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Clinical and laboratory risk factors of thrombotic complications after pacemaker implantation: a prospective study

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Aims Venous lesions, including obstruction and thromboembolism (VTE), are not uncommon after pacemaker implantation. The purpose of this prospective study was to assess the role of various patient and procedure-related risk factors in the development of these complications.

Methods and results A prospective venography-based study of 150 consecutive pacemaker implantations with a 6-month follow-up was conducted. Current case–control study included all cases ($n = 47$) with a new venous lesion, and their matched controls. Several surgical and technical factors, i.e. lead burden, choice of venous access, operator experience and procedure duration, as well as patient-related classic risk factors of VTE were assessed. Plasma markers of coagulation and endothelial activation [prothrombin fragment 1 + 2 (F1 + 2), D-dimer (DD), von Willebrand factor (vWF), thrombomodulin (Tm)] were used to evaluate the extent of acute surgical trauma. All cases with venous lesions were also screened for thrombophilia. None of the procedure-related variables were predictive of VTE. Mean levels of vWF, F1 + 2 and DD increased significantly ($P < 0.001$) and equally in both cases and controls. No single clinical factor predicted venous lesions, but significant ($P < 0.05$) clustering of classic clinical VTE risk factors was seen among the cases. Thrombophilia was overrepresented in patients with symptomatic pulmonary embolism (2/5, 40%).

Conclusion Pacemaker implantation induces a transient hypercoagulable state, but its degree does not predict subsequent venous thromboembolism, and neither did the grade of endothelial damage as reflected by plasma markers. The aetiology of these lesions seems to be multifactorial, and clustering of classic thrombotic risk factors plays a role in the pathogenesis.

Keywords Pacemakers • Complications • Thrombosis • Embolism • Risk factors

Introduction

Venous thromboembolism (VTE) is known to occur after implantation of permanent transvenous pacing leads,[1–8] but its predisposing factors are not fully understood. Lead implantation itself always causes some degree of venous endothelial injury, which can be further exacerbated by continuous friction rub and irritation by the electrode. The number and diameter of the electrodes, as well as the access route chosen for the implantation can potentially affect blood flow. Several previous studies were not able to ascertain any significant electrode-related risk factors for these events,[1,2,5,6] while other investigators have indicated an increased risk for thrombosis in patients with multiple leads.[8] Also certain underlying cardiac conditions can promote stasis by reducing the rate of flow and/or by elevating central venous pressure. Surgical procedures and injuries in general are known to induce a hypercoagulable state, and several patient-related hereditary or acquired conditions are known to predispose to VTE,[9–11] but their role in pacemaker lead thrombosis is unclear.

The aim of this prospective case–control study was to assess the role of various potential background attributes in the

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Table 1 Study endpoints after pacing device implantation

Venous thromboembolic complications	*n*
Major endpoints	
TVO	3
Pulmonary embolism with TVO	2
Pulmonary embolism with lead thrombus in TEE	2
Pulmonary embolism alone	1
Acute symptomatic UEDVT	1
Total	9
Other endpoints	
Venographic stenosis	14
Lead thrombus, venography	20
Lead thrombus, TEE	4
Total	38
All venous thromboembolic complications (=cases)	47

TVO, total venograhic occlusion; TEE, transesophageal echocardiography; UEDVT, upper extremity deep venous thrombosis.

development of venous complications after pacemaker implantation by determining the role of (i) device implantation technique and lead features as well as (ii) degree of implantation-induced activation of coagulation, and (iii) patient-related risk factors for VTE.

Methods

Study population

The current study is a part of a wider protocol in progress in our institutions in Western Finland to assess the thrombotic and bleeding complications of invasive cardiac procedures.[12,13] A total of 150 patients admitted for implantation of their first cardiac pacing device were enrolled into a prospective 6-month follow-up study between November 2003 and August 2005. The study was approved by the ethical committees and hospital administrations of both institutions. An informed, written consent was obtained from all patients willing to participate. Study protocol imposed no alterations to device implantations or medical treatments, which was conducted according to current guidelines and local practices. The choice of venous access as well as electrode and device types was left at the discretion of the operators. Background features of the study population have been presented previously.[14,15]

Patient selection

All patients who developed lead thrombosis, intracardiac thrombus, pulmonary embolism, or venous obstructive lesions ($n = 47$, mean age 65 years, 26 men) were selected for this case–control analysis (*Table 1*). A detailed description of the distribution of the endpoint lesions and their diagnostic methods has been published before.[14,16] One control without any venous obstruction or thromboembolism was assigned to each of the cases. The controls were matched by age (± 5 years) and sex. Matching by age was successful in 97.8% and by sex in 95.7%. In order to search for predictors for clinically significant lesions, a subgroup ($n = 9$) of major endpoints was formed including all cases with pulmonary embolism, venographic total occlusion or acute symptomatic upper extremity thrombosis.

Thrombus and venous lesion imaging

Several diagnostic methods were utilized in the detection of venous thrombi and lesions. Intravenous contrast venography was performed serially at baseline immediately prior to the implantation procedure and at 6 months post-operatively in all patients. The technique and contraindications of the venography, the criteria for venous obstruction and thrombi, as well as the methodology for venous diameter measurement utilized in this study have been described previously.[14,16] Transthoracic echocardiography was performed at baseline and at 6 months. A subset ($n = 66$) of the study group underwent transesophageal echocardiography at 6 months to detect the potential thrombus formations in the superior vena cava or in the right atrium.[15] When clinically indicated, an assessment for pulmonary embolism was accomplished by means of ventilation-perfusion scanning or spiral computed tomography as chosen by the treating physician. Venous Doppler ultrasound was used to assess the upper extremity veins if symptoms suggestive of acute deep venous thrombosis were encountered during the follow-up period of 6 months.

Clinical and procedural variables

Procedural data and patient-related risk factors for VTE and a complete cardiac history were obtained by a detailed chart review and interview. Likewise, data on cardiovascular disease were collected, and all current medical therapies including antithrombotics were reviewed (*Tables 2 and 3*). In addition to the role of any single clinical risk factor, we also assessed the absence or clustering of classic VTE risk factors: obesity, congestive heart failure, advanced age (≥75 years), previous deep venous thrombosis or pulmonary embolism, history of cancer, and hypertension in the patient groups.[11,17–20]

Laboratory assays

The surgical trauma from implantation was quantified by measuring the plasma prothrombin fragment 1 + 2 (F1 + 2) and D-dimer (DD), which can be used as markers of thrombin formation, and of fibrin generation and breakdown.[21,22] Von Willebrand factor antigen (vWF) and soluble thrombomodulin (Tm) were assessed in order to quantitate the vascular endothelial activation.[23–26] Blood samples for plasma vWF, Tm, DD, and F1 + 2 were obtained (i) at baseline prior pacemaker implantation and (ii) on the first post-operative day. Blood for plasma analysis was collected in 3.2% sodium citrate. Plasma was separated by centrifugation at 2500 g and stored at −70° C. DD was assessed using enzyme immunoassay Asserachrom™ D-Di, vWF using STA-Liatest® vWF, and Tm using enzyme immunoassay Asserachrom thrombomodulin (all from Diagnostica Stago, Asnières, France). F1 + 2 was measured using Enzygnost TM F 1 + 2 micro (Dade Behring, Marburg, Germany). All the analyses were done in duplicates. Coefficients of variation of the methods were 5.4, 1.1, 8.7, and 3.7%. A sample for the determination of international normalized ratio (INR) was obtained from warfarin users at baseline and at 6 months.

Patients with venous complications were tested for thrombophilia by using the following assays: PTT-LA (Lupus Anticoagulant-Sensitive APTT Reagent) and dRVVT (STA-Staclot® dRVV Screen), antithrombin activity (Stachrom® AT III), protein C activity (Stachrom® Protein C), protein S activity (Staclot® Protein S), thrombin time (STA®—Thrombin), all from Diagnostica Stago, Asnières, France; anti-cardiolipin antibodies (detected by ELISA, as described previously[27]); anti-beta-2-glycoprotein 1 antibodies (QUANTA Lite ™ B2GPI I IgG, INOVA Diagnostics, Inc., San Diego, CA, USA); F V Leiden (R506Q) and prothrombin mutation (Factor V Leiden Kit and Factor II, prothrombin, G20 210A Kit with LightCycler® instrument, Roche Diagnostics GmbH, Mannheim, Germany). When a thrombophilic condition, except mutations, was

Table 2 Background features, venographic and echocardiographic measurements

	Cases ($n = 47$)	Controls ($n = 47$)	P
Background features			
Current smoker	5 (11.9)	4 (9.5)	1.00
Obese (body mass index >30)	11 (23.4)	11 (23.4)	1.00
Diabetes mellitus	7 (14.9)	7 (13.0)	1.00
History of stroke	1 (2.1)	2 (4.3)	1.00
Coronary artery disease	11 (23.4)	14 (28.3)	0.64
Valvular heart disease	5 (11.4)	7 (15.6)	0.76
Severe heart failure	9 (19.1)	5 (8.5)	0.13
Hypertension	17 (36.2)	9 (19.1)	0.06
Atrial fibrillation at implantation	12 (25.5)	7 (14.9%)	0.20
History of VTE	2 (4.3)	2 (4.3)	1.00
History of malignancy	2 (4.3)	0	0.49
Baseline medications			
Warfarin	15 (31.9)	16 (34.0)	1.00
Aspirin	20 (43.5)	17 (36.2)	0.53
Clopidogrel	1 (2.1)	0	1.00
LMWH	1 (2.2)	5 (10.6)	0.20
Beta-blocker	22 (47.8)	22 (47.8)	1.00
ACE-I or ARB	28 (60.9)	22 (47.8)	0.21
Calcium channel blocker	11 (23.9)	6 (13.0)	0.18
Diuretic	18 (39.1)	16 (34.8)	0.67
Baseline contrast venography			
Minimum diameter (mm)	10.7 ± 3.1	10.9 ± 2.7	0.57
Abnormality[a]	3 (6.4)	3 (6.4)	1.00
Echocardiography			
LV ejection fraction (%)	53.0 ± 14.0	58.0 ± 16.2	0.10
Left atrial dimension (mm)	40.1 ± 6.5	40.4 ± 7.0	0.89
Tricuspid valve gradient (mmHg)	26.6 ± 9.1	25.9 ± 8.6	0.71
6 months (mmHg)	28.0 ± 8.6	24.3 ± 7.4	0.01

The values in parenthesis are given in percentages. Venous thromboembolism; LMWH, low molecular-weight heparin; ACE-I, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker.
[a]Baseline venographic abnormalities: stenosis ($n = 4$), venous anomaly ($n = 2$), persistent left superior vena cava ($n = 1$).

Table 3 Pacing indications and aspects of device implantation procedure

	Cases	Controls	P
Primary pacing indications			
Sick sinus syndrome or bradycardia	24 (51.1)	23 (48.9)	1.00
Atrioventricular conduction defect	12 (25.5)	17 (36.2)	0.37
Ventricular tachycardia or fibrillation	5 (10.6)	4 (8.5)	1.00
Cardiac resynchronization therapy	6 (12.8)	3 (6.4%)	0.49
Operator experience			
Number of implants >100	34 (72.3)	32 (68.1)	0.82
Implant side			
Left	39 (83.0)	40 (85.1)	1.00
Access vein(s)[a]			
Cephalic	27 (57.4)	31 (66.0)	0.52
Subclavian	20 (42.6)	17 (36.2)	0.67
Axillary	3 (6.4)	2 (4.3)	0.67
Leads			
1 lead	13 (27.7)	16 (34.0)	0.66
2 leads	33 (70.2)	28 (59.6)	0.39
3 leads	1 (2.1)	3 (6.4)	0.62
Total lead diameter (mm)	3.74 ± 1.10	3.58 ± 1.13	0.74
Total lead diameter/BL_Dmin[b]	0.38 ± 0.15	0.35 ± 0.14	0.53
Duration of implant procedure (min)	87.5 + 74.1	75.8 + 39.3	0.81

The values in parenthesis are given in percentages.
[a]Six patients with biventricular devices had two access veins: cephalic and subclavian or axillary.
[b]BL_Dmin, baseline minimum venous diameter.

found in the initial sample, the test was repeated from another sample taken 6 months apart (concurrent with the latter venography). Only patients with a genetic mutation or positive results in repeated samples were regarded to have thrombophilia.

Statistical analysis

Continuous variables are presented as means (SD) unless otherwise indicated, and study groups were compared by the Mann–Whitney *U*-test. Categorical variables are presented as counts and percentages and were compared by the χ^2 or Fisher's exact test. Wilcoxon signed rank test was used to assess the significance of the changes in paired samples of laboratory variables. Univariate and multivariable logistic regression analyses were performed to identify the independent predictors for VTE during the 6 months follow-up. A multivariable linear regression model was performed to determine the independent predictors for implantation-induced changes in laboratory parameters. A two-sided *P*-value of <0.05 was required for statistical significance. Statistical analyses were performed using SPSS (version 16.0, SPSS Inc, Chicago, Ill, USA). The authors had full access to the data and taken responsibility for its integrity.

Results

Clinical- and procedure-related risk factors for thrombosis

There were no significant differences in univariate analysis between the cases and controls with regard to the presence of any classic patient-related risk factors for VTE (obesity, congestive heart failure, age ≥75 years, previous VTE, history of cancer, and hypertension) or any other clinically relevant background features (*Table 2*). Although no single classic VTE risk factor emerged as

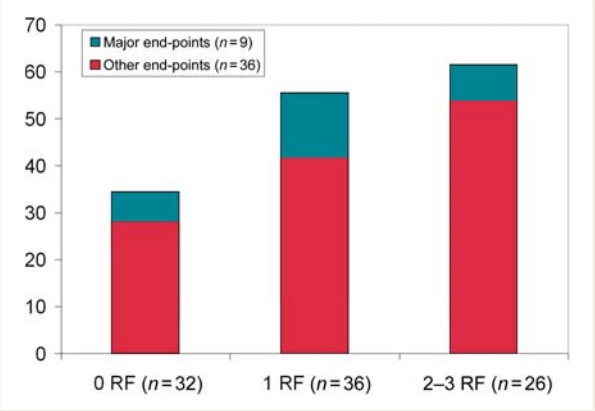

Figure 1 Relative incidence of major and other study endpoints (see *Table 1*) categorized by number of venous thromboembolism risk factors (0, 1, or >1; $P = 0.036$, linear-by-linear association). Height of the bars represents percentage of cases in the three risk factor categories.

a predictor for endpoint events, the majority ($n = 36$, 77%) of the cases with an endpoint were found to have at least one classic VTE risk factor, whereas 21 (45%) of the controls had none ($P = 0.049$). The relative frequency of endpoint lesions showed an increasing trend with higher cumulative number of risk factors ($P = 0.036$, linear-by-linear association; *Figure 1*). Also, among cases with an obstructive lesion (stenosis or total occlusion) in 6-month venography, a significantly higher proportion ($n = 18$, 95%) had at least one VTE risk factor compared with controls ($n = 26$, 55%, $P = 0.002$).

Operator experience, venous access type and implantation procedure duration were not different between cases and controls (*Table 3*). There was also no difference on lead burden.

Haemostatic parameters

For the entire case–control study group, a significant procedure-induced increase was demonstrated in the mean level of vWF, reflecting trauma-related endothelial activation and secretion, as well as in the mean levels of F1 + 2 and DD as signs of thrombin generation, fibrin formation and fibrin degradation. Implantation resulted in an abnormal DD level (≥0.3 μg/mL) in the majority (94%) of the patients, and a minimum of two-fold rise from baseline was seen in 54%. Procedure-related changes in all of these parameters were, however, comparable in the cases with thrombotic endpoints and their controls (*Figure 2*). Moreover, the changes in these parameters were comparable in the nine patients with major thromboembolic endpoints.

The post-operative DD levels were significantly lower in warfarin users compared with non-users (1.23 ± 0.95 vs. 2.69 ± 2.95 μg/mL, $P = 0.008$; *Figure 3*). Multivariate analysis confirmed warfarin to be an independent predictor of a lower post-operative DD and F1 + 2 levels ($P < 0.001$).

Only 3 (6.4%) of the 47 patients with endpoints were found to have a prothrombotic coagulation disorder, but 2 (40%) of the 5 cases with symptomatic pulmonary embolism had thrombophilia (*Table 4*). The hereditary or acquired thrombophilia was not known prior to this study in any of the cases, and none of the cases with thrombophilia had a previous history of deep venous thrombosis or pulmonary embolism.

Antithrombotic therapies

There were no statistically significant differences in the utilization of anticoagulant or other antithrombotic therapies between cases and controls (*Table 2*), although none of the nine patients with major endpoints were receiving therapeutic-level warfarin or low-molecular-weight heparin at the time of the pacemaker implantation. In the multivariate regression analysis, the absence of therapeutic anticoagulation remained a significant predictor of major endpoints ($P = 0.017$; OR, 16.5; 95% CI: 1.7–164.7).

Discussion

Our study shows that the development of venous obstruction and thrombosis, which are not uncommon after pacing device placement, cannot be predicted by any technical parameters of leads or implantation surgery. Instead, patient-related established risk factors for VTE in general seemed to predispose also to pacemaker lead-associated thrombosis. In our study the relative frequency of endpoint lesions was observed to increase in a linear fashion as the cumulative number of risk factors rose. Also, thrombophilia was overrepresented in the symptomatic patient group. Pacemaker implantation—like other surgical procedures—activates the coagulation system, but the degree of transient acute activation, as measured by markers of thrombin generation, fibrin formation, or endothelial secretion and activation, did not explain the thromboembolic complications. A long-term use of anticoagulation protected against symptomatic thromboembolic disease. Importantly, the levels of plasma DD became abnormal in the vast majority of the patients after pacemaker implantation and, thus, DD cannot be used to screen for venous thromboembolism early after implantation.

Pacemaker lead-associated thrombus formation is multifactorial and is likely to involve all three components of the classic Virchow's triad, i.e. injury to vessel walls, impairment of blood flow and hypercoagulability. Implantation procedure *per se* probably causes a varying degree of venous endothelial injury, which can subsequently be exacerbated by inflammation and irritation from friction rub by the transvenous leads over time.[28] Even an attempted pacemaker implantation may lead to venous occlusion.[29] Multiple surgical and technical factors, such as choice of venous access, operator experience and procedure duration, could potentially affect the extent of trauma, but such factors were found to predict endpoints neither in the current nor in the majority of previous studies.[2,6,7,30,31]

In order to quantify the pacemaker implantation-induced acute surgical trauma, F1 + 2 and DD were used as markers of coagulation, and vWF and Tm as markers of endothelial activation. Upon thrombin generation, a key event in blood clotting, prothrombin is cleaved into two peptides the active thrombin and the prothrombin fragment F1 + 2 (19). Therefore F1 + 2 is a specific marker of thrombin formation. Further, thrombin cleaves fibrinogen to fibrin and plasma DD, which as one of

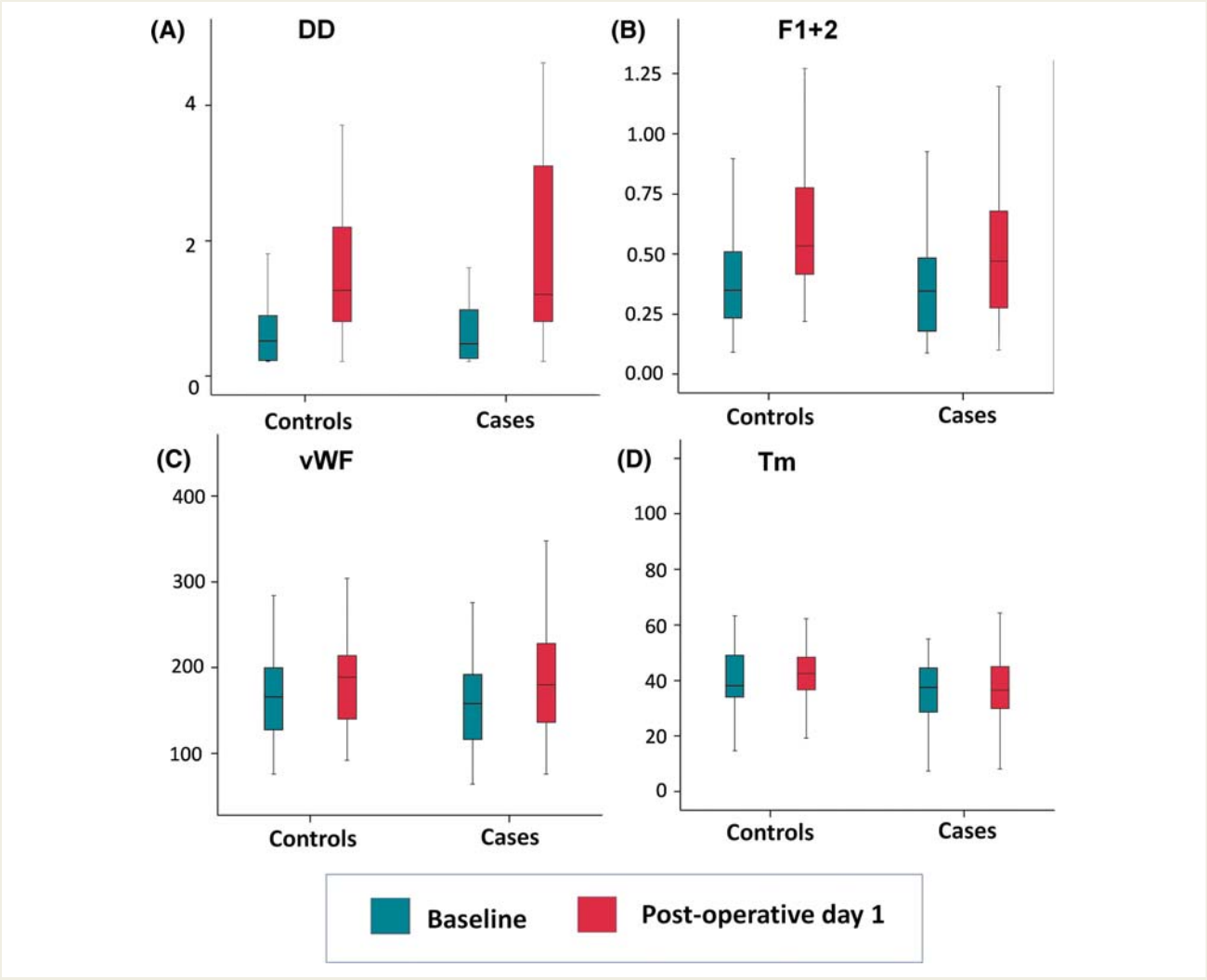

Figure 2 Baseline to first post-operative day changes in the levels of plasma biomarkers. (*A*) Mean plasma D-dimer (μg/mL) increased significantly in both the case and control groups ($P < 0.001$), but post-operative levels did not differ between the groups ($P = 0.631$). (*B*) Prothrombin fragment F1 + 2 (nmol/L) also increased significantly in cases ($P < 0.001$) and controls ($P = 0.001$) with no difference between groups ($P = 0.06$). (*C*) von Willebrand factor (%) with significant increase in both the groups ($P < 0.001$) and no inter-group difference ($P = 0.949$). (*D*)Thrombomodulin (ng/mL) with no significant change in either group. Graphics presented as Tukey's box plots: box length represents values from low to upper quartile, whiskers encompass 5th to 95th percentile, and the boxes are divided by median.

fibrin degradation products can be used as a measurement of both fibrin formation and breakdown.[22] It is known from previous studies that a surgical procedure, such as implantation of transvenous pacemaker, by itself induces a hypercoagulable state, even without apparent venous thrombosis.[32] Our findings are in agreement with these previous observations, as a significant activation of coagulation (measured by F1 + 2 and DD) was seen both in patients with thromboembolism and in controls with an uneventful follow-up. However, it is possible, that the elevation of these biomarkers may primarily reflect processes limited locally to the wound area, rather than indicate a hypercoagulative state in the entire body. Plasma DD levels were elevated post-operatively in nearly all tested patients precluding the use of DD as a screening test for VTE in patients with recent pacemaker implantation.

No ideal plasma marker for assessment of local venous injury exists. vWF, a plasma glycoprotein, synthesized by endothelial cells and megakaryocytes, has been utilized as a plasma marker for endothelial activation, despite its poor specificity.[23] Tm, a membrane protein expressed on surfaces of endothelial cells, functions as a cofactor in the anticoagulant pathway by amplifying thrombin-induced activation of protein-C. Soluble Tm in plasma can also be used as a biomarker for vascular damage.[24,25] In this study, we measured both vWF and Tm, but a procedure-induced increase was seen only in vWF. This is conceivable, however, since Tm is a marker of generalized, and not local, endothelial activation. Morevoer, vWF is an acute phase reactant. We found no significant difference in the levels of these parameters between cases and controls.

Impediment of blood flow or stasis is difficult to demonstrate directly in pacemaker patients. Pacemaker leads occupy venous

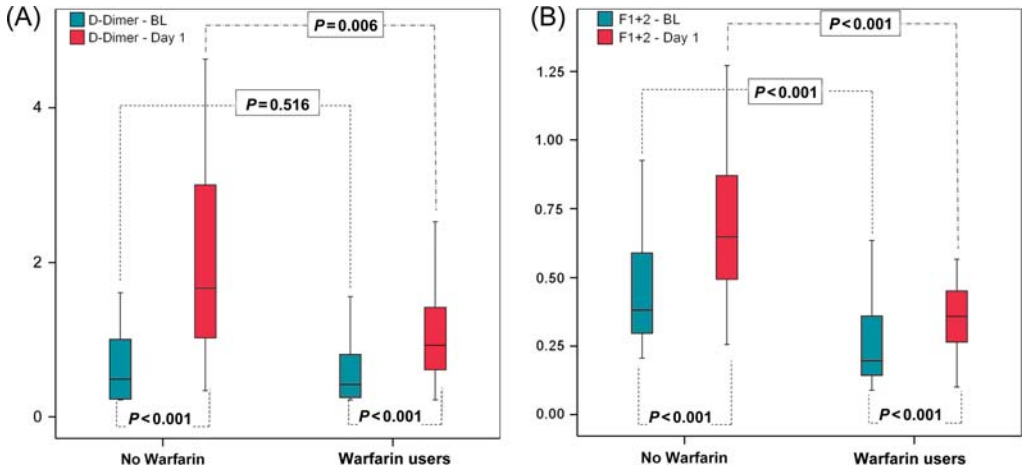

Figure 3 D-dimer (*A*; μg/mL) and prothrombin fragment F1 + 2 levels (*B*; nmol/L) at baseline (BL) and after pacemaker implantation in patients with and without warfarin treatment (Tukey's box plots, see *Figure 2*).

Table 4 Cases with thrombophilia

Patient number	Gender	Age	Coagulation defect	Endpoint condition	Indication for device implantation	Device type
1	Male	74	Factor V Leiden heterozygosity and antithrombin deficiency (50%)	Total venous occlusion and PE	III Degree AV block	DDD
2	Male	74	Antithrombin deficiency (65%, 69%, normal value >87%)	Non-occlusive venographic thrombus	Left ventricular failure	Biventricular pacemaker
3	Male	67	Strongly positive anti-cardiolipin antibodies (IgM 1280 MPL and 895 MPL in two samples)	Total venous occlusion and PE	Left ventricular failure	Biventricular pacemaker

MPL, M-isotype phospholipid antigens. Upper limit of the reference values in our laboratory is 24 MPL.

luminal space and may introduce some stasis. Lead burden as assessed by the number and the combined diameters of the implanted leads or indexed to the venous diameters were not associated with the development of venous lesions. The lack of association between number of pacemaker leads to the venous lesions is in agreement with the majority of the previously published (mostly cross-sectional) studies,[2,5–7,30] with the exception of one.[8] The latter, however, was based on clinical signs and Doppler ultrasound with no systematic venographic data in all patients. Serial quantitation of venous diameter before and after pacemaker implantation was a unique feature of our study, but vessel size was not associated with endpoint events. Congestive heart failure[33–35] and atrial fibrillation[36,37] are known to be associated with hypercoagulation, and it is reasonable to assume that they could potentially slow the rate of central venous flow, and thus increase the risk for thrombosis by stasis as well. The current study could not reveal an association between these factors and VTE. One possible explanation for this is the fact that patients with these conditions were more often anticoagulated with warfarin. Some studies have suggested that anticoagulation with warfarin protects against pacemaker lead thrombosis.[8,38,39] Our study gives some support to these observations, since no symptomatic thromboembolic events or total venous occlusion occurred in patients on warfarin anticoagulation during implantation.

Many of the classic clinical risk factors for VTE, such as cancer, previous history of thromboembolism, obesity, or inflammation, may cause a hypercoagulative state, but were not, as singular variables, associated with the development of venous lesions and thromboembolism in the present or in the majority of the previously published studies.[1,2,6,30] Although this is one of the largest prospective studies on venous complications after pacemaker implantation, the power is limited to assess the predictive role of single potential risk factors with a low prevalence. However, in the current study, endpoints appeared to be associated with clustering of classic VTE risk factors, as the occurrence of endpoint lesions was observed to increase in a linear fashion together with a cumulating number of risk factors. One group of investigators has reported a significant association for VTE in pacemaker patients with female hormone use as well as with a history of previous

venous thrombosis.[8] Similarly, systemic infection was a promoter of venous occlusion in a study using lead extraction experience.[31]

One unique feature of our study was the assessment for the role of thrombophilia in the thrombotic complications after pacemaker implantation. New hereditary or acquired thrombophilia was found in 6.4% of the patients with venous lesions and thromboembolism. This prevalence was comparable to the frequency of thrombophilia in the general Finnish and Western European populations.[40–44] Of note, however, two of five (40%) patients with pulmonary embolism had thrombophilia (*Table 4*). Hereditary thrombophilia has previously been reported to be common in patients with pacemaker-induced superior vena cava syndrome,[45] but Factor V Leiden/prothrombin G20 210A mutation and the activity of Factor VIII/C were not identified as independent risk factors for venous thrombosis after pacemaker implantation in another study.[8]

There are certain limitations to the current study. Our study had limited power to assess the predictive value of potential risk factors with a low prevalence, although this is one of the largest prospective investigations into venous complications after pacemaker implantation. Systematic venographies formed the basis for the diagnosis of venous lesions. Although additional diagnostic methods were often used, the true incidence of central venous thrombi and clinically silent pulmonary embolism is likely to be an underestimation. Some of the venous lesions may have fibrotic encroachment of the vessel wall rather than thrombosis. Tests for thrombophilia were only conducted in the cases with endpoints, but not in the controls. This precludes a direct comparison of the prevalence of thrombophilia between the groups, and, thus, comparisons can only be made against literature-derived prevalence data in the general population.

In conclusion, venous thromboembolism and occlusion seem to be common after pacemaker implantation. The majority of the lesions are asymptomatic and clinically benign, although symptomatic pulmonary embolism or upper extremity deep venous thrombosis occur in some patients, and venous obstruction may hamper future lead replacements even in asymptomatic patients. Device implantation causes a hypercoagulable state, but no singular laboratory or clinical parameter predicted the development of venous thrombosis or obstruction. Thus, it is likely that the aetiology of these lesions is multifactorial, and clustering of risk factors plays a role in the pathogenesis.

Ethics

This study complies with the Declaration of Helsinki. The research protocol was approved by the local ethics committees of both participating hospitals. An informed written consent was obtained from each of the study subjects. All authors have read and agreed to the manuscript as written.

Conflict of interest: none declared.

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