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Implanted endocardial lead characteristics and risk of stroke or transient ischemic attack

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Abstract

Introduction—Patent foramen ovale (PFO) has been recently implicated as a strong predictor of stroke or transient ischemic attack (TIA) in patients with implanted pacemaker or defibrillation leads. Leads in the right heart can form thrombi that embolize to the pulmonary circulation and raise pulmonary pressure. This increases right-to-left shunting through PFO or intrapulmonary shunts and can result in paradoxical embolism. We sought to determine whether certain lead characteristics confer a higher thrombogenic risk resulting in stroke/ TIAs in patients either with or without a PFO.

Methods—We retrospectively analyzed 5,646 patients (mean age 67.3 ± 16.3 years, 64 % male) who had endocardial device leads implanted in 2000–2010. We performed univariate and

multivariate-adjusted proportional hazards models to determine association of lead characteristics with stroke/TIA during follow-up.

Results—On univariate analysis, passively fixated tined leads were associated with more stroke/TIAs (HR 1.77, 95 % CI 1.27, 2.47; $p<0.001$), whereas presence of defibrillation coil was associated with fewer stroke/TIAs (HR 0.59, 95 % CI 0.42–0.84; $p=0.003$). Number of leads per patient, presence of atrial lead, maximum lead size, tip shape, and type of insulating material were not associated with stroke/TIA. On multivariate analyses adjusting for age, sex, diagnosis of PFO, and prior history of stroke/TIA, the presence of tined leads was associated with stroke/TIA (HR 1.41, 95 % CI 1.00–1.97; $p=0.049$). Defibrillation coils were no longer associated with lower stroke/TIA on multivariate analysis.

Conclusions—Most physical characteristics of contemporary leads do not impact rate of stroke/TIA among patients receiving implantable devices. The presence of a PFO is a major risk factor for stroke/TIA in patients with endovascular leads.

Keywords

Device; Leads; Stroke; TIA; Patent foramen ovale

1 Introduction

The last two decades have witnessed an increase in cardiovascular implantable electronic devices (CIEDs) due to the safety of transvenous implantation, efficacy in management of various arrhythmias, and recognition of new indications [1–3]. Endocardial leads frequently have thrombus formation [4–7] that can result in subclinical pulmonary embolisms [8–11]. Lead-related thrombi can result in paradoxical systemic embolization through a PFO or intrapulmonary shunts, leading to stroke or transient ischemic attack (TIA) [12–16].

A quarter of the adult population is estimated to have a persistent connection between the right and left atria through a patent foramen ovale (PFO) [17]. We have recently demonstrated in a large retrospective study that patients with endocardial leads and a PFO are at a substantially increased risk of stroke/TIA as compared to patients with endocardial leads but no documented PFO [16]. In that study, PFOs were mostly diagnosed on routine echocardiography with non-standardized utilization of color Doppler and agitated saline injection. This resulted in an under-detection of PFOs (5.6 %) compared to prevalence of PFO from autopsy studies (~25 %) [18, 19]. Chronic pulmonary embolism from endocardial lead thrombi increases right heart pressures [7], and we hypothesized that this results in more right-to-left shunting by opening otherwise clinically inconsequential PFOs. It is possible that only these enlarged PFOs were detected on echocardiography, and PFO detection was driven in part by thrombogenic lead characteristics. Lead characteristics might thus have been an unidentified confounder in our original study.

Intrapulmonary shunting can occur in patients with pulmonary embolisms due to hypoxia and increased pulmonary arterial pressure [20]. It is possible that patients with thrombogenic leads developed intrapulmonary shunts due to chronic pulmonary embolization. Paradoxical embolism through intrapulmonary shunts is increasingly recognized as an etiology of stroke/TIA [14, 15]. Since there was no way to retrospectively confirm the anatomic

presence of small PFOs, intrapulmonary shunts, and thrombus burden on leads, we evaluated the association of lead characteristics with stroke/ TIA in all CIED patients. It is possible that certain characteristics of the leads conferred greater thrombogenicity and thereby increased the rate of stroke/TIA independent of the incidental detection of PFO.

We sought to determine whether certain physical lead-related factors such as number of leads, presence of an atrial lead, presence of defibrillation coils, mechanism of lead fixation, insulating material, and lead size are associated with rate of stroke/TIA. The secondary aim of this study was to identify if certain lead characteristics increased the risk of stroke/TIA among CIED patients with definitively identified PFO.

2 Methods

Study population

The study population consisted of all patients who had implantation of at least one endocardial lead at Mayo Clinic, Rochester between January 1, 2000 and October 25, 2010. All patients had authorized the review of their medical records for research purposes. De-identification of data was performed to protect patient confidentiality. Electronic medical records were reviewed to collect all data. Patients lacking sufficient detail in medical records regarding the timing, mechanism, or cause of stroke/TIA were excluded.

Assessment of variables

We obtained basic demographic characteristics of the patients through chart review. Data regarding comorbidities were obtained from the diagnosis codes (ICD-9, HICDA, and Berkson Mayo Clinic coding system) for all clinical encounters up until date of lead implantation. Data regarding lead positioning, lead number, and model numbers of implanted leads were entered into a database after review of the electronic medical record. Model numbers of implanted leads were used to collect information regarding maximum lead diameter per subject, insulating material, mechanism of fixation, presence of defibrillation coils, and tip shape. These were confirmed by contacting company representatives and/or by review of product details on company websites. Identification of PFO was by color-flow Doppler and/or injection of intravenous agitated saline during transthoracic or transesophageal echocardiography. Patients that were coded as “possible” or “probable” PFO, and thus not definitively confirmed, were excluded from this study.

Determination of outcomes

Data regarding outcomes were obtained from a centralized electronic medical record system that contains complete records for all patients treated and followed at Mayo Clinic and its affiliate hospitals. These records provide detailed history and diagnosis for all outpatient encounters, emergency room visits, inpatient admission, home, and nursing home visits [21]. Diagnosis codes suggesting cerebrovascular events were used to identify patients with possible stroke or TIA. A board-certified vascular neurologist (A.A.R.) reviewed records for the absence or presence of a documented ischemic stroke or TIA consistent with a cardioembolic etiology. Cases where a definitive alternative cause for stroke or TIA was documented, such as intracranial hemorrhage, severe ipsilateral carotid stenosis,

radiologically proven small subcortical stroke with lacunar presentation, and severe intracranial stenosis in the relevant vessel were excluded. Mortality and date of death were obtained from multiple sources including the Mayo Clinic registration database and Accurint (LexisNexis, Philadelphia, Pennsylvania), an institutionally approved fee-based Internet research and location service.

Statistical analysis

The cumulative probabilities of stroke/ TIA and of death following device implant among the population were estimated using the Kaplan-Meier method. Potential confounders that could attribute risk of stroke/TIA or mortality were evaluated using Cox proportional hazards regression models. Univariate and multivariate-adjusted proportional hazards models (adjusting for age, sex, prior history of stroke/TIA, comorbidities, anticoagulation use, and lead characteristics) were used to determine differences in stroke/ TIA and death during follow-up. Additional covariates were added to the model using stepwise selection. A two-tailed α -level 0.05 was considered the threshold for statistical significance for all tests. SAS version 9.3 (Cary, North Carolina) was used for statistical analysis.

3 Results

A total of 5,646 patients were analyzed. The mean age at implantation of endocardial device leads was 67.3 ± 16.3 years, with 64 % being male (Table 1). History of atrial fibrillation was present in 45 % patients, and 33 % were on warfarin anticoagulation at the time of lead implantation. A mean of 2.0 ± 0.9 leads were implanted per patient, and 72 % patients had right atrial leads in addition to ventricular leads. Lead insulation comprised of silicone alone in 3,164 patients (56 %), polyurethane alone in 606 patients (11 %) and 1,876 patients (33 %) had lead insulation with both materials. Defibrillation coil electrodes were present in 2,414 patients (43 %). In 1,166 patients (21 %), tined passively fixated leads were used. The lead tip shape was straight in 47 % of the patients. The mean maximum lead size per patient was 7.5 ± 0.9 French. PFO was noted in 316 patients (6 %). The PFO and non-PFO groups were largely similar (Table 1). Fewer patients in the PFO group had a history of past stroke/TIA (9 % vs. 15 %; $p=0.001$). Patients with PFO had greater number of leads on average compared to non-PFO patients. Significantly more patients in the PFO group had tined leads compared to patients in non-PFO group (29 % vs. 20 %; $p<0.001$).

On univariate analysis, tined lead was significantly associated with the primary outcome of stroke/TIA during follow-up (hazard ratio, HR 1.77, 95 % confidence interval, CI 1.27, 2.47; $p<0.001$) (Fig. 1). Patients with tined leads were older than patients without tined leads (70.0 ± 13.6 vs. 66.6 ± 16.9 years; $p<0.0001$). Presence of defibrillation coil electrode was protective of the primary outcome (HR 0.59, 95 % CI 0.42–0.84; $p=0.003$). Number of leads per patient, presence of atrial leads, maximum lead diameter, tip shape, and type of insulating material were not associated with stroke/TIA. Among demographic variables, older age, female sex, documented PFO, history of hypertension, history of cerebrovascular disease, history of hyperlipidemia, and history of carotid occlusion were significantly associated with stroke/TIA ($p<0.05$). History of atrial fibrillation, coronary artery disease, heart failure, peripheral vascular disease, and diabetes were not associated with the primary outcome and neither was history of anticoagulation (HR 1.02, 95 % CI 0.72–1.44; $p=0.91$).

On multivariate analysis, among patients with endocardial leads, the presence of tined leads was associated with an increased rate of stroke/TIA (HR 1.41, 95 % CI 1.00–1.97; $p=0.049$) (Fig. 2). The other significant independent predictors of stroke/TIA were older age, female sex, documented PFO, prior history of stroke/TIA.

Among the subgroup of 316 patients who had a definitive diagnosis of PFO, a prior history of stroke/TIA was associated with an increased risk of stroke/TIA (HR 3.84, 95 % CI 1.82–8.10; $p<0.001$). None of the physical characteristics of leads predicted an increased risk in this subgroup with PFO diagnosis (Fig. 3).

4 Discussion

Systemic embolization of lead thrombus through PFO, resulting in stroke/TIA, has been described as a biologically plausible phenomenon in case series [12, 22]. We recently demonstrated in a large retrospective study a strong association between PFO and stroke/TIA in patients with endocardial leads [16]. This current analysis further explores the contributory mechanisms for this association and suggests lack of a major role of lead-related factors. The only lead characteristic that had a statistically significant association was tined leads with an estimated 41 % higher rate of stroke/TIA ($p=0.049$). This association however could be a chance finding based on the borderline statistical significance, multiplicity of associations that were tested, and potential for residual confounding. Among the subgroup of patients who had a definitive diagnosis of PFO, there was no lead characteristic that predicted the risk of stroke/TIA. The lack of a major association between lead characteristics and stroke/TIA suggests that it is the presence of a PFO itself rather than any particular lead-related factor that is responsible for strokes/TIA among CIED patients. These data suggest that differences in thrombogenicity of leads are trivial; and stroke/TIA occurs secondary to shunting across PFO regardless of physical characteristics of leads.

Leads with thrombogenic physical characteristics have the hypothetical potential to cause stroke/TIA by two mechanisms. First, recurrent subclinical pulmonary embolisms can increase the right heart pressures [7] and cause right-to-left shunting across already existing PFOs. It is possible that leads contributing to a higher thrombus burden and causing higher RVSP, stretch open PFOs to a larger size, thus making them easily visible on echocardiography. This right-to-left shunting in the setting of lead thrombi could thus explain the very strong association of detectable PFOs with stroke/TIA that we previously reported [16]. Second, thrombogenic leads could result in stroke/TIAs independent of PFO by causing increased intrapulmonary shunting. Chronic pulmonary embolism causes pulmonary hypertension and hypoxia that enlarges small intrapulmonary arteriovenous anastomoses [20, 23, 24]. Intrapulmonary shunting is being increasingly recognized as an etiology of paradoxical embolism and stroke/TIA [14, 15].

The main finding of this analysis is that lead-related factors such as number of leads, maximum diameter of leads, chamber in which leads are present, lead insulation, and the presence of coil electrode are not associated with stroke/TIA in patients with CIED and endocardial leads. Although coil electrodes appeared to decrease the risk of stroke/TIA in univariate analysis, this was not observed in the stepwise multivariate model after

adjustment for comorbidities (Figs. 1 and 2). ICD recipients are younger, and more likely to be anticoagulated, which could account for the findings on univariate analysis. Tined leads were associated with significantly increased risk of stroke/TIA, but patients with tined leads were significantly older than patients without tined leads. Although tined leads were in place for a longer duration than other leads, the time to event proportional hazards model accounts for duration of implantation, and thus, the association of tined leads with stroke/TIA is independent of duration of implantation. Moreover, clinical practice has evolved away from tined leads and actively fixated leads have become the preferred choice. These results strongly suggest that the increased stroke/TIA risk in patients with PFO is due to the PFO itself rather than the variation in lead-related factors. Older age, female sex, PFO diagnosis, and prior stroke/TIA were the other independent predictors of stroke/TIA. Among patients with documented PFO, none of the aforementioned lead characteristics were associated with stroke/TIA (Fig. 3).

There are no prior studies that have systematically evaluated the relationship between lead-related factors and development of stroke/TIA. Prior studies have shown that asymptomatic venous thrombosis is not uncommon after lead implantation. Risk factors for venous thrombosis in CIED patients include presence of multiple leads, absence of anticoagulation and prior history of venous thrombosis [9, 25–28]. We anticipated the presence of multiple leads to increase the thrombus burden and increase rates of paradoxical embolism; however, we found no association between the number of leads and stroke/TIA. The presence of multiple leads was similarly not associated with venous thrombosis in a cross-sectional study [29] or in a small prospective study [30]. Analogous to this, thicker leads may intuitively offer greater surface area for thrombosis, but our study does not support a higher risk of stroke/TIA with increased lead size. Supple et al. reported that lead-related thrombus was more common in the right atrium compared to the right ventricle [7]. This was likely due to the atrium being an area of low flow compared to the ventricle. Regardless, both atrial and right ventricular leads have to traverse the right atrium and our data did not suggest any increased association of stroke/TIA with right atrial lead. A porcine study showed silicone-insulated leads to be more thrombogenic than polyurethane-coated leads [31]. Chow et al., however, found more lead-related thrombi with polyurethane leads versus silicone leads [32]. In our study, either material was not associated with stroke/TIA. A previous study in patients referred for lead extraction found no difference in venous thrombosis in patients with silicone versus polyurethane leads [25]. There is no published data on the thrombogenicity of leads with active fixation versus passive fixation. We found more stroke/TIAs with passively fixated tined leads. This possibly could reflect the tined tip to be a nidus for initiation of thrombus formation. However, it must be remembered that tined leads were predominantly used in the initial part of our study period and were thus more likely to stay in for longer duration.

Among patients with a definite PFO, it is unknown if any of the physical characteristics of leads predisposed to stroke/TIA. Identification of any lead-related risk factors would have important implications for lead implantation in patients with known PFO. In our study, however, the number of leads, lead size, mechanism of fixation, and insulating material were not associated with increased risk of stroke/TIA among patients with PFO. Only prior history of stroke/TIA was associated with recurrent events in this subgroup. These results

suggest that future attempts to prevent stroke/TIA in patients with PFO are best directed at avoiding endocardial leads, closing the PFO, or consideration of anticoagulation, rather than attempting to modify endocardial lead design. It is unclear whether avoidance of endocardial leads in patients with PFO has a role to play in decreasing stroke/TIA risk among this population.

Limitations

Despite the multivariable adjusted analysis to account for some of the major confounding variables, this is a retrospective study and is subject to biases that are a part-and-parcel of retrospective research. This is underscored by the fact that known risk factors for stroke/TIA, such as atrial fibrillation, diabetes, and vascular disease, were not significant predictors of stroke/TIA on multivariate analysis. Risk factors were recorded at the start of the study alone. Review of subsequent device interrogation records for detection of AF was out of the scope of the current analysis. Detection of most PFOs on TTE likely selected larger PFOs more susceptible to shunting. Assessment of PFO size is out of the scope of the current study.

We were unable to assess for presence, size, or location of lead thrombus, neither did we have perfect information on anticoagulation status and systemic risk of ischemic neurologic events. The best assessment of thrombogenicity of leads would be by direct visualization of lead thrombus by imaging, which was beyond the scope of this analysis. In context of these limitations, the main purpose of this study was not necessarily to find a definitive lead characteristic causally associated with stroke, but rather to explore the underlying mechanisms that might be at play in the pathophysiology of stroke/TIA in CIED patients, especially those with a PFO.

5 Conclusion

Physical characteristics of endocardial leads, such as number, size, insulating material, presence of coil, and tip shape, are not associated with stroke/TIA. The presence of a PFO is the strongest predictor of stroke/TIA among CIED patients (Fig. 4). Given our findings that no specific lead characteristic conferred a higher risk of stroke in patients with a definitive diagnosis of PFO, alternate strategies to mitigate this risk need to be considered. Avoiding endocardial lead implantation among patients with PFO may be a reliable strategy to prevent stroke/TIA among patients with PFO. Whether closure of the PFO, concurrent anticoagulant therapy, or avoiding endovascular leads altogether represents the best approach to decrease risk of stroke/TIA from the newly identified major risk with PFO in patients with endovascular leads requires clarification.

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Abbreviations

CI	Confidence interval
CIED	Cardiovascular implantable electronic device
HR	Hazard ratio
PFO	Patent foramen ovale

RVSP Right ventricular systolic pressure
TIA Transient ischemic attack

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Fig 1. Forest plot depicting hazard ratios (HR) for demographic characteristics, comorbidities, lead-related characteristics and presence of PFO, for the primary outcome (univariate analysis). *Horizontal bars*, 95 % confidence intervals (CI)

Fig 2.

Forest plot depicting hazard ratios (HR) for demographic characteristics, comorbidities, lead-related characteristics and presence of PFO, for the primary outcome (multivariate analysis). *Horizontal bars*, 95 % confidence intervals (CI)

Fig 3.

Forest plot depicting hazard ratio (HR) for demographic characteristics, comorbidities and lead-related characteristics among patients with PFO (univariate analysis). *Horizontal bars*, 95 % confidence intervals (CI)

Fig 4. Probability of survival free of primary outcome (stroke/TIA) by presence of PFO, history of stroke/TIA, age, tined fixation, presence of coil electrode, number of leads, lead insulation type, lead diameter, and presence of atrial leads

Table 1
Baseline demographics, comorbidities, and lead characteristics

Variable	All patients (N=5,646)	PFO (N= 316)	No PFO (N=5,330)	p value
Age at implant, years	67.3 (16.3)	67.0 (15.7)	67.3 (16.3)	0.71
Gender (female)	2,032 (36)	131 (41)	1,901 (36)	0.037
Comorbidities				
Atrial fibrillation	2,535 (45)	153 (48)	2,382 (45)	0.20
Coronary artery disease	2,575 (46)	140 (44)	2,435 (46)	0.63
Carotid artery disease	402 (7)	17 (5)	385 (7)	0.22
Congestive heart failure	2,677 (47)	144 (46)	2,533 (48)	0.50
Diabetes	1,345 (24)	67 (21)	1,278 (24)	0.26
Hypertension	3,461 (61)	183 (58)	3,278 (62)	0.20
Hyperlipidemia	2,968 (53)	157 (50)	2,811 (53)	0.29
Cerebrovascular occlusion	193 (3)	9 (3)	184 (3)	0.57
Peripheral vascular disease	656 (12)	33 (10)	623 (12)	0.50
History of stroke/TIA	852 (15)	28 (9)	824 (15)	0.001
Anticoagulation	1,864 (33)	91 (29)	1,773 (33)	0.10
Number of leads	2.0 (0.9)	2.1 (1.2)	2.0 (0.9)	0.05
Atrial lead	4,068 (72)	215 (68)	3,853 (72)	0.12
Tip shape				0.35
Straight	2,666 (47)	137 (43)	2,529 (47)	
J-shaped	112 (2)	6 (2)	106 (2)	
Both	2,868 (51)	173 (55)	2,695 (51)	
Maximum lead size (French)	7.3 (1.1)	7.4 (1.0)	7.3 (1.1)	0.15
Insulation				0.41
Silicone	3,164 (56)	184 (58)	2,980 (56)	
Polyurethane	606 (11)	27 (9)	579 (11)	
Both	1,876 (33)	105 (33)	1,771 (33)	
Tined lead	1,166 (21)	91 (29)	1,075 (20)	<.001
Coil electrode	2,414 (43)	150 (48)	2,264 (43)	0.07