/TIA</td>
<td>3.30 (2.19–4.96)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Multivariable adjusted†</td>
<td>3.36 (2.23–5.07)‡</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

TIA indicates transient ischemic attack.

*P value testing for hypothesis hazard ratio = 1.
†Adjusted for age, sex, previous stroke/TIA, history of atrial fibrillation, use of aspirin and warfarin at time of index device implant forced in the model, and additional covariates by using stepwise selection with statistical level for inclusion in model P=0.05.
‡No additional covariates reached statistical level for inclusion.
§Additionally adjusted for diabetes mellitus, coronary artery disease, hyperlipidemia, hypertension, peripheral vascular disease, congestive heart failure, and CHA2DS2-VASc score.
leads. The cumulative incidence curve of stroke or TIA in patients with PFO only begins to diverge from that of non-PFO patients 6 months after device implantation (Figure 1A). This is consistent with a temporal delay, because thrombi develop on the leads and right-sided cardiac pressures increase subsequent to subclinical pulmonary embolisms after device implantation, consequently promoting right-to-left blood flow shunting and paradoxical embolism. Previous studies have demonstrated increased pulmonary artery systolic pressure in patients with thrombi found on device leads with the use of intracardiac echocardiography. The fact that these thrombi are small (and thus rarely seen with TTE) may account for the delay in pulmonary artery pressure elevation. Their small size may also account for the lack of increased mortality seen in patients with PFO. Small thrombi may be less likely to occlude a sufficiently large vascular territory to cause fatal strokes. Other competing factors may also have accounted for the lack of mortality difference. The impact of the underlying cardiovascular disease that led to device implantation on mortality may have been sufficiently large as to overwhelm any influence of PFO-mediated thromboembolism.

Our findings have important clinical implications. They suggest that it may be reasonable to screen patients undergoing endocardial lead placement to determine whether a PFO is present. In the presence of a significant PFO, concomitant anticoagulation, PFO closure, or epicardial or subcutaneous device placement should be considered. The clinical impact of these findings is large, given that an estimated 25% of the general population has a PFO. In 2009, there were 1 million

Figure 2. Kaplan–Meier survival curves for the development of stroke/transient ischemic attack in various subgroups of patients with implanted endocardial leads. Stratified by age <65 vs age ≥65 years (A), sex (B), without vs with history of previous stroke/transient ischemic attack (C), without vs with history of atrial fibrillation (D), not using vs using aspirin at baseline (E), not using vs using warfarin at baseline (F), and CHA2DS2-VASc score 0 to 2 vs ≥3 (G). The solid line represents those with patent foramen ovale, and the dotted line those without patent foramen ovale. Hx indicates history; PFO, patent foramen ovale; and TIA, transient ischemic attack.
Figure 2. (Continued)
pacemakers and 328 000 defibrillators implanted worldwide, translating to ≈332 000 devices in patients with PFOs that year alone. In our study, we found a 8% risk of stroke/TIA at 5 years. Based on these numbers, this would translate to ≈26 500 people annually with potentially preventable neurological events.

Our results are best interpreted in the context of study limitations. This was a retrospective study and is thus prone to all of the inherent biases associated with such study designs. Specifically, causality and evidence in favor of any clinical interventions cannot be provided. Moreover, any inferences are limited by the possibility of detection and classification biases, both in the clinical course and in the conduct of the study. We sampled antiplatelet and anticoagulant usage at limited points in time, although they varied only to a minor extent between the 2 groups. Surprisingly, we did not see any attenuation of the increased stroke/TIA risk among patients with PFO with baseline antiplatelet or anticoagulant use, and it is not clear whether this was attributable to the lack of efficacy of such therapies or methodological pitfalls like missing or time-variable data, confounding, or ascertainment bias.

TEE is more sensitive than TTEs for the detection of PFOs. In our overall cohort of 6075 patients, independent of the study indication, the PFO detection rate was higher when TEE was performed (14.1% versus 4.8% without TEE). We explored the possibility that patients who had a stroke/TIA outcome were more likely to have had a TEE that consequently would have biased toward a higher detection of PFOs. Extrapolating from the above detection rates and assuming no real association between PFO and stroke/TIA; merely owing to a higher rate of TEEs among stroke/TIA patients (32.7% versus 12.1% in those without stroke/TIA), we would expect to detect more PFOs among stroke/TIA patients (7.9% versus 5.9% in those without stroke/TIA). This modest bias, however, cannot explain the actual discrepancy in PFO prevalence in the 2 outcome groups, 20.4% (30/147) in patients with stroke/TIA versus 5.6% (334/5928) in those without stroke/TIA.

We detected an overall lower prevalence of PFO in our study (364/6075, 6.0%) than has been reported by autopsy evaluations.10 This may reflect underreporting and reduced sensitivity of routine TTE for PFO detection, especially if done in patients with endocardial hardware and without an intravenous agitated saline bubble study with the use of the Valsalva maneuver. It is conceivable; however, that those PFOs that were detected were large or had high-risk characteristics, accounting for the increased risk of stroke/TIA in patients with echocardiographically detected PFOs. Only a minority (32.7%) of our PFO diagnoses were based on the more sensitive TEE,32 and a minority of echocardiographic studies (28%) were requested specifically for PFO evaluation. We had a 14.1% PFO detection rate when TEE evaluations were performed. We further underestimate the prevalence by excluding 74 cases with probable/possible PFO and another 11 PFO diagnoses made after the patient had a stroke or TIA. It is likely that a proportion of patients, especially in the non-PFO group, had undetected PFOs. Despite this misclassification bias toward null, there was a significant difference in stroke or TIA during follow-up, further supporting the magnitude of the interaction between endocardial leads and PFO. In any case, our study shows that the more apparent PFOs that were identified without a protocolled method to evaluate for their presence were attributable toward a substantial increase in risk of embolic ischemic events.

In conclusion, in patients with endovascular pacemaker or defibrillator leads, the presence of a PFO is independently associated with a significantly increased risk of stroke or TIA, which persists during long-term follow-up. Lead thrombi and paradoxical embolisms likely account for this observation. A confirmatory prospective cohort study to establish this association between PFO and stroke/TIA among recipients of endocardial CIED leads is warranted. If the association is confirmed, antithrombotic therapy, PFO closure, or nonvascular lead placement could be considered in patients with PFO who are undergoing placement of endocardial CIED leads.
Acknowledgments

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Disclosures

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Endovascular leads placed in the right heart represent a foreign body that can promote formation of mobile thrombi that dislodge to the pulmonary circulation. Whether or not patients with endovascular leads and an echocardiographically detected patent foramen ovale (PFO) are at risk for systemic thromboembolism leading to transient ischemic attack or stroke is presently unknown. We report our findings from a large retrospective study of >6000 patients with cardiac implantable electronic devices. A 3-fold increased risk of cardioembolic stroke/transient ischemic attack was found among patients with a PFO in comparison with those with no documentation of PFO. The cumulative incidence of stroke/transient ischemic attack among patients with cardiac implantable electronic devices who have a known PFO was 7.9% at 5 years. Notably, this increased risk was independent of other recognized stroke risk factors, atrial fibrillation, and anticoagulation status. Because retrospective transthoracic echocardiography grossly underestimates the true incidence of PFO, it remains possible that a significantly larger true risk of systemic thromboembolism with endovascular implanted devices exists. At present, the best method to ameliorate this risk is undefined. Prospective studies are needed to confirm the increased risk of stroke/transient ischemic attack in patients with PFO and endovascular leads. Further studies to determine whether prophylactic PFO closure, high-intensity anticoagulation, or the avoidance of endovascular leads will be the best method to prevent stroke in patients at risk.
Stroke or Transient Ischemic Attack in Patients With Transvenous Pacemaker or Defibrillator and Echocardiographically Detected Patent Foramen Ovale

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