Transvenous Pacing Leads and Systemic Thromboemboli in Patients With Intracardiac Shunts: A Multicenter Study

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Background—The risk of systemic thromboemboli associated with transvenous leads in the presence of an intracardiac shunt is currently unknown.

Methods and Results—To define this risk, we conducted a multicenter, retrospective cohort study of 202 patients with intracardiac shunts: Sixty-four had transvenous leads (group 1), 56 had epicardial leads (group 2), and 82 had right-to-left shunts but no pacemaker or implantable cardioverter defibrillator leads (group 3). Patient-years were accrued until the occurrence of systemic thromboemboli or study termination. Censoring occurred in the event of complete shunt closure, death, or loss to follow-up. Mean ages for groups 1, 2, and 3 were 33.9 ± 15.0 years, respectively. Respective oxygen saturations were 91.2 ± 9.1%, 88.1 ± 8.1%, and 79.7 ± 6.7%. During respective median follow-ups of 7.3, 9.3, and 17.0 years, 24 patients had at least 1 systemic thromboembolus: 10 (15.6%), 5 (8.9%), and 9 (11.0%) in groups 1, 2, and 3, respectively. Univariate risk factors were older age (hazard ratio [HR], 1.05; P = 0.0001), ongoing phlebotomy (HR, 3.1; P = 0.0415), and an transvenous lead (HR, 2.4; P = 0.0421). In multivariate, stepwise regression analyses, transvenous leads remained an independent predictor of systemic thromboemboli (HR, 2.6; P = 0.0265). In patients with transvenous leads, independent risk factors were older age (HR, 1.05; P = 0.0080), atrial fibrillation or flutter (HR, 6.7; P = 0.0214), and ongoing phlebotomy (HR, 14.4; P = 0.0349). Having had aspirin or warfarin prescribed was not protective. Epicardial leads were, however, associated with higher atrial (P = 0.0407) and ventricular (P = 0.0270) thresholds and shorter generator longevity (HR, 1.9; P = 0.0176).

Conclusions—Transvenous leads incur a >2-fold increased risk of systemic thromboemboli in patients with intracardiac shunts. (Circulation. 2006;113:2391-2397.)

Key Words: heart defects, congenital ■ implantable cardioverter defibrillators ■ pacemakers ■ shunts ■ stroke

Cardiac defects are among the most common causes of congenital disease, afflicting 75 of 1000 live births.1 Atrial and ventricular intracardiac shunts are prevalent among such malformedations and may occur in isolation or as components of more complex structural disease. Moreover, palliative surgical interventions for congenital heart disease may allow long-term survival despite incomplete elimination of shunting.2,3 Additional sources of intracardiac shunts include deliberately created interatrial communications and baffle leaks.4,5

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As a result of hemodynamic or hypoxic stress, conduction-system variants, and/or surgical sequelae, indications for pacemakers or implantable cardioverter defibrillators (ICDs) may arise in patients with intracardiac shunts.5,8 When confronted with this need, the risks and benefits of transvenous versus epicardial approaches should be weighed. Foremost among these considerations is an unquantified potential for paradoxical systemic thromboemboli arising from transvenous leads.8 Nevertheless, given the multifactorial nature of thrombotic risk factors in patients with cardiac shunts,9,10 it is unknown whether intracardiac leads substantially contribute to systemic embolic risk. Moreover, epicardial leads require a thoracotomy and have been associated with higher chronic pacing thresholds and reduced generator longevity.11 We therefore conducted a multicenter...
cohort study to elucidate the thromboembolic risks associated with transvenous leads in the presence of intracardiac shunts.

**Methods**

**Study Population**
The study population consisted of patients with intracardiac shunts born before January 1990 with any of the following diagnoses: atrial septal defect (ASD), ventricular septal defect (VSD), atrioventricular canal defect, tricuspid atresia, Ebstein’s anomaly with ASD, pulmonary atresia with VSD, tetralogy of Fallot, mitral atresia, double-inlet right or left ventricle, double-outlet right ventricle, congenitally corrected transposition of the great arteries with VSD, transposition of the great arteries with intra-atrial baffle repair and baffle leak, and Fontan procedure with ASD or fenestration. Patent ductus arteriosus and patent foramen ovale did not qualify for enrollment.

Patients were classified into 3 groups. Groups 1 and 2 had transvenous leads and epicardial leads, respectively, with persistent intracardiac shunting at the time of device implantation. Eligible candidates from all 6 participating centers were included. Group 3 patients, recruited from participating Canadian centers, had cyanotic heart disease with right-to-left shunting, resting oxygen saturation <90%, and no permanent pacemaker or ICD.

**Data Collection and Follow-Up**
A population-based, multicenter, retrospective cohort study was performed. The main exposure variable was defined categorically as the presence of a transvenous lead(s), epicardial lead(s), or no pacing or ICD lead. For groups 1 and 2, time zero was defined as the time of device implantation. For group 3, time zero was defined as the time of the first patient recruiting center visit that met the inclusion criteria. For all groups, patient-years were accrued from time of entry until occurrence of the primary outcome (ie, systemic thromboembolic event), complete shunt closure, or study termination. Patients were censored in the event of death or loss to follow-up. Thus, every patient contributed patient-years to the respective exposure category while under observation.

After institutional review board approval, data were collected from electronic and paper cardiological, surgical, electrophysiological, echocardiographic, hemodynamic, and radiographic charts and databases, supplemented by records from referring physicians. Baseline characteristics included standard demographics, anatomic location of the residual intracardiac shunt, date of implantation, biochemistry, oxygen saturation, systemic and pulmonary ventricular ejection fraction, presence of right-to-left shunting, resting oxygen saturation <90%, systemic thromboembolic event, complete shunt closure, or study termination. Patients were censored in the event of death or loss to follow-up. Thus, every patient contributed patient-years to the respective exposure category while under observation.

Baseline characteristics are summarized in Table 1. Of note, patients with transvenous leads were older at the time of device implantation, had a greater proportion of ASDs and VSDs, and had fewer complex congenital defects, such as double-inlet left ventricle, tricuspid atresia, and pulmonary atresia with VSD and aortopulmonary collaterals. By design, group 3 patients had more right-to-left shunting, lower oxygen saturations, and higher hemoglobin and hematocrit levels.

**Thromboembolic Event**
The main outcome variable, systemic thromboembolic event, encompassed neurological, renal, peripheral arterial, and mesenteric thromboemboli. Neurological events were classified as transient ischemic attack (TIA) or stroke. TIA was defined as a brief episode of neurological dysfunction deemed by a neurologist to have been caused by focal brain or retinal ischemia from a thromboembolus, without evidence of acute infarction.12 Stroke was defined as a documented, focal neurological deficit (on computed tomography scan, magnetic resonance imaging, or positron emission tomography scan) due to a thromboembolic cause.12 This definition incorporated complete recovery of function or persistent deficit. For renal emboli, confirmation by renal angiography, intravenous pyelography, renal scanning, magnetic resonance imaging, or computed tomography scanning with contrast medium was mandated. Peripheral arterial emboli were characterized clinically by pain, paresis, numbness, and coldness in the involved extremity with loss of pulse, cyanosis or pallor, mottling, and decreased skin temperature. Mesenteric emboli required angiographic confirmation. Relevant detailed documentation of all suspected systemic thromboemboli was reviewed by an independent, blinded adjudicating committee that classified outcomes.

**Statistical Analysis**
Continuous variables are presented as mean±SD or median and interquartile range (IQR), depending on distribution of the data. Dichotomous variables are summarized as frequencies and percentages. Baseline characteristics by exposure category were compared with I-way ANOVA, Kruskal-Wallis, or χ² tests where appropriate. Probability of event-free survival was estimated from the product-limit Kaplan-Meier method and compared by log-rank statistics. Cox regression multivariate models were used to control for covariates after regression diagnostic testing was performed to verify the proportionality assumptions. Predictors of systemic thromboembolic events were explored in all patients and subgroups. Transvenous and epicardial lead and generator longevities were plotted using Kaplan-Meier curves and compared by log-rank statistics. Hazard ratios (HRs) and 95% confidence intervals (CIs) were derived from Cox regression models. Two-tailed probability values <0.05 were considered statistically significant. Testing was performed with SAS software version 9.1 (SAS Institute, Cary, NC).

**Results**

**Baseline Characteristics**
A total of 202 patients with documented intracardiac shunts were included: 64, 56, and 82 in groups 1, 2, and 3, respectively. Baseline characteristics are summarized in Table 1. Of note, patients with transvenous leads were older at the time of device implantation, had a greater proportion of ASDs and VSDs, and had fewer complex congenital defects, such as double-inlet left ventricle, tricuspid atresia, and pulmonary atresia with VSD and aortopulmonary collaterals. By design, group 3 patients had more right-to-left shunting, lower oxygen saturations, and higher hemoglobin and hematocrit levels.

**Systemic Thromboembolic Events**
The overall median follow-up was 11.8 (IQR, 13.4) years: 7.3 (IQR, 8.9), 9.3 (IQR, 13.1), and 17.0 (IQR, 18.2) years for groups 1, 2, and 3, respectively (P<0.0001). During follow-up, 24 patients experienced at least 1 systemic thromboembolic event, corresponding to mean annualized rates for the first 10 years of 2.1% for group 1 compared with 0.5% for group 2 (P=0.0321) and 0.7% for group 3 (P=0.0465), with a nonsignificant difference between groups 2 and 3. Patient characteristics at the first event are summarized in Table 2. Cumulative hazards and systemic thromboembolic event-free survival are depicted in Figure 1.

Accounting for follow-up duration, univariate risk factors for systemic thromboemboli were older age (HR, 1.05; 95% CI, 1.02 to 1.07; P=0.0001), ongoing phlebotomy (HR, 3.1; 95% CI, 1.0 to 9.0; P=0.0415), and transvenous leads (HR, 2.4; 95% CI, 1.0 to 5.5; P=0.0421). In a multivariate, stepwise Cox regression analysis that included all univariate risk factors for systemic thromboemboli, transvenous leads remained an independent predictor of outcome (HR, 2.6; 95% CI, 1.1 to 6.2; P=0.0265). By further controlling for nonsignificant variables on the basis of substantive knowledge, including sex, level and direction of shunting, prior thromboembolic event, atrial fibrillation or flutter, aspirin, and warfarin, the point estimate for
transvenous leads was little altered, though less precise (HR, 2.1; 95% CI, 0.6 to 7.1; \(P = 0.2274\)).

In multivariate analysis of the subgroup of patients without transvenous leads, older age was likewise predictive (HR, 1.06; 95% CI, 1.00 to 1.11; \(P = 0.0326\)). In addition, lower mean corpuscular hemoglobin volume emerged as an independent risk factor for systemic thromboemboli (HR, 0.92; 95% CI, 0.87 to 0.98; \(P = 0.0124\)).

**Risk Factors in Patients With Transvenous Leads**

In subgroup analyses of patients with transvenous leads, independent risk factors for systemic thromboemboli were older age (HR, 1.06; 95% CI, 1.01 to 1.11; \(P = 0.0326\)), atrial fibrillation or flutter (HR, 6.7; 95% CI, 1.3 to 33.4; \(P = 0.0214\)), and ongoing phlebotomy (HR, 14.4; 95% CI, 1.2 to 172.7; \(P = 0.0349\)). Anatomic level of shunting (atrial, ventricular, or both), confirmed right-to-left shunt, oxygen saturation, hemoglobin value, hematocrit value, ventricular function, lead position, number of leads, and type of device (ie, pacemaker or ICD) did not modulate thromboembolic risk. No protective effect from aspirin or warfarin could be demonstrated. Of 14 systemic thromboemboli, 8 were classified as stroke, 4 as TIA, 1 as peripheral arterial, and 1 as renal. Nine of these events occurred despite warfarin therapy with or without aspirin, with international normalized ratios \(\geq 2.5\) in 3 patients, \(\leq 2.0\) in 4, and unknown in 2.

**Lead Thresholds and Impedances**

At implantation, epicardial leads had higher atrial (2.5±1.7 versus 1.6±1.4 V at 0.5 ms; \(P = 0.0407\)) and ventricular (2.5±2.0 versus 1.6±1.4 V at 0.5 ms; \(P = 0.0270\)) pacing thresholds. Transvenous leads were associated with a nonsignificant trend toward better ventricular sensing (R-wave amplitude,
7.8±6.1 versus 5.8±4.5 mV; \( P=0.1723 \). Transvenous and epicardial leads had similar atrial sensing thresholds (2.4±2.1 versus 2.2±1.5 mV) and impedances (atrial, 584±185 versus 634±272 \( \Omega \); ventricular, 652±176 versus 630±280 \( \Omega \)). At 6 to 12 months’ follow-up, atrial and ventricular thresholds and impedances were not statistically different from baseline for both transvenous and epicardial leads.

### Device Complications and Longevity

Acute and late complications are summarized in Table 3. All hemorrhages requiring transfusion after epicardial pacemaker implantation occurred in patients having concomitant congenital heart surgery. One 35-year-old patient with tricuspid atresia and an obstructed classic Fontan expired 10 days after Fontan conversion to an intracardiac fenestrated lateral tunnel and epicardial atrial pacing. The postoperative course was complicated by hemorrhage, pneumothorax, and pulmonary embolism.

As depicted in Figure 2, epicardial generators had shorter longevity, with a half-life of 6.2 years compared with 11.0 years with transvenous devices (\( P=0.0176 \)). Regression analysis revealed a 1.9-fold greater risk for generator replacement with epicardial versus transvenous devices (HR, 1.9; 95% CI, 1.1 to 3.2; \( P=0.0195 \)). However, the need for lead reintervention was similar for transvenous and epicardial leads (HR, 1.4; 95% CI, 0.8 to 2.5; \( P=0.3012 \)), with comparable lead half-lives (10.8 versus 11.4 years; \( P=0.2991 \)). On long-term follow-up, 7 patients with single-chamber transvenous and 2 with epicardial systems were upgraded to dual-chamber devices.

### Discussion

Except in the youngest patients, technological advances have facilitated the almost-universal adoption of transvenous approaches for pacing and ICD implantation in structurally normal hearts. In congenital heart disease, logistical challenges such as underdeveloped or absent vascular structures, surgical reconstruction, and underlying or associated extracardiac malformations may preclude transvenous lead implantation, but these can often be overcome.13,14

In the presence of an intracardiac shunt, the risk of paradoxical embolization from transvenous leads was previ-
ously suspected but undefined. Two case reports cautioned against intracardiac leads.15,16 A 7-year-old boy with a restrictive VSD and minimal predominant left-to-right shunting experienced a stroke 30 days after transvenous ventricular pacemaker implantation.15 No thrombus was identified. In a subsequent report, an adult with a large ASD and an aneurysmal septum developed a thrombus on a transvenous right atrial pacing lead and experienced multiple systemic emboli.16 Despite the paucity of such reported cases, a growing body of evidence sustains a plausible pathophysiological mechanism for paradoxical embolization, including thrombus formation on intracardiac pacing leads,17,18 pulmonary emboli resulting from such thrombi,19,20 and reports of stroke after inadvertent left ventricular lead placement.21,22

The population-based nature of this multicenter study allowed quantification of incidence-density systemic thromboembolic rates in the presence of intracardiac shunts with and without transvenous leads. A >2-fold increased risk was associated with intracardiac leads. Because some systemic thromboemboli are unrelated to such leads, other baseline hazards must be considered. In cyanotic heart disease, hematological disorders result in both hemorrhagic and thrombotic complications.10,23,24 Chronic cyanosis may lead to erythrocytosis, hyperviscosity, and an imbalance between the biosynthesis of thromboxane A2 and prostacyclin, resulting in platelet aggregation and vasoconstriction.34 Additionally, varicose veins can serve as a nidus for thrombus formation.10,25 Atrial tachyarrhythmias and systolic ventricular dysfunction may coexist, predisposing to intracavitary thrombus formation.6,26 Among risk factors identified in this study, older age and atrial fibrillation or flutter are well-established determinants of stroke.27,28 The association between repeated phlebotomies and stroke is less clear but may be mediated in part by increased viscosity of iron-deficient red blood cells.29,30

Consistent with this notion, a lower mean corpuscular hemo-

Figure 1. A, Cumulative hazard values over time are depicted for patients with transvenous leads, epicardial leads, and intracardiac shunts without pacing or ICD leads. Note the similar and lesser risk among the 2 groups of patients without transvenous leads. B, Kaplan-Meier survival curves for freedom from systemic thromboemboli are plotted and compared for patients with and without transvenous leads.

TABLE 3. Acute and Late Device Complications

<table>
<thead>
<tr>
<th></th>
<th>Transvenous System (n=64)</th>
<th>Epicardial System (n=56)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute complication, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hematoma</td>
<td>4 (6.3)</td>
<td>1 (1.8)</td>
</tr>
<tr>
<td>Pneumothorax</td>
<td>0 (0)</td>
<td>1 (1.8)</td>
</tr>
<tr>
<td>Lead displacement</td>
<td>6 (9.4)</td>
<td>2 (3.6)</td>
</tr>
<tr>
<td>Oversensing</td>
<td>0 (0)</td>
<td>1 (1.8)</td>
</tr>
<tr>
<td>Hemorrhage requiring transfusion</td>
<td>0 (0)</td>
<td>4 (7.1)</td>
</tr>
<tr>
<td>Pacemaker syndrome</td>
<td>1 (1.6)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Death</td>
<td>0 (0)</td>
<td>1 (1.8)</td>
</tr>
<tr>
<td>Late complication, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lead related</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intravascular constriction</td>
<td>2 (3.1)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Lead dislodgement/failure to capture</td>
<td>11 (17.2)</td>
<td>12 (21.4)</td>
</tr>
<tr>
<td>Oversensing</td>
<td>0 (0)</td>
<td>1 (1.8)</td>
</tr>
<tr>
<td>Endocarditis</td>
<td>1 (1.6)</td>
<td>3 (5.4)</td>
</tr>
<tr>
<td>Generator related</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pain</td>
<td>0 (0)</td>
<td>3 (5.4)</td>
</tr>
<tr>
<td>Erosion</td>
<td>1 (1.6)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Infection</td>
<td>2 (3.1)</td>
<td>2 (3.6)</td>
</tr>
<tr>
<td>Migration</td>
<td>0 (0)</td>
<td>1 (1.8)</td>
</tr>
</tbody>
</table>

Figure 2. Kaplan-Meier curves for freedom from generator reintervention are plotted and compared for patients with transvenous versus epicardial pacemakers or ICDs.
globin volume was found in patients without transvenous leads who had systemic thromboemboli.

Comparison of the procedural risks associated with the 2 approaches is obscured by the common practice of implanting epicardial devices during concomitant congenital heart surgery. Nevertheless, epicardial systems were associated with higher atrial and ventricular lead thresholds and reduced generator longevity. These findings are consistent with prior reports of higher chronic thresholds and exit block with epicardial systems.11,31 As observed, previous investigations have likewise reported no differences in reinterventions for lead failure.32,33 A retrospective study of 1007 leads in congenital heart disease and pediatric cases found that fracture and exit block occurred more frequently with epicardial leads, whereas transvenous leads were subject to insulation breaks and dislodgements.34

Disconcertingly, in patients with intracardiac shunts and transvenous leads, a risk reduction with aspirin or warfarin therapy could not be demonstrated, and no trend favored either therapy. This must be interpreted within the constraints of the present study, which was not designed or statistically powered to definitively address this important issue. Of 9 systemic thromboemboli in patients with transvenous leads who were taking warfarin, 3 occurred despite international normalized ratios >2.0. In a review of 27 patients with leads inadvertently placed in the left ventricle, 10 experienced thromboemboli, 3 of whom were on antiplatelet therapy.35 Leads were removed from 6 patients and anticoagulation was pursued in the remaining 4, with no recurrent events. This review, therefore, supports the lack of benefit with antiplatelet therapy but does not exclude a potential role for anticoagulation. Naturally, in patients with intracardiac shunts, the indication for anticoagulation may exist beyond transvenous leads.

Additionally, shunt characteristics did not reliably identify a lower-risk patient subgroup. Systemic thromboembolic risk was not modulated by oxygen saturation, hemoglobin or hematocrit values, level of shunting, or evidence of right-to-left flow. Some degree of right-to-left shunting was documented in 64% of patients with transvenous leads and in all but 2 patients with transvenous leads and systemic thromboemboli. The safety of transvenous leads in the context of small shunts with no detectable right-to-left flow, therefore, remains to be demonstrated. Perceiving a small degree of right-to-left flow is highly dependent on the sensitivity of the diagnostic technique and additional provocative maneuvers.36 The finding of an exclusive, unidirectional, left-to-right shunt, particularly at the atrial level, should be interpreted with caution.37

Finally, this study may have implications for patients with patent foramen ovale, present in >25% of adults.38 Mounting evidence implicates patent foramen ovale in the genesis of paradoxical embolization.39–40 Although this diagnosis did not qualify for study entry, the systemic thromboembolic risk incurred by intracardiac leads in the presence of even small degrees of right-to-left shunting raises the question of whether risk is increased in this setting. This potential association merits further study.

Limitations
Analysis of studies encompassing various congenital heart malformations are challenged by marked heterogeneity. In addition, the nonrandomized, retrospective design allows for potential confounding by indication, as physician selection of the pacing or ICD approach is influenced by the underlying pathology. On the basis of substantive knowledge, clinical and laboratory variables most likely to be associated with exposure and outcome parameters were collected and adjusted for in analyses. The direction of residual confounding effects is likely toward the null hypothesis, because patients deemed at highest risk for systemic thromboemboli are more likely to receive epicardial systems. Moreover, the control group of patients with no pacemaker or ICD was deliberately selected to provide a conservative ascertainment of risk associated with transvenous leads, as all patients had cyanotic heart disease with documented right-to-left shunts. These selection criteria also ensured the reliable identification of appropriate candidates, given that subclinical cyanotic congenital heart disease is unlikely. Thus, a substantial underestimation of risk associated with transvenous leads cannot be excluded.

Conclusions
In this multicenter study, the baseline risk of systemic thromboemboli in patients with intracardiac shunts was 0.5% to 0.7% per year. Transvenous pacemaker or ICD leads increased this risk >2-fold. A low-risk subgroup could not be identified on the basis of shunt characteristics. These results lend credence to the notion that transvenous leads should be avoided in the presence of an intracardiac shunt.8 In light of this evidence, efforts to eliminate shunting should be pursued before transvenous lead implantation, and if this is not feasible, an epicardial approach should be considered.

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Disclosures
None.

References
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CLINICAL PERSPECTIVE

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