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Incidence and Risk Factors of Early Venous Thrombosis Associated with Permanent Pacemaker Leads

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Risk of Pacemaker Lead-Associated Venous Thrombosis. ***Introduction:*** **Pacemaker lead implantation can cause thrombosis, which can be associated with serious local morbidity and complicated by pulmonary embolism. Few reliable estimates of the incidence of thrombosis have been reported. The contribution of established risk factors to venous thrombosis in patients with implanted pacemaker leads is unknown.**

Methods and Results: **One hundred forty-five consecutive patients n = 145) underwent routine clinical and Doppler ultrasound evaluation for thrombosis before and 3, 6, and 12 months after lead implantation. Established risk factors for venous thrombosis were assessed in detail for all patients. Clinical outcome, including clinically manifest thrombosis, pulmonary embolism, associated pacemaker lead infection, complicated reinterventions, and death, was evaluated. Thrombosis was observed in 34 (23%) of 145 patients. Thrombosis did not cause any signs or symptoms in 31 patients but resulted in overt clinical symptoms in 3 patients. The absence of anticoagulant therapy, use of hormone therapy, and a personal history of venous thrombosis were associated with an increased risk of thrombosis. The risk of thrombosis increased in the presence of multiple pacemaker leads compared to a single lead.**

Conclusion: **Established risk factors for venous thrombosis and the presence of multiple pacemaker leads contribute substantially to the occurrence of thrombosis associated with permanent pacemaker leads. Risk factor assessment prior to implantation may be useful for identifying patients at risk for thrombotic complications. Preventive management in these patients is warranted.** *(J Cardiovasc Electrophysiol, Vol. 15, pp. 1258-1262, November 2004)*

pacemaker, thrombosis, Doppler ultrasound, risk factor

Introduction

Patients who undergo implantation of a pacemaker or defibrillator are at risk for thrombosis associated with transvenous leads.[1,2] Thrombosis may lead to severe local morbidity and can be a source of pulmonary embolism.[3-5] Thrombosis may cause complications associated with reinterventions, such as lead extraction or reimplantation, even when the thrombosis itself does not cause overt clinical symptoms.

Few reliable estimates of the risk of thrombosis associated with permanent pacemaker leads are available.[1,6-10] Evaluation of the contribution of established risk factors for venous thrombosis (e.g., factor V Leiden) is lacking. Such data are clinically relevant because they provide insight into the difference in thrombotic risks among patients prior to implantation. These data can be used to guide subsequent anticoagulant prophylaxis.

The primary aim of this study was to assess the incidence of thrombosis, the contribution of established thrombotic risk factors, and the clinical outcome of thrombosis associated with permanent pacemaker leads. We conducted a large cohort study in patients who underwent implantation of a pacemaker or defibrillator.

Methods

Patients and Study Design

This prospective observational study was performed at the Department of Cardiology of the Leiden University Medical Center (LUMC), The Netherlands. The study protocol was approved by the institutional ethics committee, and all participating patients gave written informed consent.

Consecutive patients (age ≥16 years) undergoing elective permanent pacemaker or internal cardiac defibrillator implantation were considered eligible for study participation. Transvenous leads were inserted via the cephalic or subclavian vein in the catheterization laboratory using standard implantation techniques. Doppler ultrasound evaluation was performed in all participating patients within 48 hours before the insertion procedure to detect upper limb venous stenosis or occlusion. Patients with abnormal Doppler ultrasound findings were excluded from the study. Patients in whom Doppler ultrasound prior could not be performed prior to insertion or during follow-up because of technical reasons were excluded from the study. The decision regarding

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anticoagulant or antiplatelet therapy was made by the attending physicians. Implantation of pacemaker leads was not a reason to initiate anticoagulant or antiplatelet therapy.

Surveillance and Follow-Up

Follow-up was performed clinically and by routine scheduled Doppler ultrasound during the first year after implantation. Clinical follow-up was performed by attending physicians who examined patients in the outpatient clinic for symptoms and signs suggestive of upper limb thrombosis, such as pain, discoloration, local swelling or edema, or visible collateral circulation. Patients with clinically suspected thrombosis were referred to the radiology department for Doppler ultrasound. If no thrombosis was found, patients underwent unilateral venography. In addition to clinical follow-up, all patients were examined by routine color Doppler ultrasound (Acuson XP128, Acuson, Mountain View, CA, USA) by an independent physician during the first year after implantation, at 3, 6, and 12 months postimplantation. Doppler ultrasound was always performed by the same ultrasonographer according to a standardized protocol. Doppler ultrasound examinations were performed bilaterally, and the following venous segments were identified: brachial, axillary, subclavian, and jugular vein. All real-time examinations were coded and recorded on video tape (S-VHS Sony SVO 9500 MDP, Sony, Tokyo, Japan). After the study ended, recordings were assessed by a panel of two blinded observers experienced in Doppler ultrasound evaluation. A third expert opinion was solicited in case of disagreement.

Established risk factors for venous thrombosis were assessed in detail for all patients. At entry into the study, patients were asked about their personal and family history of venous thrombosis, use of female hormones (oral contraceptives, hormone replacement therapy), and anticoagulant and antiplatelet medication. Factor V Leiden, prothrombin G20210A mutation, and factor VIII levels (factor VIII:C) were determined in all patients as described previously.[11-13] At each visit, patients were asked if they suffered from cardiac disease (e.g., myocardial infarction or congestive heart failure), active cancer, chronic obstructive pulmonary disease, diabetes mellitus, or inflammatory bowel disease, had undergone major surgery or trauma, or had recently changed medication.

Outcome Measures

Two types of thrombosis were distinguished: clinically manifest thrombosis and subclinical thrombosis. Clinically manifest thrombosis was defined as thrombosis demonstrated by Doppler ultrasound or venography following signs or symptoms suggestive of upper limb thrombosis. Subclinical thrombosis was defined as thrombosis demonstrated by routine scheduled Doppler ultrasound assessed by a blinded panel, in the absence of signs or symptoms.

Doppler ultrasound diagnosis of thrombosis was made according to predefined criteria. For veins accessible to direct insonation, the criteria of noncompressibility (if possible and adequately performed), visualization of echogenic intravascular mass, and absence of respiratory variation were used (jugular, axillary, subclavian vein).[14-17] For veins inaccessible to direct insonation, the criterion of monophasic flow (spectral Doppler) was used (middle part of subclavian vein, brachiocephalic, superior caval vein) to detect occlusive thrombosis.[18]

Criteria for contrast venography included an intraluminal contrast filling defect of a venous segment and persistent nonfilling of a venous segment in the presence of collateral circulation.[19] Contrast venography according to a standardized protocol was used when thrombosis was clinically suspected but Doppler ultrasound findings were normal or inconclusive.

The primary study endpoint was pacemaker lead-related thrombosis as demonstrated by scheduled Doppler ultrasound examination. Secondary study endpoints were clinically manifest thrombosis as noted by attending physicians between scheduled follow-up visits and possible complications of thrombosis (pulmonary embolism, infection, complicated reinterventions, death). Pulmonary embolism was diagnosed as the presence of a high-probability ventilation-perfusion lung scintigram or positive spiral computed tomographic scan or pulmonary angiogram, based on overt clinical signs and symptoms. When pulmonary embolism was present, Doppler ultrasound of the upper and lower extremities was performed to identify the possible embolism source. Device-related infection was defined as a positive wound or device culture (local infection) with positive blood cultures (bloodstream infection) of identical types of microorganisms. The decision to obtain microbiologic cultures was made by the attending physicians based on clinical signs and symptoms.

Statistical Analysis

Cumulative incidences were calculated as the number of first events divided by the number of patients at baseline. The ratios of the cumulative incidences were the relative risks (RR). The 95% confidence intervals (CIs) were based on standard errors for binomial distributions. Factors associated with thrombosis in univariate analysis were analyzed by Mantel-Haenszel statistics, and corresponding 95% CIs derived from the model were calculated.

Results

Patients

During the study period, 179 consecutive patients were considered for enrollment; 153 gave written informed consent (86%). Three patients were excluded from the study because they met one of the exclusion criteria. Four patients were excluded from analysis because of incomplete data: determination of coagulation parameters failed in two patients, and two patients were lost to follow-up. One patient withdrew informed consent after the study started. Overall, complete datasets of 145 patients were available for evaluation. Table 1 lists the baseline characteristics of the study patients. Nineteen of the 580 recordings (3%) were not interpretable. Both observers agreed with regard to diagnosis of thrombosis for 539 (96%) of 561 recordings ($\kappa = 0.83$).

Incidence of Thrombosis

Overall, thrombosis was diagnosed in 34 of 145 patients, resulting in a 1-year cumulative incidence of 23.4% (95% CI: 16.6%–30.3%). Most thrombotic events were subclinical (n = 31). Thrombosis was clinically manifest in 3 patients (2.1%; 95% CI: 0%–4.3%). The three patients suffered from multiple symptoms and signs of upper limb thrombosis, such

TABLE 1

Baseline Characteristics of the Study Patients

Age (years)	62.4 (19–94)
Height (cm)	174.3 (142–204)
Weight (kg)	78.8 (45–130)
Body mass index (kg/m^2)	25.9 (16–38)
Systolic blood pressure (mmHg)	132 (230–80)
Diastolic blood pressure (mmHg)	77 (130–50)
Male sex	104 (71.7%)
Caucasian race	131 (90.3%)
Current smoker	30 (20.7%)
Diabetes mellitus	23 (15.9%)
Underlying disease	
Ventricular tachycardia/fibrillation	62 (42.8%)
Dilating cardiomyopathy	31 (21.4%)
Atrial fibrillation/flutter	18 (12.4%)
AV block	17 (11.7%)
Sick sinus syndrome	13 (8.9%)
Other	4 (2.8%)
Device	
Pacemaker	70 (48.3%)
Internal cardiac defibrillator	75 (51.7%)
No. of implanted leads	
Single	28 (19.3%)
Double	82 (56.5%)
Triple	35 (24.1%)
Implantation site	
Subclavian vein	168 (56.6%)*
Cephalic vein	129 (43.4%)*
Left-sided	129 (89%)
Anticoagulant treatment	86 (59.3%)
Antiplatelet treatment	41 (28.3%)

Values are given as mean (range) or number (percent).
*Based on the number of implanted pacemaker leads (n = 297).

as pain (n = 2), arm edema (n = 2), discoloration (n = 1), and visible collateral circulation (n = 1). Thrombosis was diagnosed by Doppler ultrasound in two of the patients and by additional venography in one patient. All three events were occlusive and confirmed by subsequent scheduled Doppler ultrasound.

Among the 31 patients diagnosed with subclinical thrombosis based on scheduled Doppler ultrasound, 20 events were small and nonocclusive, and 11 were occlusive. Subclinical thrombosis that subsequently progressed to clinically manifest thrombosis was not observed in any patient.

Most cases of thrombosis occurred within 3 months after implantation (n = 20/34 [59%]). Eight new events (24%) were observed between 3 and 6 months. Six new events (18%) were noted between 6 and 12 months. The observed risks for the different time intervals are summarized in Table 2. In the three patients with clinically manifest thrombosis, diagnosis was made 2 weeks, 2 months, and 5 months after implantation, respectively. The three patients were treated with low-molecular-weight heparin for 5 days, followed by oral anticoagulants in two patients, aiming at an international normalized ratio (INR) of 2.0 to 3.0. One patient had already received acenocoumarol treatment but was insufficiently anticoagulated at the time of clinical diagnosis (INR 1.4). The leads were not extracted in any of the three patients. In all three patients with clinically manifest thrombosis, a large venous collateral network was observed at Doppler ultrasound examination 12 months after implantation. None of the patients had clinical signs of postthrombotic syndrome after 7 to 12 months of follow-up.

TABLE 2

Observed Incidence of Pacemaker Lead-Induced Thrombosis Assessed by Routine Doppler Ultrasound at Different Time Intervals

	Follow-Up Interval		
	3 Months	**6 Months**	**12 Months**
Patients before assessment	145	143	138
Available recordings	143	138	129
Thrombosis (new events)	20 (14%)	8 (6%)	6 (5%)

Risk Factors for Thrombosis

The risk estimates for established risk factors for venous thrombosis are summarized in Table 3. In univariate analysis, a personal history of venous thrombosis, use of female hormones, and absence of anticoagulant treatment were associated with an increased risk of thrombosis (Table 3). The risk of thrombosis was increased in patients with multiple (two or three) pacemaker leads compared to a single lead (27.4% vs 7.2%; RR 3.8, 95% CI: 1.0–15.0). Analysis of other factors (including those listed in Table 1; data not shown) did not reveal any other contributors to the risk of thrombosis. Congestive heart failure was inversely related to the risk of thrombosis; however, this finding likely was related to the protective effect of anticoagulant treatment in these patients (Table 3). After multivariate analysis, the lack of anticoagulant treatment and hormone therapy still was associated with a substantially increased risk of thrombosis (Table 4). A personal history of thrombosis was slightly associated with pacemaker lead-associated thrombosis (Table 4).

Secondary Endpoints

One patient suffered from proven pulmonary embolism, the source of which was unclear. Doppler ultrasound of the upper and lower extremities was normal. Pulmonary embolism in another patient was clinically suspected but was not confirmed by diagnostic imaging (normal perfusion lung scan). Doppler ultrasound was normal in this patient.

Two patients suffered from device-related infections (one local, one bloodstream infection); one of these two patients had clinically manifest thrombosis. Fourteen patients died during follow-up, mostly as a result of primary cardiac disease (64%). No deaths were related to thromboembolic complications. Thirteen reinterventions occurred during the study period. A complicated reintervention was related to occlusive thrombosis in one patient. In this patient, lead reimplantation and positioning of a third lead failed 1 month after an episode of clinically manifest thrombosis because of severe stenosis of the brachiocephalic vein.

Discussion

This study showed a substantial 23% 1-year cumulative incidence of thrombosis associated with permanent pacemaker lead implantation as demonstrated by routine Doppler ultrasound examination. The majority of the thrombotic events occurred within the first 3 months after implantation and did not cause any clinical symptoms.

The risk of venous abnormalities associated with pacemaker leads in prospective studies reported in the literature ranges from 5.5% to 64%.[2,6-10] Only one study systematically used Doppler ultrasound to specifically detect venous

TABLE 3

Risk of Pacemaker Lead-Associated Venous Thromboembolism for Established Risk Factors in Venous Thromboembolism

	Patients with Thrombosis (%)	Relative Risk (95% CI)
Sex		
Male	23/104 (22.1%)	
Female	11/41 (26.8%)	1.2 (0.7–2.2)
Age (years)*		
<71.8	22/109 (20.2%)	
>71.8	12/36 (33.3%)	1.7 (0.9–3.0)
Body mass index (kg/m^2)*		
<27.9	24/109 (22.0%)	
>27.9	10/36 (27.8%)	1.3 (0.7–2.4)
History of venous thromboembolism		
No	28/133 (21.1%)	
Yes	6/12 (50%)	2.4 (1.2–4.6)
Active cancer		
No	30/132 (22.7%)	
Yes	4/13 (30.8%)	1.4 (0.6–3.2)
Major surgery/trauma		
No	29/129 (22.5%)	
Yes	5/16 (31.3%)	1.4 (0.6–3.1)
Hormone therapy		
No	28/137 (20.4%)	
Yes	6/8 (75.0%)	3.7 (2.2–6.2)
Factor V Leiden/prothrombin G20210A		
No	31/135 (23.0%)	
Yes	3/10 (30.0%)	1.3 (0.5–3.5)
Factor VIII:C (IU/dL)*		
<205.5	25/109 (22.9%)	
>205.5	9/36 (25%)	1.1 (0.6–2.1)
Family history of venous thromboembolism		
No	30/124 (24.2%)	
Yes	4/21 (19.0%)	0.8 (0.3–2.0)
Acute myocardial infarction		
No	30/134 (22.4%)	
Yes	4/11 (36.4%)	1.6 (0.7–3.8)
Congestive heart failure		
No	29/101 (28.7%)	
Yes	5/44 (11.4%)	0.4 (0.2–1.0)
Chronic obstructive pulmonary disease		
No	27/113 (23.9%)	
Yes	7/32 (21.9%)	0.9 (0.4–1.9)
Upper limb paralysis		
No	33/142 (23.2%)	
Yes	1/3 (33.3%)	1.4 (0.3–7.3)
Lack of anticoagulant treatment		
No	12/86 (14.0%)	
Yes	22/59 (37.3%)	2.7 (1.4–5.0)

*Cutoff values of these parameters correspond with the 75th percentile.

thrombosis after pacemaker implantation. The study reported a cumulative incidence of pacemaker lead-related thrombosis of only 5.5%, 4 years after implantation.[7] This study of a Chinese population evaluated patients with a single pacemaker lead only. The reported incidence of 5.5% is similar to our finding (7%) in patients with a single pacemaker lead. The risk of thrombosis was substantially higher in patients with multiple pacemaker leads (27%).

TABLE 4

Risk Factors for Thrombosis Associated with Permanent Transvenous Pacemaker Leads

Risk Factor Risk Factor	$RR_{Univariate}$ (95% CI)	$RR_{Multivariate}$ (95% CI)
Age	1.7 (0.9–3.0)	Not performed
Personal history of thrombosis	2.4 (1.2–4.6)	1.8 (0.6–5.5)*
Hormone therapy	3.7 (2.2–6.2)	3.2 (1.0–10.5)†
Absence of anticoagulant treatment	2.7 (1.4–5.0)	2.5 (1.1–5.5)†

*Adjusted for age and hormone therapy.
†Adjusted for age and personal history of thrombosis.
*RR = relative risk.

Other studies that used routine venography to detect venous abnormalities after lead implantation reported a higher incidence of venous lesions of up to 64%. The findings of these studies are difficult to compare with our results because the studies included the criterion of venous stenosis using different definitions, which may have resulted in the higher reported incidences. In addition, the reported sensitivity of the Doppler ultrasound technique we used ranges from 78% to 96%.[14-18] As a consequence, the incidence of thrombosis in our patients could be underestimated, as Doppler ultrasound would have led to a 4% to 22% false-negative rate in our patient group. We were aware of this issue prior to the start of the study; however, the invasive nature of venography made its repeated use unacceptable in this vulnerable patient group. Use of Doppler ultrasound would not have affected our

relative risk estimates for established risk factors in venous thrombosis.

The presence of established thrombotic risk factors, such as use of oral contraceptives or hormone replacement and a personal history of venous thrombosis, clearly contributed to an increased risk of thrombosis associated with permanent pacemaker leads. Only one small case series suggested a relationship between oral contraceptive use and a high risk of thrombosis associated with permanent pacemaker leads.[20]

The findings of our study suggest a benefit effect of anticoagulant treatment on thrombosis risk. One third of our study patients did not receive anticoagulant treatment, and no randomized trials have evaluated the effect of anticoagulant prophylaxis in such patients. A benefit of low-dose heparin (5,000 IE, 2–3 times daily for 2 weeks) in reducing the risk of pulmonary embolism after pacemaker implantation has been reported.[21] A 15% rate of pulmonary embolism was diagnosed by routine screening pulmonary scintigram at day 14 in patients who did not receive heparin compared with no events in the group of patients who were given heparin prophylaxis.The source of the pulmonary embolism was not determined but was believed to be pacemaker lead related. Based on our data, pulmonary embolism as a complication is infrequently observed. The present study determined clinically manifest pulmonary embolism. A "true incidence" estimate of pulmonary embolism would require systematic screening of all of our patients by ventilation perfusion scan because embolic events may not be noted clinically,[21] This was not the primary aim of our study and would require a different design.

Analogous to patients with cancer and central venous catheters, prophylactic doses of low-molecular-weight heparin or a fixed low dose of warfarin can be studied in patients not receiving routine anticoagulation.[22-24] In our study, most events were observed within the first 3 months after implantation, and a short-term course of prophylactic anticoagulation may be sufficient. The findings of other studies support the concept that thrombosis risk is substantial shortly after implantation.[9,10,21] In addition, patients who undergo pacemaker implantation reach a temporary state of hypercoaguability.[25] Whether these patients would benefit from short-term prophylaxis is unknown and requires prospective validation.

In conclusion, this study showed a high incidence of thrombosis may be observed in patients with pacemaker and defibrillator leads. Anticoagulant treatment may protect against thrombosis. The presence of established risk factors for venous thrombosis in patients not undergoing anticoagulant treatment may substantially increase the risk of pacemaker lead-associated thrombosis. Use of short-term prophylactic anticoagulants may be warranted in these patients but requires prospective evaluation.

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