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VENOUS THROMBOEMBOLISM AND OBSTRUCTION AFTER PACEMAKER IMPLANTATION

A Prospective Study of 150 Consecutive Cardiac Pacing Device Implantations

by

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To my Family

ABSTRACT

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- A prospective study of 150 consecutive cardiac pacing device implantations

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Background: Pacemaker implantation (PMI) may predispose to venous thromboembolism (VTE) and obstruction (VO). This prospective study aimed at quantifying changes in venous calibers, and at determining the incidence of symptomatic and asymptomatic VTE/VO after PMI. Further goals included an assessment of the role of transesophageal echocardiography (TEE) in the diagnosis of lead-related central venous thrombi (CVT), and determination of predictors for VTE/VO.
Methods: 150 (mean age 67; 61% male) consecutive patients with first PMI were enrolled and followed for 6 months. Contrast venography was performed at baseline and 6 months after PMI to measure venous diameters, and to detect stenosis, total occlusions and thrombi. TEE was conducted in 66 patients. Based on clinical suspicion, work-up for pulmonary embolism (PE) or acute deep vein thrombosis (DVT) were performed as needed. A total of 50 cases underwent longer-term (mean 2.4 years) follow-up venography. All cases with VTE/VO during the initial 6 months, and their matched controls, were selected for a case-control study focused on possible predictive role of laboratory and patient-related factors for the development of VTE/VO.
Results: 10 (7 %) patients were found to have baseline venous abnormalities (e.g. 8 obstructions). Mean venous diameters diminished significantly during the first 6 months, but no further reduction occurred in late follow-up. New VO was discovered in 19 patients (14 %; 14 stenosis, 5 total occlusions; all asymptomatic). Small non-obstructive thrombi were found in 20/140 (14 %) 6-month venograms. TEE at 6 months disclosed CVT in 6 (9 %) patients. One (0.7 %) patient had acute symptomatic upper-extremity DVT, and PE was discovered in 5/150 (3.3 %) patients during the first 6 months with no further cases thereafter. At 6 months, the total number of cases with VTE/VO amounted to 47 (31.3 %). Additionally, the later 2-year venograms (n=50) disclosed 4 (8 %) total occlusions and 1 (2 %) stenosis. In the case-control study, no parameter was predictive of venous end-points as a single variable, but there appeared to be significant clustering of traditional VTE risk-factors among the cases. Laboratory parameters showed a definite acute hypercoagulative state induced by PMI, but its degree did not predict subsequent development of VTE/VO.
Conclusions: This study shows that VTE/VO is relatively common after PMI with an overall incidence of at least 30 %. Although the majority of the lesions are asymptomatic and clinically benign, cases of PE were also encountered, and totally occluded veins may hamper future upgrading or replacement of pacing system. Venous complications seem difficult to prognosticate as firm predictors were not identified from a wide range of parameters analyzed in this study, although clustering of classic VTE risk factors may be a predisposing factor. Parameters related to implantation procedure or pacing systems and the severity of implantation-induced trauma did not emerge as predictors.
Key words: adverse events, biventricular pacemaker, cardioverter-defibrillator, pacemaker, venography, venous obstruction, venous thrombosis

TIIVISTELMÄ

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Laskimoiden verihyytymät ja ahtaumat tahdistinasennuksen jälkeen

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Tausta: Pysyvän sydäntahdistimen asentaminen voi altistaa laskimoiden hyytymille, keuhkoveritulpalle ja laskimoahtaumille. Tämän Turun yliopistollisessa keskussairaalassa ja Satakunnan keskussairaalassa toteutetun etenevän tutkimuksen tavoitteina oli selvittää tahdistinasennukseen liittyvien laskimokomplikaatioiden esiintyvyyttä ja niille altistavia tekijöitä Lisäksi tavoitteena oli selvittää ruokatorvianturilla tehdyn sydämen kaikukuvauksen (TEE) soveltuvuutta keskeisissä laskimoissa ja sydämen oikeassa eteisessä olevien tahdistinjohtoihin liittyvien hyytymien toteamisessa.

Aineisto ja menetelmät: Tutkimukseen otettiin 150 potilasta (61 % miehiä, keskim. ikä 67 v.), jotka tulivat ensimmäiseen pysyvän tahdistimen asennukseen. Potilasjoukkoa seurattiin 6 kk:n ajan ja kolmasosa osallistu lisäksi jatkoseurantaan. Keskeisin tutkimusmenetelmä oli laskimoiden varjoainekuvaus, joka tehtiin ennen tahdistimen asennusta, 6 kk asennuksesta ja 50 potilaalle runsaan 2 vuoden kuluttua. Varjoainekuvista mitattiin laskimoiden minimi- ja maksimiläpimitat sekä todettiin mahdolliset ahtaumat ja hyytymät. TEE-tutkimus tehtiin 66 potilaalle 6 kk:n kohdalla. Lisäksi kliinisen epäilyn perusteella tehtiin tarvittaessa diagnostinen selvittely keuhkoveritulpan tai syvän laskimotukoksen toteamiseksi. Laskimotapahtumien riskitekijöiden arviointia varten suoritettiin erillinen tapaus-verrokkitutkimus, jossa mukana olivat kaikki 6 kk:n seurannan aikana todetut päätetapahtuma-potilaat sekä kaltaistetut verrokit, joilla tapahtumaa ei ollut. Tapaus-verrokkitutkimuksen menetelminä käytettiin veren hyytymisaktiivisuutta ja verisuonen sisäkalvovauriota kuvaavia laboratoriotutkimuksia sekä vertailtiin asennustoimenpiteeseen ja potilaan sairaushistoriaan liittyvien taustatekijöiden yhteyttä laskimotapahtumiin.

Tulokset: Laskimon anatominen poikkeavuus todettiin 10 (7 %) potilaalla jo ennen tahdistimen asennusta. Varjoainekuvauksissa (6 kk) todettiin uusi ahtauma 19 (14 %) potilaalla (kaikki oireettomia), joista 5 oli täydellisiä tukoksia. Eteisvärinä ja ns. biventrikulaarisen tahdistimen asennus näyttivät altistavan ahtaumien synnylle. Pieniä ei-ahtauttavia hyytymiä todettiin 20 (14 %) potilaalla. Akuutti oireinen yläraajan laskimotukos kehittyi 1 potilaalle. TEE paljasti keskuslaskimotason hyytymän 6 (9 %) tutkituista. Keuhkoveritulppa diagnosoitiin 6 kk:n seurannassa 5:llä (3,3 %). Jokin laskimotapahtuma kehittyi 6 kk:n seurannassa kaikkiaan 47 (31,3 %) potilaalle. Lisäksi 2 vuoden seurannassa löytyi varjoainekuvauksessa 4 uutta täystukosta ja 1 ahtauma. Tapaus-verrokkitutkimuksessa mikään yksittäinen tekijä ei osoittautunut merkittäväksi päätetapahtuman ennustajaksi, mutta yleisesti tunnettujen laskimotukosten klassisten riskitekijöiden verrokkeja runsaampaa kasautumista todettiin tapauksilla. Laboratorioanalyysit osoittivat tahdistinasennuksen aiheuttavan merkittävän hyytymisjärjestelmän aktivoitumisen, mutta sen aste ei ennustanut myöhempien laskimotapahtumien ilmaantumista.

Johtopäätökset: Tutkimus osoitti tahdistimen asennuksen aiheuttavan varsin usein laskimovikoja (esiintyvyys ainakin 30 %). Valtaosa todetuista poikkeavuuksista oli kuitenkin oireettomia ja kliinisesti hyvänlaatuisia, mutta myös keuhkoveritulppia ilmeni. Laskimon täystukos voi haitata tahdistinjärjestelmän mahdollista myöhempää vaihtoa tai päivittämistä. Eteisvärinällä ja biventrikulaarisen tahdistimen asennuksella näytti olevan yhteyttä laskimoahtaumien syntyyn ja klassisten laskimotukoksen riskitekijöiden kasautuminen saattaa olla hyytymien ja ahtaumien yhdistetylle päätetapahtumalle altistava tekijä. Sen sijaan asennustoimenpiteeseen liittyvät tekijät eivät altistaneet yhteispäätetapahtumalle.

Avainsanat: haitat, sydäntaudit, tahdistimet, tromboosi

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ABBREVIATIONS

AF	Atrial fibrillation
BMI	Body mass index
CAD	Coronary artery disease
CI	Confidence interval
CVT	Central venous thrombi
DD	Plasma D-dimers
Dmax	Maximum venous diameter (venography)
Dmin	Minimum venous diameter (venography)
DVT	Deep vein thrombosis
F1+2	Plasma prothrombin fragment 1+2
FVL	Factor V Leiden mutation
ICD	Implantable cardioverter-defibrillator
ICV	Intravenous contrast venography
INR	International normalized ratio
LMWH	Low molecular weight heparin
LV	Left ventricle
LVEF	Left ventricular ejection fraction
NYHA	New York Heart Association
OR	Odds-ratio
PE	Pulmonary embolism
PM	Pacemaker
RA	Right atrium
SVC	Superior vena cava
SVCS	Superior vena cava syndrome
TEE	Transesophageal echocardiography
Tm	Plasma thrombomodulin
TRG	Tricuspid valve regurgitation gradient
TTE	Transthoracic echocardiography
TVO	Total venous occlusion
UEDVT	Upper extremity deep vein thrombosis
VTE	Venous thromboembolism
vWF	Plasma von Willebrand factor antigen

LIST OF ORIGINAL PUBLICATIONS

The study is based on the following publications, which are referred to in the text by Roman numerals (I–IV). Unpublished data is also included.

I Korkeila PJ, Saraste MK, Nyman KM, Koistinen J, Lund J, Airaksinen KEJ. Transesophageal echocardiography in the diagnosis of thrombosis associated with permanent transvenous pacemaker electrodes. Pacing Clin Electrophysiol. 2006;29(11):1245-1250.

II Korkeila P, Nyman K, Ylitalo A, Koistinen J, Karjalainen P, Lund J, Airaksinen KEJ. Venous obstruction after pacemaker implantation. Pacing Clin Electrophysiol. 2007;30(2):199-206.

III Korkeila P, Ylitalo A, Koistinen J, Airaksinen KEJ. Progression of venous pathology after pacemaker and cardioverter-defibrillator implantation: A prospective serial venographic study. Ann Med. 2009;41(3):216-223.

IV Korkeila P, Mustonen P, Koistinen J, Nyman K, Ylitalo A, Karjalainen P, Lund J, Airaksinen KEJ. Clinical and Laboratory Risk Factors of Thrombotic Complications after Pacemaker Implantation. A Prospective study. Europace, accepted for publication.

1. INTRODUCTION

The number of implanted cardiac pacing devices continues to grow worldwide as indications broaden and more patients gain access to these treatments. Novel insights to pathophysiology and new technologies have introduced device-based therapies to expanding patient populations such as those with severe left ventricular failure. Currently there are more than two million patients world-wide with an implanted permanent pacemaker (PM) or a cardioverter-defibrillator (ICD) [1]. This increased utilization of the pacing devices will also subject more patients to potential complications related to implantation procedures and indwelling transvenous leads. Eventually there will also be an increasing number of patients in whom an upgrade of the pacing system and/or replacement of the leads is warranted, which can be rendered considerably more difficult in the event of complications to the access vein, such as complete occlusion.

Central venous catheters and PM leads are known to predispose to thrombus and stenosis formation in veins [2-9]. Such lesions may impede extraction of old leads [2], give rise to pulmonary emboli [4, 5, 9, 10], induce superior vena cava syndrome [11, 12], impact on hemodialysis access patency [13] or, very rarely, even upper extremity gangrene [14]. Several methods of detecting thrombosis associated with PM or ICD leads have been described [9, 15-17]. Venous Doppler ultrasound has been utilized in some prospective studies in the diagnosis of venous lesions induced by PM leads [9, 16], but venography can be considered the gold standard [18]. Transesophageal echocardiography (TEE) may be useful in the detection of thrombosis in the superior vena cava (SVC) [19-21], and several case reports have described PM-related thrombi diagnosed by TEE [22-24]. However, systematic studies focused on the role of TEE in the diagnosis of electrode associated thrombosis are rare [25].

The incidence of venous obstruction and thromboembolism related to pacemaker therapy is somewhat unclear. There are several cross-sectional studies and case reports describing venous thrombosis and occlusion after permanent pacemaker lead implantation [4, 26-28], but fewer prospective studies have assessed the incidence of such lesions in patients implanted with PM [7, 8] or ICD [6, 25, 29].

Predisposing factors for venous thromboembolism (VTE) occurring after implantation of permanent transvenous pacing leads are not fully understood. Several previous studies were not able to ascertain any significant electrode-related risk factors for these events [2, 3, 6, 7], while other investigators have indicated an increased risk for thrombosis in patients with multiple leads [9]. All components of the classic Virchow's triad, i.e. injury to vessel walls, impairment of blood flow and hypercoagulability, may be involved in the pathogenesis of VTE after PM implantation. Lead placement itself, either by venipuncture or by dissection of the

access vein, inevitably causes some degree of venous endothelial injury, which can potentially be further exacerbated by continuous friction rub and irritation by the lead. The number and diameter of the leads, as well as the access route chosen for the implantation can potentially affect blood flow and introduce a degree of venous stasis. 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, but their role in pacemaker lead thrombosis is unclear.

This study aimed to assess the incidence and spectrum venous obstructive and thrombotic complications, both asymptomatic and symptomatic, after pacing device implantation in a prospective fashion and based on systematic venographies. A goal of the venographies was also to quantitate potential changes in venous diameters after transvenous lead placement. This study also aimed to identify potential predictors for the development of the end-point venous lesions from a wide range of clinical patient-related and implantation procedure-related parameters, as well to assess the degree of early implantation-induced trauma by utilizing laboratory assays reflecting endothelial injury and consequent hypercoagulation, and the potential association of the grade of injury with subsequent end-point venous lesions. Furthermore, we sought assess the feasibility of transesophageal echocardiography in the detection of central venous thrombi, and to determine the incidence of such thrombi diagnosed by TEE.

2. REVIEW OF THE LITERATURE

2.1. Pacemaker complications – a general perspective

The first successful pacing of a human patient using a transvenous endocardial electrode was accomplished in 1958 [30], and in 1959, the first published report came out describing two patients paced with transvenous electrodes for Stokes-Adams seizures [31]. These initial events launched an ongoing era of technological advancement in pacing generators, lead design and implantation techniques. The many new innovations and broadened indications have allowed increasing patient populations to benefit from implantable cardiac pacing devices. Like any form of therapy cardiac pacing comes with a price, the potential for complications is inherent with PM therapy. All physicians involved with a patient's therapy process, beginning from initial evaluation for pacing device indications and extending to eventual follow-up, should be well aware of the various possible untoward events related to the therapy. The potential for a complication is a concern especially for the implanting physician, who has to be focused not only on avoidance of these events but also on their recognition and treatment. Patients should also be informed both on the benefits as well as on the potential hazards of the therapy.

Complications were reported already in the first published series of 25 transvenously paced patients [32]. These adverse events included lead dislodgment and fracture, infection, electronic and pacemaker battery failure, but yet no thrombosis or thromboembolism. The first study published in English language on the incidence of venous thrombosis following long-term transvenous pacing is that of Dr. Stoney and co-workers published in 1976 [33]. Since then venous obstruction (VO) and VTE have been reported in multiple case studies and patient series, which, however, have been mostly retrospective or cross-sectional in nature [2, 3, 6-9, 16, 17, 25, 29, 34-44].

Complications related to pacing devices can be classified by their temporal occurrence to acute and delayed events, but the time course of the development of VO and VTE in PM patients has remained somewhat unclear. Upper extremity deep vein thrombosis (UEDVT) or pulmonary embolism (PE) can develop acutely in the immediate post-operative period after device implantation, but a more gradual delayed occlusion of the access vein is also know to occur.

TABLE 1. Prevalence and incidence of venous thrombosis and obstruction associated with pacemaker therapy in previous studies

Author	Reference	Year	N	Study type	Devices	Method(s)	Time from implant	Obstructed (%)	Total occlusion (%)	Baseline imaging
Stoney	[33]	1976	32	Cross sectional at replacement	PM	Venography	Mean 24 months	~ 80 %	21 %	No
Crook	[34]	1977	125	Retrospective, PM clinic	PM	Clinical, venography per clinical findings	3 – 60 months	2.4 %	2.4 %	No
Mitrovic	[36]	1983	100	Cross sectional, PM clinic	PM	Venography	44 + 10 months	39 %	15 %	No
Antonelli	[2]	1989	40	Prospective, new PM implantation	PM	Venography (3 times)	1-6, 12-18 and 18-24 months	35 % (overall)	8 %	No
Zuber	[16]	1998	56	Cross sectional, setting not disclosed	PM	Clinical and ultrasonography	41 + 45 months	57 %	11 %	No
Celiker	[40]	1998	52	Cross sectional, setting not disclosed	PM	Nuclear venography	67.0 + 47.5 months	32 %	5.7 %	No
Goto	[3]	1998	100	Cross sectional at replacement	PM	Venography	6.0 + 1.4 years	23 %	12 %	No
de Cock	[17]	2000	48	Retrospective, PM clinic	PM, 2 vs. $\geq$3 leads	Clinical and TTE	7.4 + 2 years	17 %	5 %	No
Sticherling	[6]	2001	36	Cross sectional at replacement	ICD	Venography	45 + 21 months	50 %	3 %	No
Do Carmo da Costa	[8]	2002	202	Prospective, new PM implantation	PM	Venography	6 months	64 %	6 %	No
Oginosawa	[7]	2002	131	Prospective, new PM implantation	PM	Venography	Baseline and 44$\pm$6 months (60%)	33 %	12.6 %	Yes
Bracke	[41]	2003	89	Cross sectional, lead extraction	PM, ICD	Venography	72.1 $\pm$ 59.0 months	Not available	25 %	No
Chow	[45]	2003	220	Cross sectional	ICD	TEE	120 $\pm$ 213 days	Lead-thrombi: 33%	Obstructions: no data	No
van Rooden	[9]	2004	145	Prospective	PM	Doppler ultrasonography	Baseline, 3, 6 and 12 months	23.4 %	2.7 %	Yes
Lickfett	[29]	2006	105	Cross sectional at replacement	ICD	Venography	47 $\pm$ 12 months	25 %	9 %	No
Haghjoo	[44]	2007	100	Cross sectional, system revision/upgrade	PM or ICD	Venography	8.09 $\pm$ 4.48 years	26 %	9 %	No

2.2. Epidemiology of venous obstructive and thromboembolic complications in pacing device therapy

The rate of VO (partial and/or complete) after PM implantation averages to approximately 36 % (range 2-80 %) from all of the previously published studies (total combined N=1581 patients), and that of total venous occlusion (TVO) to 10 % (range 2-25 %) (Table 1) [2, 3, 6-9, 16, 17, 25, 29, 33, 34, 36, 40, 41, 44]. However, the majority of these studies have been cross-sectional in nature as they were conducted in conjunction with system replacement or upgrade, and only a few have been prospective [7-9]. As some patients may have venous anomalies and obstructions present already before PM placement [46], a baseline evaluation of the access veins prior to device implantation, preferably by venography, should be incorporated into a study assessing the incidence of lead-induced new lesions. A baseline venous evaluation was conducted in only 2 of the previous studies [7, 9]. However, in one of these the data is lacking on follow-up venograms, which were not performed systematically in all patients [7], and the other was based mainly on a clinical evaluation and Doppler ultrasound rather than venography, which was conducted only in a part of the study population [9].

Several studies following patients with various implanted PM and ICD types have been conducted to address the rate of complications in general, and not specifically the incidence of venous adverse events, but have reported acute cases of symptomatic thrombosis. One of these was an early study of ICD experience by Marchlinski et al in 1986, in which 1 of 33 (3 %) patients developed an acute UEDVT [37]. In another study of ICD patients (n=170) 3 cases (1.8 %) developed acute subclavian thrombosis, confirmed by Doppler imaging [38]. In a randomized multicenter study of VVIR vs. DDDR pacing in the elderly (age $\geq$ 65), implantation-related complications included 2 (0.5 %) patients with an acute subclavian vein thrombosis 7-14 days postoperatively [39]. One (1 %) patient developed acute symptomatic UEDVT in a study of DDD pacing for prevention of recurrent vasovagal syncope [42].

Post-mortem data on transvenous leads and thromboembolic events is scarce, and mostly limited to small series of cases [47-50]. Investigators in Malmö, Sweden, have conducted studies on cardiovascular pathology and mortality risks based on data from systematic autopsies performed according to a standardized protocol [43]. During a period from 1970 and 1982 a total of 28196 deaths occurred in the Malmö area, and the overall autopsy rate was 88 %. The autopsies revealed intracardiac thrombus formation in 7.2 % of the cases, 38 % of which also had manifest PE. When the intracardiac thrombus was located in the right ventricle, the rate of concomitant PE was 55 %. Out of all patients with any form of thrombus 3.7 % had a pacemaker vs. 1.0 % of patients with no thrombus ($p<0.001$). However, in nested case-control analysis no significant difference in PE rate was found between thrombosis patients with (27.0 %) or without (38.3 %) a pacemaker electrode (P=0.085). In another post-mortem study conducted on PM-leads partial or complete fibrous encapsulation was found encircling the venous portion of the electrodes in all leads [50].

In Finland, there are no previous studies conducted in PM patient material specifically addressing thrombotic or venous complications. One report provides details from very early experience with implantable PMs [51]. This was a series of 100 patients (devices implanted between 1961 and 1967) with either epicardial electrodes placed in thoracotomy (n = 70) or transvenous ventricular leads (n = 30). All patients had a transvenous temporary pacing lead inserted prior to implantation. No systematic search for thrombi had been conducted, but at implantation 3 (3 %) patients were diagnosed with asymptomatic thrombosis in the axillary or jugular vein (probably secondary to the temporary lead). No apparent PE was seen, although very little data was presented from post-operative follow-up period. Another early study of permanent PM experience comes from Turku University Hospital [52]. This retrospective study presents complications and follow-up data on 90 patients all of whom had transvenous permanent electrodes implanted. One patient died from autopsy-proven massive PE during the first post-operative month, but the authors did not attribute this to PM therapy. Otherwise no mention of any search for signs or symptoms of VTE is provided in the report. Data from more modern era is provided by Kiviniemi and co-workers (1999) in their retrospective assessment of 446 patients with an implanted permanent PM [53]. Again, patients had not been systematically evaluated for symptoms or signs of VTE. However, 1 (0.2 %) patient was diagnosed with acute UEDVT ipsilateral to the implanted device. Apparently, during late follow-up, no clinically evident cases had been encountered.

2.3. Clinical presentation of thromboembolism in pacemaker-patients

Temporally thrombus formation in vivo can be both an acute and a chronic process [54], and VTE in the paced patients can thus present as an acute and highly symptomatic event, or develop more gradually with perhaps only subtle or even no symptoms. Thrombus formation causing symptoms has been described at multiple locations from the veins of the upper extremity to the cardiac chambers, and in some patients thrombosis leads to embolic events. Clinically symptomatic VTE in patients with pacing devices can be divided into three main types (which may coexist): UEDVT, the superior vena cava syndrome (SVCS), and pulmonary embolism (PE). Intracardiac thrombi are not typically symptomatic per se, but can embolize into the pulmonary circulation. On occasion, thrombosis has been discovered in unusual locations or associated with systemic embolization, as detailed below.

UEDVT typically presents with swelling and pain in the affected limb, often with erythema and/or cyanotic discoloration. A delayed slowly developing occlusion may develop with little or no subjective discomfort, but may exhibit edema and dilated collateral veins on the skin [55, 56]. Clinical diagnosis of UEDVT is rather non-specific, and its prevalence is 50 % among patients exhibiting the suggestive upper extremity symptoms [57]. Of all symptomatic cases of DVT, only approximately 1-4 % involves the upper extremities [58, 59], although asymptomatic cases are likely to be much more prevalent [57]. In various studies UEDVT has lead to pulmonary embolism in 4-30 % of

the patients [55, 57, 60, 61], and it has been associated with increased mortality, although this association does not appear to be a causative one [62]. Acute symptomatic UEDVT after PM or ICD implantation has been described to occur usually soon after the implantation procedure (within days or some weeks) [38, 39]. Both temporary and permanent transvenous pacemaker leads may induce symptomatic UEDVT as is illustrated in the many case studies reported in the literature [26, 27, 63-65]. One of the earliest studies addressing the incidence of symptomatic subclavian vein thrombosis among PM-implanted patients was that of Williams et al (1978) which found an incidence of approximately 2 % [35]. Other investigators have reported similar rates (1.8-2.6 %) of upper extremity symptoms or clinical findings of venous occlusion in PM-patients [8, 9, 16, 34]. Yet, in one prospective study, all (100%) patients, who were found to have obstructive lesions in follow-up venograms, were asymptomatic [7]. In lead extraction material, the incidence of symptomatic occlusions may be higher, and 8 % of the patients developed new symptoms of venous thrombosis in one series of lead extractions using laser sheaths [66].

Obstruction of the superior vena cava (SVC) associated with a transvenous electrode may result from venous thrombosis, venous fibrotic constriction, or both. Thrombosis in the absence of coexistent stenosis tends to occur early [67], whereas in clinically apparent cases occurring at least one year after implantation, there is typically new thrombus formation present on chronic fibrous stenosis [68]. SVC stenosis most often develops at a site just above the right atrium [68]. A characteristic constellation of symptoms and clinical signs in conjunction with SVC obstruction is called superior vena cava syndrome (SVCS). Malignancy is the most common cause (60 %) of this condition, but the majority of the benign cases are caused by indwelling central catheters or pacing leads [69]. The condition is potentially lethal as it may, although rarely, be complicated by PE [70-73]. SVCS is a rare event among patients with transvenous pacing leads, although several case studies have been presented in the literature [4, 68, 74]. Prevalence rates have varied from 3 in 10 000 [75] to 4 in 1000 [76] in retrospective series of large numbers of pacemaker patients. No cases of SVC obstruction were encountered in two prospective venography-based follow-up studies of consecutive patients (n=100-229) implanted with pacemakers [7, 8]. In a series of patients scheduled for replacement of their first ICD 3 (2.9 %) of 105 patients were found to have venographic SVC obstruction, ranging from mild to complete [29]. Difficulties arise at PM implantation when an incidental SVC obstruction is encountered in an asymptomatic patient [77, 78].

PE has a relatively high prevalence both in the hospital and in the community, and it is associated with significant morbidity and mortality [79]. The vast majority of the cases arise from DVT in the lower extremities, but in some individuals the initial thrombus may form in the upper extremity veins [10]. Multiple risk factors for PE have been identified [80, 81], but approximately 25 to 50 % of the emboli cannot be readily explained [80, 82]. Recently published data suggest that a significant portion of these emboli may arise within the right heart chambers [43]. Multiple case studies have been published in which PE was found in conjunction with a pacing lead-associated

thrombus [22, 83, 84], but no systematic data is available on the incidence of PE among recipients of permanent cardiac pacing devices. Clinical experience suggests that symptomatic PE is infrequent and that fatalities from PE are very rare in the PM-patient population. Pacing devices did not emerge as major contributors to mortality from PE in a population based autopsy study on thromboembolism in Sweden [43]. However, in a prospective study, 6 (2.6 %) of 229 PM-patients developed symptomatic PE, which was fatal in 3 (50 %) cases [8]. In a community study of PE risk factors, placement of a central venous catheter or transvenous pacemaker lead accounted for a similar proportion (9 %) of venous thromboembolism as trauma (12 %) and congestive heart failure (10 %) [80]. On the other hand, unrecognized clinically silent PE may occur under various circumstances [43, 85, 86], and it could conceivably be relatively common also after cardiac pacing device implantation.

In addition to UEDVT, PE in PM-patients could potentially be a consequence of central venous thrombosis. Several case studies have been published on PM lead-associated thrombi in the right atrium (RA). Some of these lesions were found coincidentally [87, 88], and others in association with pulmonary embolism [28, 83, 89]. However, systematic searches of central venous thrombosis in PM patients are scarce: in one study 185 consecutive patients with an ICD underwent transesophageal echocardiography (TEE), which revealed lead-attached thrombi within RA in 19 % of the patients, and at SVC-RA junction in further 8 % [25]. However, thrombi within the right ventricle (RV) were found in only 1.6 % of the patients. Partially this may be due to the fact that the diagnosis of thrombus formation in the RV can be more difficult. Population-based autopsy data have shown that thrombi are as common in the RV as in the left ventricle, but RV thrombi remain more often clinically undetected [43]. In this post-mortem analysis (n=23796) a PM was present in 8.5 % of the cases with thrombosis in RV.

Case reports have described thrombi in unusual locations and unique clinical presentations in isolated patients with implanted pacing devices: coronary sinus [90], external [91] and internal [92] jugular veins, the inferior vena cava [93-95], and even a thrombus-induced case of Budd-Chiari syndrome [96]. In a population-based multicenter retrospective cohort study, transvenous PM leads were found to be an independent predictor of systemic thromboembolic events among patients with intracardiac shunts (HR 2.6; 95 % CI 1.1 - 6.2; p=0.0265) [97]. Cases of paradoxical cerebral embolism have been suspected to occur as a consequence of a thrombosed pacing lead also in the presence of an undiagnosed atrial septal defect [98].

2.4. Pathophysiology of venous thromboembolism in pacemaker patients

The mechanism of PM lead-associated thrombus formation is likely to be multifactorial and presumably involves all components of the classic Virchow's triad introduced in the 19th century: injury to vessel walls, impairment of blood flow (stasis) and hypercoagulability [81]. 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 electrodes over time [99]. Even an attempted pacemaker implantation may lead to venous injury and occlusion [100], and it has been demonstrated, that a surgical procedure by itself induces a hypercoagulable state, even without apparent venous thrombosis [101]. Thrombin formation is the key event in blood clotting. It is generated when prothrombin is cleaved into two peptides, the active thrombin and the prothrombin fragment F1+2 [102]. Thrombin then cleaves fibrinogen to fibrin and plasma D-dimers (DD), which as one of fibrin degradation products can be used as a laboratory measurement of fibrin formation and breakdown [103]. F1+2 is a specific marker of thrombin formation, and its plasma level can be utilized as an index of coagulatory activity.

The vascular endothelium plays a pivotal role in thrombogenesis. Injury to blood vessel endothelium causes expression of tissue factor on the endothelial surface, which triggers the coagulation system. Injury also induces a release of various cytokines and adhesion molecules, which in turn favor hypercoagulability of blood [104]. In PM-patients, the complexity of the implant procedure, the choice of venous access and the number of implanted leads are likely to be key- factors affecting the degree of endothelial injury sustained during implantation, and chronic friction rub in the later phase. Methods to assess the degree of endothelial injury include measuring the levels of plasma von Willebrand Factor (vWF) and thrombomodulin (Tm). Endothelial cells and megakaryocytes synthesize vWF, a plasma glycoprotein, which has an important role in plug formation at a site of endothelial disruption, and it also protects plasma factor VIII from degradation. vWF has been utilized as a plasma marker for endothelial damage, despite its poor specificity [105]. Tm, a membrane protein expressed on the surfaces of endothelial cells, functions as a cofactor in the anticoagulant pathway by amplifying the thrombin-induced activation of protein-C. Soluble Tm in plasma can also be used as a biomarker for vascular damage [106, 107].

The indwelling leads occupying venous luminal space in PM-patients could potentially introduce some stasis into the venous flow. Also, certain underlying disease conditions can affect the rate of central venous blood flow, such as congestive heart failure and atrial fibrillation. A link between stasis and local endothelial activation could be hypoxemia of the endothelium, which derives its oxygen directly from the blood in the vessel lumen. Ischemia can rapidly activate the endothelium and thus convert it procoagulant by expressing cell adhesion molecule P-selectin, which allows an interaction of platelets and tissue-factor-containing circulating microparticles to initiate and promote coagulation [108-110].

In addition to coagulation, other types of pathology may also be involved in the development of the venous lesions seen in PM patients. In some cases the main mechanism is likely to be the activation of the coagulation cascade, whereas in others a fibrotic encroachment of the vessel wall may predominate.

2.5. Risk factors of venous thromboembolism and obstruction in the paced patients

VTE is a relatively common event in the general population and especially among hospitalized patients [111]. The incidence of DVT in the Finnish population has been estimated to be 1.4 per 1000 person-years with a life-time prevalence of 3.1 % [112]. Patients implanted with a pacing device are subjects to the same common risk factors for VTE as the general population, in which the major risk factors include prolonged immobilization, malignancy, acute myocardial infarction, congestive heart failure, major general and orthopedic surgery, spinal cord injury, and major trauma [81, 111, 113-115]. Conditions that are also associated with increased risk, but whose presence alone is not usually sufficient grounds to warrant prophylactic therapy, include prior venous thromboembolism, advanced age ($\geq$ 75 years), obesity, varicose veins, pregnancy and puerperium, oral contraceptives and acquired or hereditary thrombophilia [81, 111]. There is an independent association between increasing age and a higher risk of VTE [116-121]. Data on the influence of sex on the incidence of a first episode of VTE is somewhat conflicting, but the overall incidence seems to be similar between men and women [122]. Male sex has been shown to be associated with increased risk of VTE by some investigators [123], although others have found evidence of female predilection [117-119].

Several inherited or acquired coagulations defects have been identified [124, 125]. Congenital and acquired hypercoagulable states (thrombophilia) are a result of an imbalance between the anticoagulant and prothrombotic activities of plasma where the prothrombotic activities predominate [126]. In addition to the thrombophilic state, an environmental element, such as injury or immobility (stasis), is usually required for coagulation to occur in these patients [127]. Relatives of patients with hereditary coagulation defects are carriers of the same defects at approximately 50 % likelihood [127], and are thus faced with an increased risk for VTE. In Factor V Leiden (FVL) a point mutation (Arg506Gln) in the encoding gene of FV in the affected individuals renders the activated form of FV resistant to the proteolytic action of activated protein C (APC), which in turn is a major natural anticoagulant. FVL is the most common of the inherited thrombophilias: 3-8 % of Caucasians are heterozygous for the defect, and 1/1000 are homozygous [128]. One study found APC resistance in 17 % of Finnish patients with venous thrombosis, 83 % of whom had a mutation in FV gene [129]. This study also found a prevalence of 3.6 % for FV gene mutation in the Finnish population. Among patients with inherited thrombophilias the highest incidence of VTE is seen in the carriers of antithrombin deficiency and the lowest in individuals with the Factor V Leiden mutation, despite its higher prevalence in the population [130, 131].

TABLE 2. Risk factors of venous thrombosis and occlusion associated with pacemaker therapy in previously published studies

Author	Year	N	Study type	Devices	End-point lesions	Parameters assessed	Identified risk factors
Antonelli[2]	1989	40	Prospective, new PM implantation	PM	Venous Obstructions	lead insulation and polarity, venous route of entry	None
Celiker[40]	1998	52	Cross sectional, setting not disclosed	PM	Venous Obstructions	age, gender, mean time after implant, side and route of access, number of leads, diameter of lead body	Mean diameter of lead body (only in patients with single leads), silicone lead insulation
Goto[3]	1998	100	Cross sectional at replacement	PM	Venous Obstructions	number of leads, total combined diameter of leads, route of access, type of lead insulation, pacing mode, use of antithrombotic medications	None
Sticherling[6]	2001	36	Cross sectional at replacement	ICD	Venous Obstructions	number of implanted leads, age, sex, LVEF, age of the implanted lead, venous access route, treatment with warfarin, lead insulation, maximum lead diameter, presence of contralateral PM-leads	None
Do Carmo da Costa[8]	2002	202	Prospective, new PM implantation	PM	Venous Obstructions	age, race, sex, underlying cardiac disease, functional class of congestive heart failure (NYHA), echocardiographic LVEF, venous access to lead implant, number of leads, lead material, lead calibre, previous use of a transvenous temporary pacing electrode	LVEF < 40 %, previous use of a transvenous temporary pacing electrode
Oginosawa[7]	2002	131	Prospective, new PM implantation	PM	Venous Obstructions	age, sex, hypertension, smoking, diabetes mellitus, hyperlipidemia, atrial fibrillation, cardio-thoracic ratio on chest X-ray, left atrial dimension, left ventricular ejection-fraction, indication for PM implantation, number and body size of leads, duration of follow-up	None
Bracke[41]	2003	89	Cross sectional, lead extraction	PM, ICD	Venous Obstructions	age, time from oldest lead implant, and indications for lead extraction, device type, number of implant procedures per patient, number of implant procedures per entry site, lead number	Systemic infection
Chow[25]	2003	220	Cross sectional	ICD	Central Venous Trombi in TEE	age, gender, underlying cardiac disease, antithrombotic medications, LVEF and echocardiographic dimensions, tricuspid regurgitation, RV systolic pressure, lead insulation, number of leads, lead placement, mean time from implant	Absence of warfarin anticoagulation, polyurethane lead insulation

Table 2. Continued

Author	Year	N	Study type	Devices	End-point lesions	Parameters assessed	Identified Risk Factors
Lickfett [29]	2004	105	Cross sectional at replacement	ICD	Venous Obstructions	previous implanted pacing devices and leads, lead number and insulation material, fixation mechanism, number of incorporated shocking coils, site of implantation,	Previously implanted PM, single ICD lead with second shocking coil in SVC
van Rooden [9]	2004	145	Prospective	PM	Venous Obstructions	Medical history, age, height, weight, BMI, BP, smoking status, presence of Factor V Leiden/Prothrombin G20210A mutation, Factor VIII/C activity, family history of thrombosis, PM device type, number of leads, implantation side	Personal history of DVT, absence of anticoagulant therapy, female hormone use, multiple vs. single lead,
Bar-Cohen [132]	2006	85	Cross-sectional, PM update or replacement	PM or ICD	Venous Obstructions	Total lead diameter, maximum number of leads, lead index (lead cross-sectional area divided by BSA at the time of implant), sex, age, weight and BSA at implantation, weight and BSA change at venograms, indications for device, pacemaker vs. ICD, prior cardiac surgery, side of lead implantation	None
Haghjoo [44]	2007	100	Cross sectional, generator change, lead revision, or device upgrade	PM or ICD	Venous Obstructions	age, sex, baseline rhythm, associated cardiovascular diseases, LVEF, cardiothoracic ratio, indication for endovenous device implantation, type of device (PM vs. ICD), total lead duration, insulation material, site of implantation, route of entry, device manufacturer, number of leads, history of antiplatelet/anticoagulant therapy, presence of dilated cardiomyopathy	univariate predictors: multiple leads, presence of dilated cardiomyopathy, absence of anticoagulant or antiplatelet therapy. Multivariate analysis: number of the leads and absence of anticoagulant or antiplatelet therapy

Several groups of investigators have attempted to elucidate risk factors for VTE among patients implanted with cardiac pacing devices, but the majority of these studies did not find any significant predictors of venous thrombosis or obstruction (Table 2). Lead number or other indicators of lead burden were not significantly associated with thrombosis in the majority of the studies, with the exception of one [9]. The presence of a temporary lead was a significant predictor in one study [8], and a previous permanent PM before ICD implantation was a risk factor in another study [29]. Route or side of access or other implantation-related factors were not predictive of thrombosis in any of the studies, and only one found a significant association between lead insulation material and thrombosis, which was more frequent with polyurethane coating in that series [9]. Three studies have found the absence of anticoagulation with warfarin to be predictive of thrombosis [9, 25, 44], and one found a significant association with female hormone use as well as with a personal history of previous venous thrombosis [9]. Infection appears to be a significant promoter of occlusion based on lead extraction experience [41].

2.6. Summary of the literature review

The complications of pacemaker therapy include obstructive venous lesions and thromboembolic events. Based on available data these complications may affect as many as one third of the patients, although symptomatic and clinically apparent cases are much less frequent. However, the reliability of these epidemiological data is hampered by the scarcity of prospective studies based on venography, the gold-standard of venous imaging, and by the lack of baseline assessment of venous patency prior to device implantation. The exact pathophysiology of venous complications remains unclear, but is likely to be multifactorial, and to involve each of the three components of the classic Virchow's triad: injury, stasis and hypercoagulation. Some of the previous studies have suggested certain identifiable risk factors for VTE in PM patients, but the data are conflicting.

3. PURPOSE OF THE STUDY

In this prospective study on pacing device-implanted patients we sought to determine:

1. The incidence of venous stenosis and complete occlusion by venography
2. Quantitative changes in venous calibers after lead implantation
3. The incidence of central venous thrombi by transesophageal echocardiography
4. The incidence of symptomatic venous thromboembolism
5. The time course of the development of venous obstruction
6. Clinical, procedural and laboratory predictors of venous obstruction and thromboembolism

4. MATERIAL AND METHODS

4.1. Material

4.1.2. Main study population

The study was conducted at two centers: Turku University Hospital (Turku, Finland) and Satakunta Central Hospital (Pori, Finland) between which patients were enrolled at a ratio of 2 to 1. All consecutive adult patients scheduled for an implantation of their first permanent PM or ICD and without contraindications for venography (known allergy to radiographic contrast dye or iodine, significantly reduced renal function, or uninterrupted metformin treatment) were eligible for the study. An informed, written consent was obtained from all patients willing to participate. The recruitment of study-patients was initiated in November 2003, and completed in February 2005, when a total of 150 patients were enrolled (Table 3). Intravenous contrast venographies formed the basis of the study, and was aimed to be performed on all 150 patients (study II), and several sub-groups were formed as detailed below and in Figure 1.

Study protocol imposed no changes to device implantation procedures, which were 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 operator in charge of the procedure.

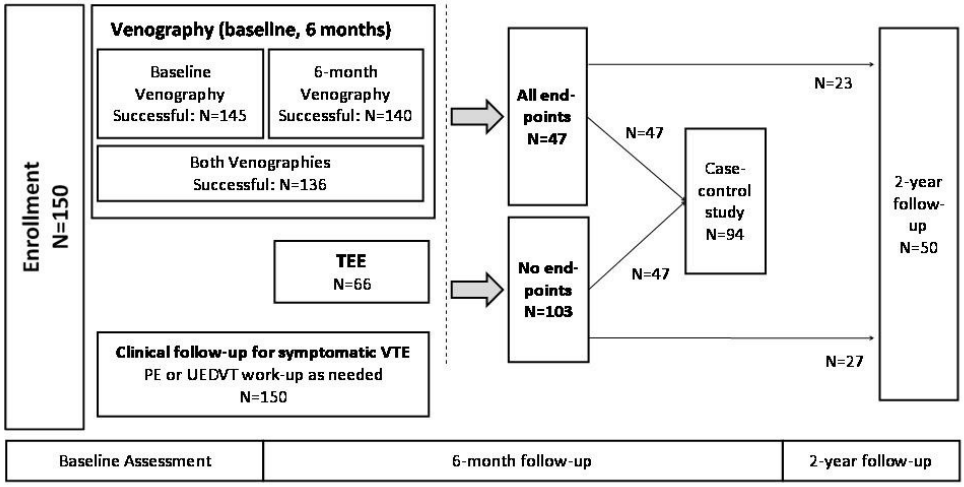

Figure 1. Enrollment of study patients and formation of sub-groups.

Table 3. Baseline demographics and clinical features of the study group (N=150).

Center	All patients N=150		TYKS N=101		SatKS N=49		p*
Age †	66.8 (28–94) ± 12.3		65.1 (28-91) ± 12.7		70.4 (37-94) ± 10.7		0.01
BMI †	28.0 (18–44) ± 5.0		27.6 (17.9-43.8) ± 4.8		28.0 (21.0-38.6) ± 4.2		0.376
	N	%	N	%	N	%	
Gender, male	91	60.7	67	66.3	24	49.0	0.051
Age 75 or higher	43	28.7	24	23.8	19	38.8	0.082
Obese (BMI ≥ 30)	31	20.7	19	18.8	12	24.5	0.519
Current smoker	12	8.0	10	11.6	2	4.1	0.210
Diabetes mellitus	20	13.3	14	14.0	6	12.2	1.00
Hypertension	37	24.7	22	21.8	15	30.6	0.312
Coronary artery disease	50	33.3	30	30.0	19	38.8	0.354
History of MI	23	15.3	16	16.0	7	14.3	1.00
PCI	14	9.3	11	10.9	4	8.2	0.550
CABG	14	9.3	9	8.9	5	5.6	0.773
Atrial fibrillation/ flutter (AF)							
AF at implantation	29	19.3	18	17.8	11	22.4	0.515
Past AF, current SR	17	11.3	7	6.9	10	20.4	0.025
History of stroke	9	6.0	5	5.0	4	8.2	0.477
Valvular heart disease	24	16.0	16	16.7	8	16.3	1.00
Mechanical heart valve	4	4.0	3	3.0	1	2.0	1.00
CHF or dilated CM	18	12.0	10	9.9	8	16.3	0.289
History of DVT and/or PE	4	4.0	4	0	0	0	0.304
NYHA class ‡							
II or less	111	74.0	79	88.8	32	69.2	0.009
> II	24	16.0	10	11.2	14	30.4	0.009
Temporary pacing lead	2	1.3	2	2.0	0	0	1.00

* Comparison between centers † mean, range , standard deviation ‡ data missing, N=15

ASD = atrial septal defect , BMI = body mass index , CABG = coronary artery bypass grafting, CM = cardiomyopathy, DVT = deep vein thrombosis, MI = myocardial infarction, NYHA = New York Heart Association, PCI = percutaneous coronary intervention, PE = pulmonary embolism, SatKS = Satakunta central hospital, SR = sinus rhythm, TYKS = Turku University hospital

4.1.3. Patient groups in sub-studies

4.1.3.1. Transesophageal echocardiography study group:

Patients (n=101) at Turku University Hospital were considered for transesophageal echocardiographic evaluation of the pacemaker leads (study I). Consent to perform TEE at 6 months post device implantation was initially obtained from 85 (84 %) of the 101 patients enrolled in this center. During the follow-up period 12 (14 %) patients withdrew their consent, and TEE could not be completed in 7 (8 %) patients due to patient's inability to swallow the probe or feeling unwell at the time of the examination. Thus, the final TEE-study group consisted of 66 individuals.

4.1.3.2. Venographic study group:

The main method of the study project was intravenous contrast venography aimed to be performed serially at baseline and at 6 months on all 150 patients (study II) in order to assess venous patency after PM implantation. A successful baseline ICV was available in 145 (96.7 %) patients, and the 6-month ICV was successful in 140 patients (93.3 %). Reasons for ICV-drop-outs are detailed in chapter 5.2.1.1. - Success of venographic studies. The group of patients (N=145) with a successful baseline ICV was entered into an analysis of the incidence of baseline venous abnormalities, whereas determination of a new obstructive lesion at 6 months mandated a successful ICV both at baseline and at 6 months (see 4.3.3.3.). Both baseline and 6-month venograms were available in 136 patients (91 %), and the incidence of new venous obstruction was determined from this group (Figure 1).

4.1.3.3. Case-control study group:

For the case-control analysis (study IV), all patients (n=47), who developed lead-thrombosis, intracardiac thrombus, pulmonary embolism, or venous obstructive lesions during the first 6 months of follow-up, were selected. One control without any VO or VTE was assigned to each of the cases (n=47). The controls were matched by age ($\pm$ 5 years), sex and lead number. Matching by age was successful in 97.8 % and by sex in 95.7 %. However, matching by lead number was exact in 51.1 %. There was a one-lead difference in 44.7 %, but no difference in the mean number of leads between case and control groups (1.74 vs. 1.73, p = NS). In order to assess the effect of lead burden (lead number and total combined lead diameter) on the development of end-point lesions, a further comparison was made between the cases (n=47) and the rest of the initial base study group (n=103) free of end-point lesions, as matching by lead was used in the selection of the control group precluding case-control analysis of this aspect. Also, an ad hoc subgroup of major end-points was formed including all cases (n=9) with PE, venographic total occlusion or acute symptomatic upper

extremity thrombosis in order to search for potential predisposing factors for these clinically significant lesions.

4.1.3.4. Long-term follow-up group:

For the long-term follow-up (study III), we aimed to restudy half of the 150 patients who participated into the 6-month follow-up. Thus, 75 patients were initially aimed for the follow-up beyond the first 6 months. The selection was conducted in two cohorts: 1) all patients with venographic abnormalities at 6 months in order to evaluate the long-term fate of the lesions and 2) a sample of patients with no venographic abnormalities at 6 months. However, 25 patients in total were excluded or dropped out due to following reasons: death (n = 5), refusal to participate (n = 6), elevated creatinine (n = 1), an allergic reaction from previous venography (n = 1), current in-patient treatment for unrelated serious disorders (n = 3), and logistic difficulties due to geographical distance (n = 6). Further 2 patients were excluded due to a failure of obtaining a venous access for venography, and one patient due a technical failure of the digital storage of the venography. Thus, a total of 50 patients (mean age 66.5 years, 55 % males) were included into the final long-term follow-up analysis. Among these 50 patients the previous 6-month ICV had shown new venous abnormalities in 23 cases (46 %), and in the remaining 27 (54 %) the findings were unchanged compared to baseline ICV. The former group includes patients with venous stenosis (n=7), total occlusions (n=3), and small non-occlusive thrombi (n=13). Implanted device types were 30 (60 %) dual chamber, 8 (16 %) single chamber, 5 (10 %) biventricular pacemakers (number of leads: 2-3, mean 2.4), and 7 (14 %) ICDs (number of leads: 1-2, mean 1.3). The long-term follow-up visits and venographies were conducted at a mean of 2.4 $\pm$ 0.3 years after the device implantation.

4.2. Consent and ethical issues

All patients gave their written informed consent before participating in the study. The study was conducted according to the principles of the Declaration of Helsinki and the study protocol was approved by the Ethics Committee of the Hospital District of Southwestern Finland.

4.3. Methods

4.3.1. Clinical evaluation

At baseline, the patients were interviewed and their charts were reviewed for previous medical and surgical history as well as for potential contraindications for venography. Data was collected on classic patient-related risk factors for VTE (obesity, congestive heart failure, age $\geq$ 75, previous VTE, history of cancer, and hypertension). Data on all active cardiovascular and antithrombotic medications was collected. Patients were instructed to contact the investigators if symptoms of dyspnea, chest pain, pain and/or swelling of the upper extremity occurred during the follow-up period. Characteristics of the implanted leads, devices and implantation methods were recorded in detail.

All follow-up visits included an interview of the patients' symptoms, and a chart review for possible PM-related and other outpatient or inpatient hospital treatments, and current cardiovascular and antithrombotic medications. Special attention was paid to potential symptoms located in the implantation area and in the ipsilateral upper extremity as well as to cardiac and respiratory symptoms. Physical examination at 6 months included an inspection of possible superficial venous collaterals and swelling of the upper extremity or neck.

4.3.2. Electrocardiography

Standard 12-lead electrocardiograms were obtained at baseline prior to device implantation and at 6-month follow-up visits. The patients' baseline cardiac rhythm was determined from these tracings.

4.3.3. Venography

4.3.3.1. Timing of venographic studies:

Intravenous contrast venographies (ICV) were performed at baseline and 6 months after pacing device implantation. A subgroup of patients was selected for a late venography conducted approximately two years after pacing device implantation (Table 4).

4.3.3.2. Venographic technique:

ICV was performed via an intravenous cannula inserted into the medial antecubital vein ipsilateral to the side of the device. In order to calibrate images for subsequent diameter measurements, a section of radio-opaque tape measure or a standard-length steel rod was placed on the skin overlying the imaged area as a measurement reference standard. A single 20 ml bolus of radiographic contrast dye (Hexabrix ®, Guerbet,

Roissy, France) was injected to image an area including the veins from proximal sections of upper extremity veins to the superior vena cava (SVC). During venography patients were instructed to breath quietly without breath-holding to avoid the Valsalva effect. The ICVs were obtained in a single plane (anterior-posterior), and stored on CD-ROM- discs for subsequent analysis and measurements. All ICVs were conducted in equal fashion.

Table 4. Study Methods and the number of patients studied by each method (% of 150)

Intravenous Contrast Venography	**N**	**%**
Successful at baseline	145	96.7
Successful at 6 months	140	93.3
Both successful	136	90.7
2 Years	50	33.3
Echocardiography		
Transesophageal at 6 months	66	44
Transthoracic		
Baseline	104	69.3
6 months	149	99.3
Nuclear Ventilation-perfusion Scan *	16	10,7
Venous Doppler Ultrasonography*		
Upper extremity	1	0.7
Lower extremities	3	2.0
Laboratory Assays (case-control)		
Coagulation and endothelial activation (baseline,1. postop.day)	94	62.7
Thrombophilia tests (baseline,6 months)	47	31.3
* Conducted during 6 month follow-up as needed per symptoms		

4.3.3.3. Venographic analysis:

Freeze-frame images with complete opacification of the lumen by contrast dye were selected for measurements. At baseline, the narrowest and widest points of the target vessels for lead placement were identified by visual inspection to obtain minimum (D_{min}) and maximum (D_{max}) venous diameters, and measurements from two to three individual calibrated frames were averaged to express the final diameters (Figure 2). A publicly available digital image measurement software program (ImageJ®, U.S. National Institute of Health) was utilized. Diameter measurements were repeated from the same venous segments in the follow-up ICVs in identical fashion. Baseline

venographies were also analyzed for potential obstructions and malformations. All diameter measurements were conducted by a single investigator (thesis author), and all images with potential anomalies and thrombi at baseline and at 6 months were interpreted by two investigators (thesis author and supervisor)

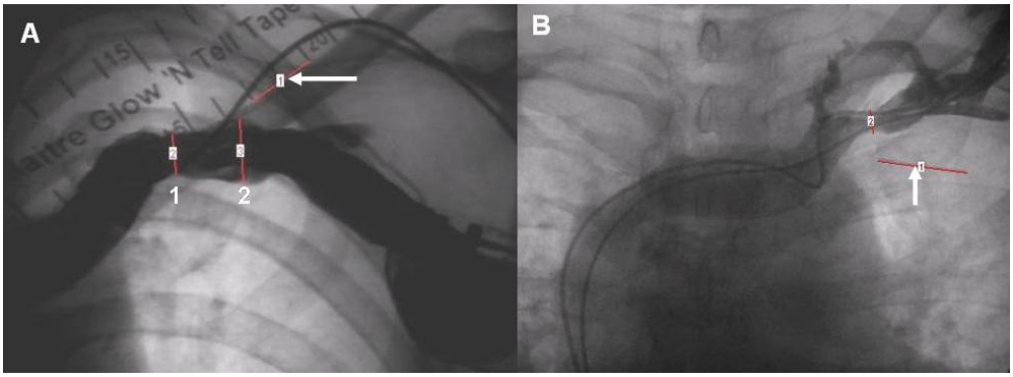

Figure 2: Venographic images were calibrated by a reference standard placed on body surface (arrows). Measurement of minimum (2) and maximum (3) venous dimensions.

In order to establish the diagnosis of venous stenosis at baseline two criteria had to be fulfilled: 1) minimum to maximum diameter ratio (D_{min}/D_{max}) of 0.40 or less, and 2) measured minimum diameter at or below the 5th percentile level of the maximum diameter measurements from the entire group. The latter criterion was used due to the fact that ectatic bulges in the veins are common and would otherwise lead to misclassification even with normal venous diameters by exaggerating the D_{min}/D_{max} – ratio.

The follow-up ICVs were analyzed for the presence of stenosis, complete occlusion and/or non-flow-limiting thrombi. A successful venography both at baseline and at 6 months was mandatory for an assessment of a new venous obstruction. Definition of a new stenosis at 6 months had to meet the following requirements: 1) a diameter reduction of at least 50 % compared to baseline ICV in a venous segment identified visually as the narrowest point in the follow-up ICV, and 2) no significant stenosis at the same location at baseline. The late ICVs were compared against both baseline and 6-month ICVs, and the same criteria for stenosis were utilized. Total occlusion was defined as a complete interruption of venous flow with or without new regional collateral veins. Non-flow-limiting thrombi were defined as venous filling defects attached to PM leads or vessel walls, but did not block flow or narrowed the lumen less than 50 %. Thus, only patients in whom both the baseline and the 6-month venograms were successfully completed could be included in the determination of a new venous stenosis. All successful 6-month ICVs were assessed for total occlusions and for potential non-obstructive filling defects suggestive of thrombus formation. The

late venographies were compared with those obtained at baseline and at 6 months post implantation to perform measurements at the same venous locations, and to assess for possible new areas of venous luminal narrowing or filling defects.

4.3.4. Transthoracic and transesophageal echocardiography

A transthoracic echocardiogram (TTE) was aimed to be performed at baseline and at 6 months (Table 4). Studies were conducted according to a routine cardiac protocol, which includes real-time and mode imaging of cardiac structure and function. Cardiac chamber dimensions were measured in standard fashion. Valvular functions were assessed by color-Doppler flow mapping, and continuous wave Doppler was used to obtain tricuspid valve regurgitation gradient in peak systole in order to estimate pulmonary pressure. In TTE studies at 6 months special attention was given to PM leads, right ventricular (RV) size, estimated RV pressure from tricuspid regurgitation, and to potential thrombus formations. All TTEs were preformed by physicians experienced in cardiac ultrasonography.

TEE was performed using a multiplane 7.0 MHz probe (Acuson Sequoia C512, Siemens- Acuson, Mountain View, CA, USA) by experienced echocardiographers. The focus of the TEE studies was to evaluate the pacemaker electrodes for the presence of thrombi and for valvular lesions in the tricuspid valve. The patency of the SVC was also assessed as well as the condition of the left-sided valvular structures.

4.3.5. Additional imaging studies

Venous Doppler ultrasonography was performed by a radiologist in order to evaluate for a possible acute deep vein thrombosis in the extremities, if symptoms suggestive of such an event arose during the 6 months after PM implantation. When a patient presented with symptoms suggestive of pulmonary embolism, a nuclear ventilation-perfusion scintigraphy (V/Q-scan) was performed. (Table 4).

4.3.6. Laboratory assays

Plasma prothrombin fragment 1+2 (F1+2) and D-dimer (DD) were measured as markers of thrombin formation, and of fibrin generation and breakdown [102, 103] (Tables 4 and 5). Von Willebrand factor antigen (vWF) and soluble thrombomodulin (Tm) were assessed in order to quantitate vascular endothelial damage [102, 103]. Blood samples for plasma vWF, Tm, DD and F1+2 were obtained 1) at baseline prior pacemaker

implantation and 2) on the first postoperative day (Table 5). Blood for plasma analyses was collected in 3.2 % sodium citrate. Plasma was separated by centrifugation at 2500 g and stored at -70^{o} C. All the analyses were done in duplicates. 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 assays listed in table 5. When a thrombophilic condition, except mutations, was 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 of functional tests were regarded to have thrombophilia.

4.4. Statistical methods

Continuous variables are presented as means $\pm$ standard deviation unless otherwise indicated, and study groups were compared by the Mann-Whitney U-test or paired T-test for variables with normal distribution. Categorical variables are presented as counts and percentages and were compared by the chi square 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 binary logistic regression analyses were performed to identify independent predictors for categorical end-points. A multivariable linear regression model was performed to determine the independent predictors for implantation-induced changes in laboratory parameters. Variables with a P-Value of less than 0.10 in univariate analyses were included in the regression analyses. A two-sided P value <0.05 was required for statistical significance. Statistical analyses were performed by using commercially available statistical software programs (SPSS for Windows versions 13.0 to 16.0, SPSS Inc, Chicago, Ill, USA; or SAS Enterprise Guide 3.0.2.446, SAS Institute Inc, Cary, NC, USA).

Table 5. Laboratory assays		
Test	**Diagnostic use**	**Method**
D-dimers	Thrombin formation, fibrin generation and breakdown	Asserachrom™ D-Di *
Prothrombin fragment 1+2	Thrombin formation, fibrin generation and breakdown	Enzygnost TM F 1+2 micro †
Willebrand factor antigen	Vascular endothelial damage and activation	STA-Liatest® vWF *
Thrombomodulin	Vascular endothelial damage and activation	Asserachrom Thrombomodulin *
Tests for Thrombophilia		
PTT-LA (Activated Partial Thromboplastin Time)	Lupus anticoagulant	Lupus Anticoagulant-Sensitive APTT Reagent *
dRVVT (dilute Russell viper venom time)	Lupus anticoagulant	STA-Staclot® dRVV Screen *
Thrombin time	Lupus anticoagulant	STA® – Thrombin *
Anti-β2-glycoprotein 1 antibodies	Anti-phospholipid syndrome	QUANTA Lite ™ B2GPI I IgG ‡
Anti-cardiolipin antibodies	Anti-phospholipid syndrome	ELISA ||
Antithrombin activity	Antithrombin III deficiency	Stachrom® AT III *
Protein C activity	Protein C deficiency	Stachrom® Protein C *
Protein S activity	Protein S deficiency	Staclot® Protein S *
F V Leiden (R506Q)	Factor V Leiden mutation	Factor V Leiden Kit with LightCycler® §
Prothrombin Factor II mutation	Prothrombin 20210 mutation	Factor II G20210A Kit with LightCycler® §

* Diagnostica Stago, Asnières, France, † Dade Behring, Marburg, Germany, ‡ INOVA Diagnostics, Inc., San Diego, CA, § Roche Diagnostics GmbH, Mannheim, Germany. || Method described previously [133]

5. RESULTS

5.1. Characteristics of the base study group and pacing device implantation

Mean age of the base study population of 150 patients was 66.8 (+/- 12.3) years, the majority of whom were males (n=91, 60.7 %). Baseline characteristics and past medical conditions are listed in table 3. Patients who were enrolled at Turku University Hospital were younger on average compared to patients recruited at Satakunta Central Hospital in Pori (mean age 65.1 $\pm$ 12.7 vs. 70.4 $\pm$ 10.7, p=0.001), and there was a borderline-significant difference in the proportion of male patients between the centers with a higher percentage in Turku (66.3 % vs. 49.0 %, p=0.051). There was also a difference between the 2 centers in the proportion of patients with either a past history of AF or current AF at PM implantation with a higher percentage of such patients in the Pori-group (42.9 % vs. 24.8 %, p=0.037).

Cardiovascular and antithrombotic medications in use during the study period are presented in table 6. The majority (79.3 %) of the patients were receiving at least one antithrombotic drug (warfarin, aspirin or low molecular weight heparin) at baseline. The only difference in medication use between patient groups in the 2 study centers was in anticoagulant therapy with more patients receiving warfarin in the group from Satakunta central hospital: 24 (49.0 %) patients in the Pori-group compared to 32 (31.7 %) in the Turku-group (0.048), the difference resulting from the higher proportion of patients with AF in Pori.

Table 6. Medications at baseline and at 6 months (N=150)

Baseline			**6 months**		
Cardiovascular drugs	**N**	**%**	**Cardiovascular drugs**	**N**	**%**
Beta blocker	75	50.0	Beta blocker	103	68.7
ACE-inhibitor or ARB	74	49.3	ACE-inhibitor or ARB	75	50.0
Calcium channel blocker	23	15.3	Calcium channel blocker	20	13.3
Diuretic	56	37.3	Diuretic	61	40.7
Nitrate	25	16.7	Nitrate	33	22.0
Antithrombotics	**N**	**%**	**Antithrombotics**	**N**	**%**
Warfarin	56	37.3	Warfarin	61	40.7
LMWH*	12	8.0	LMWH*	0	
Aspirin	65	43.3	Aspirin	56	37.3
Clopidogrel	5	3.3	Clopidogrel	8	5.3
No antihrombotics	31	20.7	No antihrombotics	30	20.0

* Low molecular weight heparin

The majority (n=121, 80.7 %) of the patients were in sinus rhythm at the time of the device implantation (with intact or blocked AV-conduction). All of the remaining patients had atrial fibrillation or flutter (n=29, 19.3 %).

Table 7. Indications for device implantation and characteristics of implantation procedure and pacing system (n=150).

Indications for device implantation (N, %)		
Sick sinus syndrome or bradycardia	72	48.0
Atrio-ventricular conduction defect	49	32.7
Ventricular tachycardia	19	12.7
Left ventricular failure	10	6.7
Implantation characteristics		
Operator experience (N, %)		
Number of procedures <50	29	19.3
50-100	14	9.3
>100	107	71.3
Access side (N, %)		
Right	22	14.7
Left	128	85.3
Venous access (N, %)*		
Cephalic (cutdown)	85	56.7
Subclavian (venipuncture)	67	44.7
Axillary vein	7	4.7
Antibiotic prophylaxis administered (N, %)	102	68.0
Procedure duration (minutes) (range, mean, SD)	15 - 480	73.8 ±50.1
Duration of hospital stay (days) (range, mean, SD)	1-23	4.3 ±4.3

Leads and devices		
Number of implanted leads		
Mean number (±SD)	1.69	±0.53
Single lead (N, %)	51	34.0
Multilead (2 to 3) (N, %)	99	66.0
Lead insulation (N, %)		
Silicone only	137	91.3
Polyurethane (at least 1 lead)	13	8.7
Implanted device types (N, %)		
Dual chamber	80	53.3
Single chamber	41	27.3
ICD	19	12.7
Biventricular	10	6.7
Pacing modes (N, %)		
AAI/AAIR†	21	14.0
VVI/VVIR ‡	23	15.3
VDD ‡	1	0.7
DDD/DDDR/DDI §	76	50.7
ICD with AAI	5	3.3
ICD with VVI	11	7.3
ICD with DDD	3	2.0
Biventricular PM	8	5.3
Biventricular PM/defibrillator	2	1.3

*more than 1 access vein in 9 patients

† atrial pacing modes, ‡ ventricular pacing modes, § dual chamber pacing modes

The most frequent indication groups for pacemaker implantation were sick sinus syndrome with or without AF (n=82, 54.7 %) and atrio-ventricular conduction defects (n=37, 24.7 %, table 7). A total of 254 leads were implanted with the majority (n=99, 66.0 %) of the patients receiving multiple (2 or 3, mean 1.69 $\pm$ 0.53) leads. Most of the implanted leads were insulated with silicone, and only a few leads had polyurethane coating (Table 7). Types of implanted devices and pacing modes are presented in table 7.

The majority (n=107, 71.3 %) of the devices were implanted by operators with an experience of more than 100 previous implantations (Table 7). Mean procedure duration (defined as time from wound opening to wound closure) was 1 hour and 14 minutes with considerable variation (Table 7). Duration of the procedure was significantly longer in patients implanted with a biventricular PM compared to other device types (mean 183 vs. 66 minutes, $p < 0.001$), and significantly longer also in patients receiving multiple as opposed to a single lead (mean 81 vs. 59 minutes, p=0.003). The cephalic vein cut-down approach was the most frequently utilized route for venous access (n=85, 56.7 %), and the majority (128, 85.3 %) of the devices were implanted on the left side.

5.2. Incidence of venous and thromboembolic lesions and clinical findings

5.2.1. Venography

5.2.1.1. Success of venographic studies

A successful baseline ICV was available in 145 (96.7 %) patients. Missing Venographies (n=5, 3.3 %) were due to technical failure of digital storage media (n=2, 1.3 %), lack of or failure of venous access (n=2, 1.3 %), and an elevated creatinine level (n=1, 0.7 %). The 6-month ICV was successful in 140 patients (93.3 %) with the failures (n=10, 6.7 %) due to a technical failure of digital storage media (n=2, 1.3 %), lack of or failure of venous access (n=4, 2.7 %), an allergic reaction in baseline venography (n=2, 1.3 %), refusal by patient (n=1, 0.7 %), and an elevated creatinine level (n=1, 0.7 %). Both baseline and 6-month venograms were available for comparative analysis and measurements in 136 patients (91 %) (study II).

All (100 %) patients enrolled into the long-term follow-up (n=50) had a successful ICV conducted at a mean of 2.4 years from device implantation (study III). Serial studies (baseline, 6 months and 2 years) were available in each of these 50 patients.

5.2.1.2. Baseline venographic findings

The mean venous minimum (Dmin) and maximum (Dmax) diameters of the 145 patients with successful baseline venograms were 10.8 ± 2.7 mm (Dmin) and 17.9 ± 4.0 (Dmax). As can be expected, venous diameters in male patients were somewhat larger than in females: Dmin 11.4 ± 2.9 mm vs. 9.8 ± 2.3 mm ($P < 0.001$), and Dmax 18.5 ± 3.9 vs. 17.0 ± 4.0 ($p=0.030$), respectively. Baseline ICV revealed a considerable inter-individual variation in the anatomic appearance of the veins. Ten patients (7 %) were classified as having venous anomalies prior to device implantation. These included 7 (4.8 %) cases of baseline stenosis with the narrowest venous diameters in the range of 4.9 to 6.7 mm (Figure 2). One (0.7 %) patient was found to have an asymptomatic complete left subclavian occlusion, which lead to switching the side of PM implantation. Of the remaining 2 patients, 1 (0.7 %) had a persistent left superior vena cava and the other (0.7 %) a double axillary vein (Figure 3). (Study II)

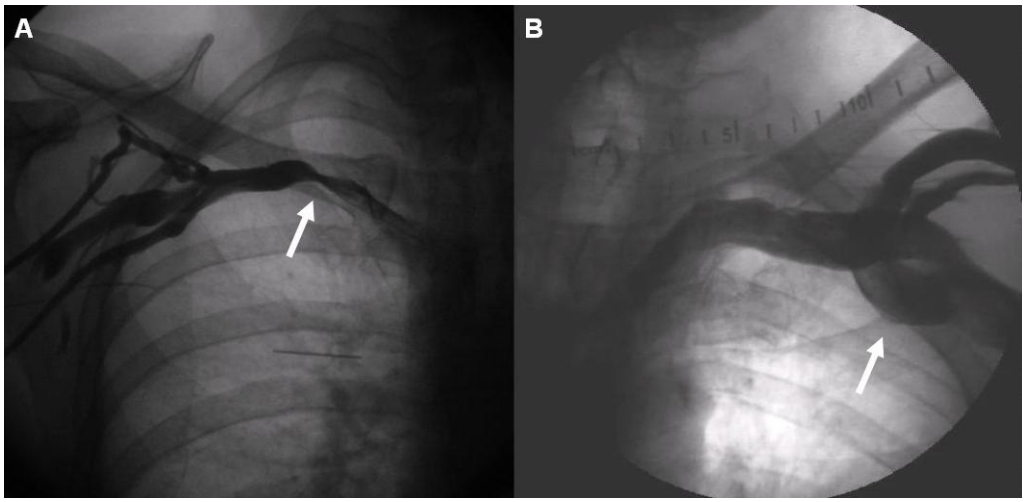

Figure 3: Baseline venographic abnormalities: stenosis in the right subclavian vein (A), and anomalous left axillary vein (B).

5.2.1.3. Six-month venographic findings

Both the minimum and maximum venous diameters in the whole study group diminished slightly, but statistically significantly, during follow-up (Table 8). Among the 136 patients with a successful baseline and 6-month ICV, a new venographic stenosis had developed in 14 (10.2 %) (Figure 4).

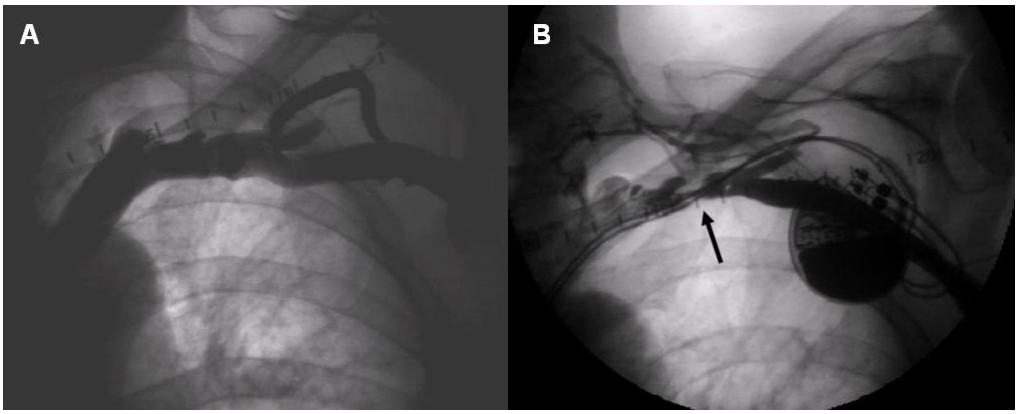

Figure 4: Baseline image (A) and a new stenosis in 6-month venography (B).

Total venous occlusion (TVO) with collateral vein development was seen in further 5 (3.6 %) patients (Figure 5). Thus, the overall incidence of a new obstructive venous lesion was 13.9 % (n=19). In patients with a non-occlusive stenosis, the mean venous minimum diameter had reduced to 4.6 $\pm$ 1.7 mm (or to 38% of the baseline diameter) (Table 8). In 12 of 14 (86 %) cases the stenosis developed in the subclavian vein at the same site where the vessel was narrowest already before the electrode implantation. Among the 8 patients with a baseline stenosis prior to PM implantation, a new stenosis developed in 1 patient, but at a separate location from the baseline lesion. No cases of TVO developed in the baseline stenosis group. In addition to these obstructive lesions, there were new small non-flow limiting filling defects suggestive of thrombus formation in 20 (14 %) of the 140 cases with a successful 6-month venogram. In total, 39 (28 %) patients had a new abnormal finding in the 6-month ICV. (Study II)

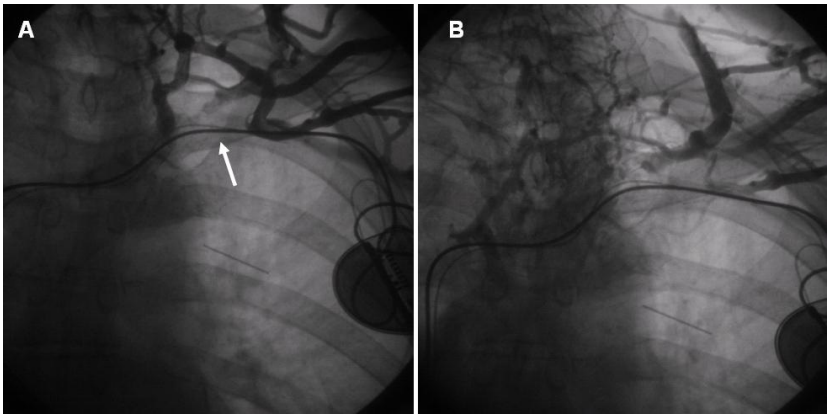

Figure 5: Complete subclavian occlusion (A) with extensive new collateral vein network (B).

Table 8. Venous diameters in 136 patients with successful venograms at baseline and at 6 months, and comparison of the findings in patients with a new venous obstruction at 6 months vs. patients with no obstruction.

Venographic measurements	All patients (N=136)	No venous obstruction (N=117)	Venous obstruction (N=19)	p*
Baseline				
Anomalous, n (%)	10 (7.4 %)	8 (6.8 %)	2 (10.5 %)	0.474
Minimum diameter (mm), mean (SD)	10.8 ± 2.8	10.9 ± 2.9	10.0 ± 2.7	0.334
female	9.9 ± 2.3	9.8 ± 2.3	8.8 ± 2.7	0.445
male	11.4 ± 2.9	11.5 ± 3.0	10.7 ± 2.6	0.451
Maximum diameter (mm), mean (SD)	17.9 ± 4.0	18.0 ± 4.2	16.5 ± 3.3	0.156
female	16.8 ± 4.1	16.7 ± 3.5	15.0 ± 3.9	0.329
male	18.5 ± 3.9	18.7 ± 4.1	17.4 ± 2.6	0.206
Minimum/maximum-ratio	0.61 ± 0.13	0.61 ± 0.13	0.61 ± 0.13	0.794
female	0.60 ± 0.11	0.60 ± 0.12	0.59 ± 0.12	0.896
male	0.62 ± 0.14	0.62 ± 0.14	0.61 ± 0.14	0.838
6 months				
Minimum diameter	9.1 ± 3.6	10.0 ± 2.9	4.6 ± 2.8 †	<0.001
Percent change from baseline, mean (SD)	-10.6 ± 27.8	-5.9 ± 2.5	-50.7 ± 16.3	<0.001
Maximum diameter	17.0 ± 4.2	17.4 ± 4.2	13.8 ± 3.1	0.002
Percent change from baseline, mean (SD)	-4.0 ± 17.2	-2.6 ± 16.8	-14.0 ± 17.4	0.028
Minimum/maximum-ratio	0.59 ± 0.24	0.61 ± 0.23	0.38 ± 0.22	<0.001
Percent change from baseline, mean (SD)	-0.9 ± 46.2	+3.9 ± 46.4	-40.8 ± 16.2	<0.001
Collateral formation, (N, %)	8 (5.9 %)	2 (2.2 %)	6 (31.6 %)	<0.001

* Comparison of non-obstructed vs. obstructed

† Patients with total occlusion excluded

5.2.1.4. Long-term Venography

The mean Dmin and Dmax did not change significantly between the 6-month and late venographies conducted at a mean of 2.4 years after implantation (Table 9). New abnormalities were discovered in 5 (10 %) patients. These included 3 confirmed cases of TVO (Figure 6), and 1 patient with borderline stenosis. The remaining 1 patient had multiple new collateral veins, but no obstructive lesion could be documented. This patient was symptomatic with intermittent upper extremity pain, but, unfortunately, in his somewhat underexposed venography the distal axillary vein was masked by the

PM generator, and the brachial vein was outside the imaged area. However, the presence of abundant collaterals was regarded as a sign of significant functional obstruction, and the patient was thus determined to be fourth case of TVO. The 3 confirmed TVOs were localized either in the subclavian (n=2) or the axillary (n=1) veins ipsilateral to the implanted device. Two male patients with confirmed TVO had presented with an abnormal venogram already at 6 months: one with a mild venous stenosis and the other with a non-occlusive lead-associated thrombus. One of the patients with a confirmed TVO (male, age 77) had experienced symptoms potentially related to the lesion (intermittent upper extremity pain), whereas the other two were asymptomatic.

There were 25 patients in the late follow-up in whom no abnormalities had been discovered in the pre-implant or in the 6-month venogram, 2 (8 %) of whom had developed a new lesion on the late venography (1 TVO and 1 borderline stenosis). Two of the 10 patients with abnormalities in baseline venography were included in the long-term follow-up, both of whom had venous stenosis, and showed no progression of the baseline lesions at 6 months or in the late follow-up ICV (Table 9).

The 6-month venography had been abnormal in 23 (46 %) of the 50 late follow-up patients. In the majority (83 %) of these cases, the late ICV revealed no progression or resolution of their lesions, although TVO developed in 3 (17 %) these patients. The small filling defects interpreted as lead-associated thrombi at 6 months (n=13) had resolved in the late venography in only 2 patients and were unchanged in 10 (Table 9). (Study III)

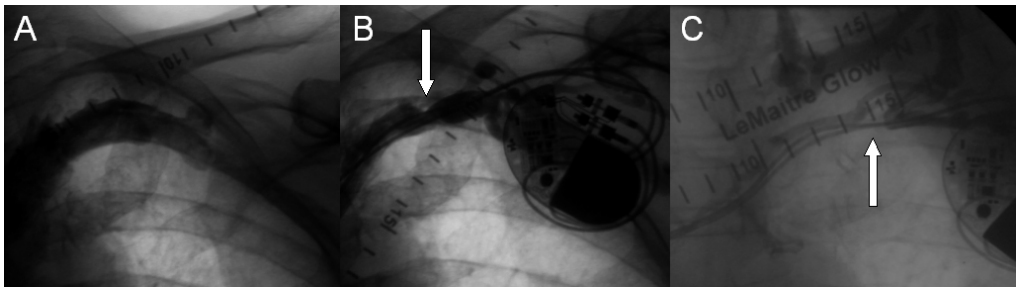

Figure 6: Development of total occlusion in a patient followed for two years: patent veins at baseline (A), subclavian stenosis at 6 months (B) and total occlusion at 2 years (C).

Table 9. Progression of Venographic findings in 50 patients at Baseline, 6 Months and at 2 Years

Baseline venography			6 Month-venography			2-Year venography		
Finding	**N (%)**		**Finding**	**N (%)**		**Finding**	**N (%)**	**New Lesion (N)**
Abnormal	**2 (4 %)**	⇒	**Abnormal**	**2 (4 %)**	⇒	**Abnormal**	**2 (4 %)**	
Stenosis	1 (2 %)		No change in baseline lesions			No change in baseline lesions		0
Borderline stenosis	1 (2 %)							
Normal	**48 (96 %)**	⇒	**Normal**	**25 (50 %)**	⇒	**Normal**	**22 (44 %)**	0
					⇒	**Abnormal**	**3 (6 %)**	
						New TVO		1
						Borderline Stenosis		1
						New Collaterals, No TVO		1
		⇒	**Abnormal**	**23 (46 %)**	⇒	**No Progression/Resolution**	**19 (38 %)**	0
			Stenosis	7 (14 %)	⇒	**Lesion Progression**	**2 (4 %)**	
			TVO	3 (6 %)		Stenosis to TVO	1	1
			Thrombus	13 (26 %)		Thrombus to TVO	1	1
					⇒	**Lesion Resolution**	**2 (4 %)**	
						Resolution of Thrombus	2	0
							Total	**5 (%)**

Venous Diameters (mm, Mean + SD)

Baseline			**6 Months**	**Δ From Baseline**	**p**	**2 Years**	**Δ From Baseline**	**Δ From 6 Months**	**p**
Dmin	10.9 ± 3.1		9.2 ± 3.2	-15.6 %	0.001	8.9 ± 2.9	-18.3 %	-3.2 %	0.536
Dmax	17.9 ± 4.2		16.2 ± 4.0	-9.5 %	<0.001	16.9 ± 4.1	-5.6 %	+4.3 %	0.261

5.2.2. Transthoracic and transesophageal echocardiography

Baseline transthoracic echocardiography was performed on 104 (69.3 %) of the study group and 149 (99.3 %) underwent TTE at 6-month follow-up visit (Table 4). There were no significant differences in the frequency of valvular disorders or chamber dimensions in patients with or without PM-lead associated thrombosis on TEE. Mean tricuspid valve regurgitation gradient (TRG), reflecting systolic pulmonary pressure, was significantly higher at 6 months among patients with a thromboembolic or obstructive end-point lesion compared to patients with no lesions (28 vs. 25 mmHg, p=0.043). Likewise, patients with a clinically significant major end-point (PE or TVO) had a higher 6-month mean TRG compared to patients with no lesions (31 vs. 25 mmHg, p=0.008). A significantly elevated pulmonary systolic pressure (TRG > 40 mmHg, mean 45 $\pm$ 5 mmHg) was seen in 7 (15.6 %) of the patients with an end-point and in 3 (3.3 %) of the patients free of lesions (p=0.016). TTE findings are summarized in table 10.

The implanted pacemaker electrodes could be visualized in proximal SVC and in the RA in all TEE-studied patients (n=66). A total of 6 (9 %) patients were found to have central venous thrombi in TEE (Figure 7). All thrombi were located within the RA or in the SVC at the atrial junction with extension into the RA. The thrombi were non-occlusive and were either attached to the lead(s) or in the immediate vicinity. No cases of stenosis of the SVC or significant electrode induced trauma to the tricuspid valve were encountered in TEE. None of the thrombi detected by TEE could be visualized in the preceding TTE or in the ICV. On the other hand, TEE did not reveal any of the defects disclosed by ICV (a filling defect suggestive of a thrombus in 11/66, 16.7 %, and TVO in 1/66, 1.5 %). TEE and ICV were thus complementary, and the two methods yielded a combined incidence of 27 % for thrombosis (n=18) among the 66 TEE-patients. There were no significant differences in the TTE-measured parameters (Table 10) between patients with a TEE-detected thrombus vs. all others or vs. those with a negative TEE study. One patient with a central venous thrombus in TEE was in AF at the time of implantation. This patient was also the sole warfarin-user (INR 1.7 at implantation) among the 6 patient with a thrombus in TEE. (Study I)

Table 10. Findings in transthoracic echocardiography (TTE) at baseline (N=104) and at 6 months (N=149).

TTE parameters	All patients	6-month end-points negative	6-month end-points positive	p†	Major end-points	p‡
Left ventricular ejection fraction (%)						
Baseline, mean (SD)	54 ± 17	55.9 ± 16.1	53.0 ± 14.0	0.293	55.5 ± 14.7	0.908
6 months, mean (SD)	59 ± 14	58.3 ± 15.0	60.2 ± 13.3	0.546	58.2 ± 8.6	0.983
Change form baseline, p-value*	0.029	0.319	0.009		0.273	
Left ventricular end-diastolic dimension						
Baseline (mm), mean (SD)	54.9 ± 9.2	54.5± 8.6	54.4 ± 9.8	0.667	51.2 ± 8.7	0.323
6 months (mm), mean (SD)	56.7 ± 9.2	56.7 ± 9.7	56.5 ± 7.7	0.792	57.2 ± 9.0	0.823
Change form baseline, p-value*	0.001	0.002	0.106		0.043	
Left atrial end-systolic dimension						
Baseline (mm), mean (SD)	41.3 ± 7.5	41.8 ± 7.8	40.1 ± 6.5	0.346	37.8 ± 4.7	0.192
6 months (mm), mean (SD)	43.4 ± 7.5	43.9 ± 7.1	42.4 ± 8.4	0.256	40.9 ± 7.8	0.342
Change form baseline, p-value*	< 0.001	0.002	0.012		0.078	
Right ventricular end-diastolic dimension						
Baseline (mm), mean (SD)	28.2 ± 6.0	27.3 ± 5.8	28.6 ± 6.1	0.478	31.5 ± 8.4	0.487
6 months (mm), mean (SD)	26.7 ± 6.6	27.0 ± 7.1	26.7 ± 8.0	0.616	27.3 ± 9.6	0.821
Change form baseline, p-value*	0.691	0.887	0.625		0.461	
Tricuspid regurgitation gradient						
Baseline (mmHg), mean (SD)	26.7 ± 10.8	26.4 ± 10.5	26.7 ± 9.1	0.639	26.7 ± 7.6	0.842
6 months (mmHg), mean (SD)	26.1 ± 7.6	25.0 ± 6.9	28.0 ± 8.6	0.043	31.4 ± 7.4	0.008
Change form baseline, p-value*	0.787	0.303	0.406		0.180	

* Wilcoxon Signed Ranks Test, in patients with paired values available

† p-value, 6-month end-point positive vs. 6-month end-point negative patients

‡ p-value, 6-month major end-point positive vs. 6-month end-point negative patients

SD = standard deviation

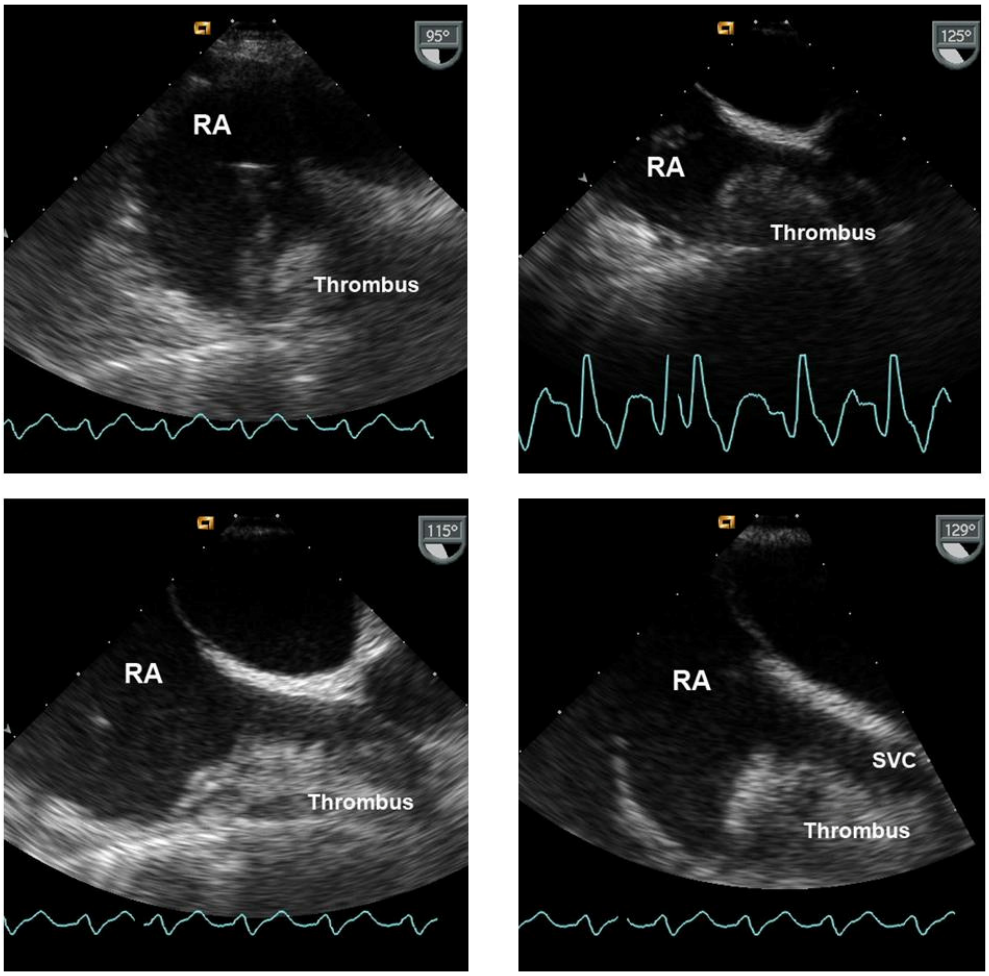

Figure 7: Pacemaker lead attached thrombus in a 78-year old male in transesophageal echocardiography. (RA = right atrium, SVC = superior vena cava)

5.2.3. Symptomatic acute deep venous thrombosis and pulmonary embolism

During the 6-month follow-up, one (0.7 %) patient developed symptomatic acute deep venous thrombosis of the upper extremity. Thrombosis was diagnosed by venous Doppler ultrasound (revealing a thrombus-filled brachial vein) 10 days after pacemaker implantation. Symptoms and treatment of this patient are detailed in section 5.3.3.. A diagnostic work-up for a lower extremity DVT was conducted in 3 patients with negative results.

During the 6-month follow-up a total of 16 (10.7 %) patients underwent V/Q scanning due to symptoms suggestive of pulmonary embolism. PE was diagnosed in 31 % of the scans, or in 5 (3.3 %, 4 males) of the 150 patients. None of the pulmonary emboli were massive, and none of the patients had hemodynamic instability. Four (80 %) of the patients with PE also had another end-point (2 with TVO in ICV, 2 with central venous thrombosis in TEE). (Studies I and III)

5.2.4. Summary of study end-point lesions

ICV was abnormal at baseline in 10 patients (7.1 % of 145 successful baseline ICVs). At 6 months, a new abnormality had developed in 39 patients (27.9 % of 140 successful ICVs). The most common lesion-type at 6 months was a small non-flow-limiting lead-associated thrombus in ICV, which was seen in 20 (14.3 % of all successful 6-month ICVs). There were also 19 cases (14 % of 136 patients with a successful ICV both at baseline and at 6 months) with a new venographic obstruction, which included stenosis in 14 (10.3 %) and TVO in 5 (3.7 %).

Table 11. Summary of study end-points 6 months after pacing device implantation

Venous obstructive and thromboembolic complications	N (%)	Sample size
New venographic stenosis	14 (10.3 %)	136 [1]
Total venographic occlusion	5 (3.7 %)	136 [1]
Venographic lead associated thrombi	20 (14.3 %)	140 [2]
Central venous thrombi (by TEE)	6 (9.1 %)	66 [3]
Acute symptomatic UEDVT	1 (0.7 %)	150
Symptomatic pulmonary embolism	5 (3.3 %)	150
Total	**47 (31 %)**	**150**

[1] patients with both baseline and 6-month venography successful

[2] patients with 6-month venography successful

[3] patients who underwent TEE at 6 months

A central venous (CV) thrombus was diagnosed in 6 (9.1 %) of the 66 patients who underwent TEE at 6 months. Pulmonary embolism was detected in 5 (3.3 %) patients, 4 (80 %) of whom also had another end-point (2 with a CV-thrombus in TEE, and 2

with TVO in ICV). Only 1 (0.7 %) patient had an acute symptomatic deep venous thrombosis of the upper extremity diagnosed by venous Doppler ultrasound.

Thus, at least one end-point lesion was diagnosed in a total of 47 (31.3 %) patients at 6 months (Table 11). Six (4 %) of these were symptomatic, and the rest (n=41, 27.3 %) were asymptomatic. One third of the study group (n=50) underwent a long-term follow-up ICV approximately 2 years post-implantation. These venographies disclosed new abnormalities in 5 (10 %) patients, which included 4 cases of TVO, and 1 patient with a borderline stenosis. The total number of complete venographic obstruction thus amounted to 9 (6 %) in the entire study group of 150 patients.

Table 12. All venous thromboembolic and obstructive end-points at 6 months subdivided into major and minor end-points. Relative frequencies of the end-points are expressed as percentages of the base study population of 150 patients.

Major End-points	**N**	**%**
Total venographic occlusion (TVO)	3	2.0
Pulmonary embolism with TVO	2	1.3
Pulmonary embolism with lead thrombus in TEE	2	1.3
Pulmonary embolism alone	1	0.7
Acute symptomatic UEDVT	1	0.7
Total	**9**	**6.0**
Other End-points	**N**	**%**
Venographic stenosis	14	9.3
Lead thrombus, venography	20	13.3
Lead thrombus, TEE	4	2.7
Total	**38**	**25.3**
All venous thromboembolic complications	**47**	**31.3**

Out of all 47 patients with 6-month end-points, a total of 9 (6 % of 150 patients) were considered to have a major end-point with clinical significance (pulmonary embolism and/or total venous occlusion, whether symptomatic or asymptomatic; table 12). Male sex was significantly more common among these patients (n=8, 88.9%) compared to those with minor end-points (n=18, 47.4 %, p=0.03). In the latter group the predominating primary pacing indication was sick sinus syndrome or bradycardia in the majority of cases (n=23, 60.5 %), whereas among patients with major end-points other indications formed the majority (n=8, 88.9 %, p=0.01). Echocardiographic mean tricuspid valve regurgitation peak gradient was higher at 6 months in patients with major end-points compared to other cases in the series (31.4 $\pm$ 7.4 vs. 25.6 $\pm$ 7.4 mmHg, p=0.013), reflecting higher mean systolic pulmonary pressures in these patients. (Studies I to III)

5.3. Implantation complications and clinical follow-up data

5.3.1. Implantation-related complications

During the first 4 weeks, significant acute complications of PM implantation developed in a total of 8 (5.3 %) of the 150 patients (Table 13). These included 3 cases (2.0 %) of atrial lead dislodgement, 2 cases (1.3 %) of pericardial effusion (1 of which mandated drainage), 1 case (0.7 %) of pneumothorax, 1 (0.7 %) wound revision, and 1 (0.7 %) major hematoma requiring drainage. Four additional cases with sizable hematomas were treated conservatively. Subacute complications after the first month included 1 (0.7 %) patient presenting with a lead failure due to subclavian crush (at 3 months), and 1 (0.7 %) patient with an impending skin perforation requiring surgical revision (at 3 months). (Study III)

Table 13. Acute (<4 weeks) complications after device implantation (N=150)

Acute complication	N (%)
Dislocated Atrial Lead (1-20 days postoperatively)	3 (2.0 %)
Pericardial effusion (1-3 days)	2 (1.3 %)
Pneumothorax	1 (0.7 %)
Hematoma with drainage	1 (0.7 %)
Wound revision	1 (0.7 %)
Total	**8 (5.3 %)**

5.3.2. Unscheduled hospital contacts and interventions

During the 6 month follow-up a total of 60 (40 %) the 150 patients had an unscheduled hospital visit, either as outpatient or inpatient. These were pacemaker clinic visits in 32 (21.3 %) cases, but in only half (n=16) of these the etiology was truly PM-related, and resulted in device reprogramming or other intervention. In 4 of the latter cases, a re-operation was required to repair a dislodged or damaged lead, and in further 2 patients an invasive procedure was performed due to pericarditis or impending skin perforation, as stated in the preceding paragraph. The initially implanted pacemaker was updated to a biventricular device in 2 patients (at 3 and 5 months after first procedure). The remaining 28 (18.7 %) unscheduled visits were mostly due to issues involving the patients' underlying cardiac disorder and were not PM-related.

5.3.3. Symptom presentation

There was no difference in baseline NYHA functional status between the patients who subsequently developed end-points compared to others (33 % vs. 32 % of patients in NYHA classes 3-4). During the first 6 months of follow-up, only one patient (0.7 %) was diagnosed with a symptomatic upper extremity deep venous thrombosis (venous Doppler ultrasound 10 days post-operatively). The patient was a diabetic male, aged 41 with no previous history of DVT, who developed acute swelling and pain in the upper extremity ipsilateral to the PM. After the diagnosis was established ultrasonographically, he was anticoagulated with warfarin for three months resulting in complete resolution of the symptoms, and a fully patent venogram at 6 months and at two years. This patient also developed impending skin perforation by the PM generator, and underwent surgical wound revision approximately 4 months after implantation.

Symptomatic pulmonary embolism was encountered in a total of 5 (3.3 %) of the 150 patients (Tables 11 and 12). All cases of PE were diagnosed by a nuclear ventilation-perfusion scan. Symptoms of PE developed 2 months after implantation in 1 patient, and in the remaining 4 the diagnosis was made due to symptom-presentation at the 6-month follow-up visit. Two of the patients with PE had a TVO in the 6-month ICV and 2 had patent veins, but no venography was available in the remaining 1 patient due to technical CD-ROM failure. The 5 patients with a TVO in 6-month venography had no localized symptoms in the ipsilateral upper extremity or in the region of the pacemaker pocket.

After 6 months no patients experienced swelling of the upper extremity, neck or the head or clinical pulmonary embolism. In the long-term follow-up group, only 2 (4 %) of the 50 patients expressed complaints of intermittent pain in the ipsilateral upper extremity. Both of these patients also presented with an abnormal late venogram. On inspection, none were found to have obvious superficial cutaneous collateral veins. Eleven (22 %) patients had needed hospital admissions after the 6-month follow-up visit, which were PM-related in only 2 cases. (Study III)

5.3.4. Antithrombotic therapies

At the time of the implantation, the majority (n=118, 79 %) of the 150 patients in the study were receiving at least one antithrombotic drug (Table 6), of which aspirin was the most frequently used (n=65, 43 %). There were 56 (37 %) patients who were anticoagulated with warfarin at baseline. Warfarin therapy had been interrupted prior to implantation in the majority (75 %) of its users 1-5 (mean 1.6 $\pm$ 1.4) days prior to the procedure, and INR was subtherapeutic (< 2.0) in 55 % of the warfarin-treated

patients. However, the mean INR (1.9 ± 0.5, range 0.9-2.9) was still close to therapeutic level despite the interruptions. Low molecular weight heparin (LMWH) was administered to a total of 12 (8 %) patients, only 1 of which was a warfarin-user (a female with no warfarin pause, but INR at 1.2). A total of 67 (45 %) of patients were thus receiving anticoagulation in the form of warfarin and/or LMWH at baseline, but when INR values are taken into account, a smaller number (n=37, 25 %) was receiving warfarin with INR within therapeutic range and/or LMWH.

There were no significant differences in the utilization of antithrombotic drugs in the 47 cases in which end-point lesions developed during the 6-month follow-up compared to the rest of the study group. The use of therapeutic-level warfarin and/or LMWH was lower among end-point patients (n=7, 15 %) compared to others (n=30, 29%), but the difference did not reach statistical significance (p=0.07).

In the sub-study of lead-associated central venous thrombosis based on TEE, warfarin therapy was less commonly used among the 6 patients diagnosed with a central venous thrombus (n=1, 17 %) compared to the 60 patients without such lesions (n=20, 33 %), but the difference was not significant (p=0.7). PE was diagnosed in 2 of the patients with a thrombus in TEE, and neither of them was a warfarin user. In the late follow-up study (n=50), the majority of the patients (n=44, 86 %) were treated with an antithrombotic medication, either warfarin (n=23, 46 %) or aspirin (n=21, 42 %). Four new cases of TVO were found in the late ICVs, 2 (50 %) of which used warfarin.

In the case-control study, there were no statistically significant differences in the utilization of anticoagulant or aspirin therapies between cases and controls at baseline, and the mean levels of INR between warfarin-treated cases and warfarin-treated controls were not different (1.97 ± 0.41 vs. 1.71 ± 0.56, p=0.101) (Table 14). None of 9 patients with major end-points (PE, TVO or acute upper extremity DVT) were receiving therapeutic-level warfarin or LMWH at the time of the PM implantation. In regression analysis with age and sex as covariates, the absence of any anticoagulation with warfarin or LMWH remained a significant predictor of a major end-point (p=0.039, OR 9.4, 95% CI 1.1-79.9). Likewise, at 6 months there was no significant difference in the proportions of case vs. control patients receiving warfarin, 16/47 (34 %) versus 21/47, (45 %), respectively (p=0.399). INR was in the therapeutic range (2.0-3.0) in the majority of warfarin users at 6 months with no difference between groups (2.2 ± 0.39 vs. 2.1 ± 0.14, cases vs. controls, p=0.800).

(Studies I to IV)

Table 14. Case-control study: 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 $\pm$ 3.1	10.9 $\pm$ 2.7	0.57
Abnormality §	3 (6.4%)	3 (6.4%)	1.00
Echocardiography			
Left ventricular ejection fraction, %	53.0 $\pm$ 14.0	58.0 $\pm$ 16.2	0.10
Left atrial dimension, mm	40.1 $\pm$ 6.5	40.4 $\pm$ 7.0	0.89
Tricuspid valve gradient, mmHg			
Baseline	26.6 $\pm$ 9.1	25.9 $\pm$ 8.6	0.71
6 months	28.0 $\pm$ 8.6	24.3 $\pm$ 7.4	0.01

* p-value, cases vs. controls

† LMWH = Low molecular-weight heparin

‡ ACE-I = Angiotensin converting enzyme inhibitor, ARB = Angiotensin receptor blocker

§ Baseline venographic abnormalities: stenosis (n=4), venous anomaly (n=2), persistent left superior vena cava (n=1).

5.4. Laboratory parameters of endothelial activation and coagulation

Laboratory assays of coagulation and endothelial activation were conducted in the case-control analysis in a total of 94 patients chosen for the study (Table 14; study IV). The degree of procedure-induced trauma and consequent activation of the coagulation system was assessed by levels of plasma von Willebrand factor (vWF) and thrombomodulin (Tm), D-dimer (DD) and prothrombin fragment F 1+2 (F1+2) at baseline and on the first post-operative day. Compared to age and sex matched controls, no difference in procedure-induced changes to the levels of these parameters were seen in patients who were diagnosed with end-points during the subsequent 6 months of follow-up (Figure 8). For the entire case-control study group (n=94), a significant increase was demonstrated in the mean level of vWF-ag, reflecting trauma-related endothelial activation, as well as in the mean levels of F1+2 and DD as signs of thrombin generation, fibrin formation and fibrin degradation. At least a minor elevation of D-dimer levels from baseline to post-operative day 1 was observed in the majority (90 %) of the patients, and a two-fold or higher rise was seen in 54 %.

As expected, anticoagulation with warfarin had a significant diminishing impact on the post-operative activity of coagulation (Figure 9). Post-operative D-dimers were significantly lower among patients treated with either warfarin or heparin at implantation time (1.36 vs. 2.66, p=0.025).

Only the case-patients were screened for thrombophilia. Three (6.4 %) of the 47 patients with end-points were found to have a prothrombotic coagulation disorder, but, interestingly, 2/6 (33 %) patients with symptomatic VTE were found to have thrombofilia. One of these patients with symptomatic pulmonary embolism was found to have Factor V Leiden heterozygosity and very low level of antithrombin in repeated measurements 6 months apart. The other patient had a very high level of anti-cardiolipin antibodies in repeated measurements 6 months apart. 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 DVT or PE. The details of the patients with thrombophilia are presented in table 15.

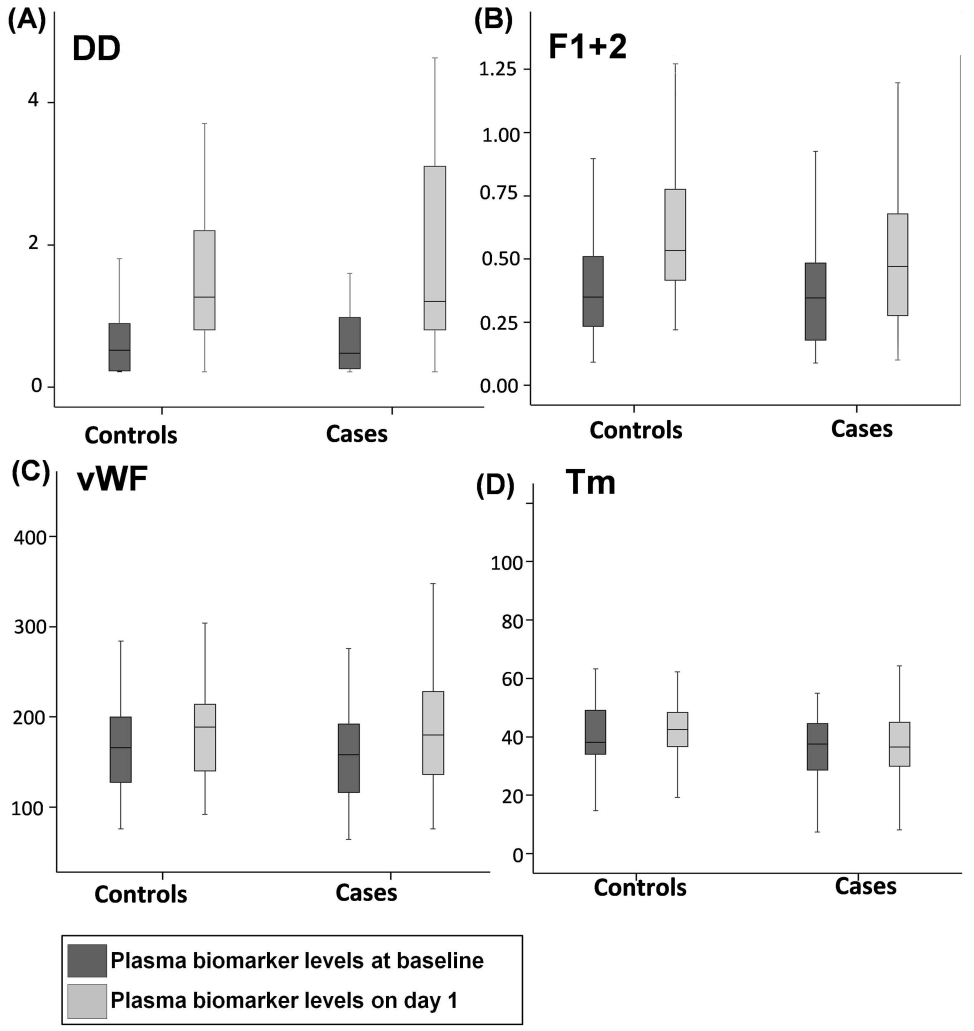

Figure 8: Baseline to first post-operative day changes in the levels of plasma biomarkers. Panel A: mean plasma D-dimer (mcg/mL) increased significantly in both case and control groups (p<0.001), but postoperative levels did not differ between the groups (p=0.631). Panel B: prothrombin fragment F1+2 (nmol/L) also increased significantly in cases (p<0.001) and controls (p=0.001) with no difference between groups (p=0.06). Panel C: von Willebrand factor (%) with significant increase in both groups (p<0.001) and no inter-group difference (p=0.949). Panel 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.

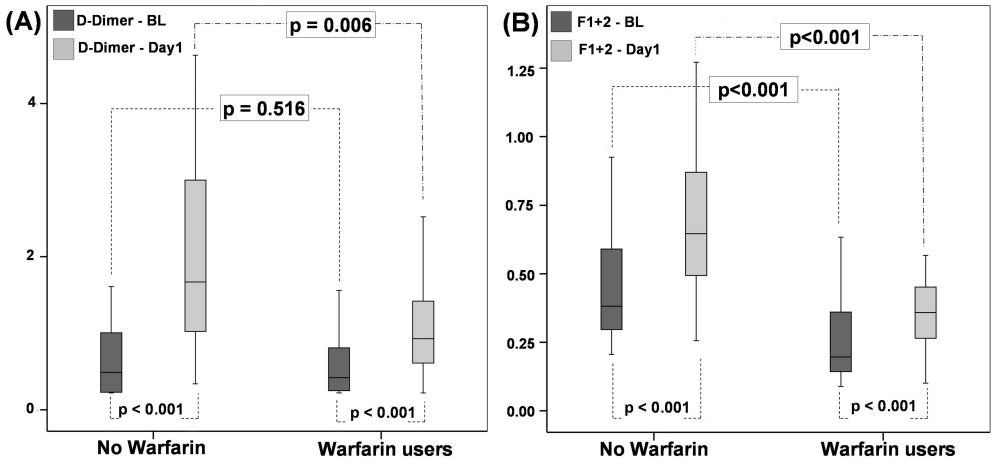

Figure 9: D-dimer (mcg/mL, Panel A) and prothrombin fragment F1+2 levels (nmol/L, Panel B) at baseline (BL) and after pacemaker implantation in patients with and without warfarin treatment.

Table 15. Cases with Thrombophilia

Case	Gender	Age	Coagulation defect	End-point Condition	Indication for Device Implantation	Device Type
1	Male	74	Factor V Leiden heterozygosity and low Antithrombin (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)*	Total venous occlusion and PE	Left ventricular failure	Biventricular pacemaker

* MPL=M-isotype Phospholipid Antigens. Upper limit of the reference value is 24 MPL (Finnish Red Cross Blood Service laboratory).

5.5. Risk factors for thrombosis and venous obstruction

5.5.1. Predictors of venous obstruction in the 6 month-study

Associations with the development of new venographic obstruction (stenosis or total occlusion) were searched from multiple clinical patient-related variables as well as from technical parameters of implantation, devices and leads among the patients with a successful baseline and 6-month venography (n=136). A larger proportion of obstructed patients (n=4, 21 %) were implanted with a biventricular PM compared to non-obstructed cases (n=6, 5 %, p=0.034). Also, atrial fibrillation at baseline was found to be more common in patients with obstructions (n=8, 42 %) than in patients with no obstructions (n=18, 15 %, p=0.021). Use of warfarin was higher among patients with AF compared to those in sinus rhythm (88 % vs. 24 %, $p < 0.001$), but the rate of warfarin use was equal (37 %) in patients with or without obstruction. AF and biventricular PM were the only univariate predictors of the development of venous obstruction. Also in logistic regression analysis (method Enter; covariates included were patient age, warfarin use and hypertension, which was non-significantly more common among cases with obstruction: 42 % vs. 22 %, p=0.085) AF at implantation and biventricular PM remained significant: OR 3.2 for AF (p=0.04, CI 1.1-9.9) and OR 5.9 for biventricular PM (p=0.02, CI 1.2-28.9). (Study II)

5.5.2. Predictors of an abnormal 6-month venography

Univariate predictors for the presence of any new abnormal finding (obstructions and non-obstructive thrombi combined) in 6m-ICV were hypertension (37.5 % vs. 19.8 %, abnormal vs. unchanged 6m-ICV, p=0.049) and CHF (22.5 % vs. 8.3 %, respectively, p=0.043). Interestingly, there were significantly fewer patients with coronary artery disease among cases with new ICV-abnormalities compared to others (15 % vs. 38.9 %, p=0.008), probably explained by the fact that a significantly smaller number of patients with CAD were on no form of antithrombotic therapy compared to other patients (2.3 % vs. 29.3 %, $p < 0.001$). At least one classic clinical risk factor for venous thrombosis (obesity, congestive heart failure, age $\geq$ 75 years, previous VTE, history of cancer, and hypertension) was present in 80 % of patients with abnormal 6m-ICV, and in 57.3 % of the other patients (p=0.009). The laboratory assessments revealed a significantly lower mean level of F1+2 postoperatively in patients with an abnormal 6m-ICV compared to others (0.48 ± 0.29 vs. 0.64 ± 0.27, p=0.017). In regression analysis, only the presence of at least one DVT risk factor was an independent predictor of an abnormal 6m-ICV (OR 4.4, 95% CI 1.2 – 16.0, p=0.022).

5.5.3. Long-term follow-up venography

After the late 2-year ICV, the number of cases of TVO was 7 (14 %) among the 50 patients included in the long-term follow-up. There were 2 additional cases with TVO at 6 months, who were not included in the longer follow-up. Thus, the total number of confirmed cases of TVO in the entire series of 150 patients amounts to 9 (6 %). Predictors for these lesions were searched from the same variables as in the 6-month study, and all cases with known TVO (n=9) were compared against the rest of the base study group without TVO (n=141). A larger proportion of patients who were in atrial fibrillation (n=29) at the time of the device implantation developed TVO compared to patients (n=121) who were in sinus rhythm (17.2 % vs. 3.3 %, p=0.014). The only feature of the implanted electrodes showing some association with TVO was lead insulation: the proportion of patients with at least one polyurethane-coated lead was more common among patients with total venous occlusion (33 % vs. 7 %, p=0.032). No parameter emerged as an independent predictor of TVO in multiple regression analysis. (Study III)

5.5.4. Case-control analysis

5.5.4.1. 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, previous VTE, history of cancer, and hypertension) or any other clinically relevant background features (Table 14). Although no singular classic VTE risk factor emerged as a predictor for end-point events, the majority (n=36, 77 %) of the cases with an end-point were found to have at least one classic VTE risk factor, while 21 (45 %) of the controls had none (p=0.049). The relative frequency of end-point lesions showed an increasing trend with higher cumulative number of risk factors (p=0.036, linear-by-linear association; Figure 10). 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 to controls (n=26, 55 %, p=0.002). No procedure-related parameter differed significantly between cases and controls (Table 16). (Study IV)

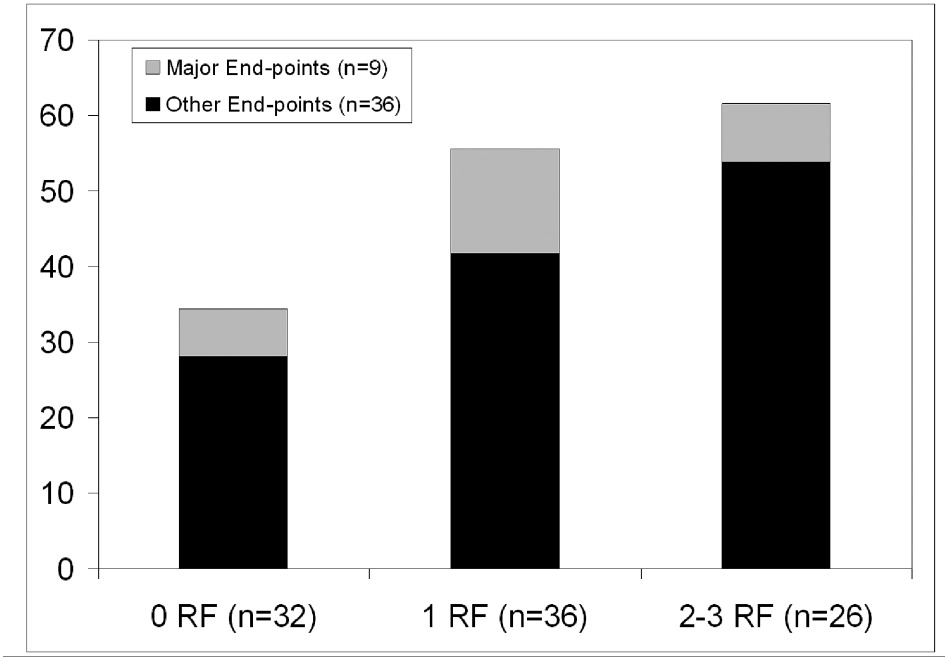

Figure 10: Relative incidence of major and other study end-points (for definition, see table 12) categorized by number of VTE risk factors (0, 1, or >1; p=0.036, linear-by-linear association). Height of the bars represents percentage of cases in the 3 risk factor categories.

5.5.4.2. 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, 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 ($\geq$ 0.3 mcg/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 end-points and their controls (Figure 8). Moreover, the changes in these parameters were comparable in the 9 patients with major thromboembolic end-points.

Warfarin use was not associated with pre-operative DD levels, but the post-operative levels were significantly lower in warfarin users compared to non-users (1.23 $\pm$ 0.95 vs. 2.69 $\pm$ 2.95 mcg/ml, p=0.008; Figure 9). Multivariate analysis confirmed warfarin to be an independent predictor of a lower post-operative DD and F1+2 levels ($p < 0.001$).

Table 16. Pacing indications and aspects of device implantation procedure in case-control study (N=94).

	Cases (N=47)	Controls(N=47)	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)*			
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 $\pm$ 1.10	3.58 $\pm$ 1.13	0.74
Total lead diameter/BL_Dmin†	0.38 $\pm$ 0.15	0.35 $\pm$ 0.14	0.53
Duration of implant procedure (min)	87.5 + 74.1	75.8 + 39.3	0.81

* 6 patients with biventricular devices had 2 access veins: cephalic and subclavian or axillary.

† BL_Dmin = Baseline minimum venous diameter.

Only 3 (6.4 %) of the 47 patients with end-points were found to have a prothrombotic coagulation disorder, but 2 (40 %) of the 5 cases with symptomatic pulmonary embolism had thrombophilia (Table 15). 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. (Study IV)

5.5.4.3. Antithrombotic therapies

There were no statistically significant differences in the utilization of anticoagulant or other antithrombotic therapies between cases and controls, although none of the 9 patients with major end-points were receiving therapeutic-level warfarin or low molecular weight heparin at the time of the pacemaker implantation. Antithrombotic therapies are detailed in section 5.3.4.(Study IV)

6. DISCUSSION

6.1. Venous pathology after pacemaker implantation

In order to determine the incidence of venous obstructive lesions, all patients were enrolled into the study based on intravenous contrast venography before PM implantation and after 6 months (study II). A total of 136 patients had a successful ICV both at baseline and at 6 months allowing comparisons of venous diameters before and after device placement, and establishing new venous obstructions. An overall incidence of 14 % for venous obstructive lesions (partial or complete) was found at 6 months after pacemaker implantation. The majority (74 %) of these lesions was non-occlusive, and total venous obstruction (TVO) was encountered in only 5 patients (3.6 %). Most obstructions (86 %) developed at the same location where the vein was at its narrowest already at baseline. None of the patients with obstruction, either partial or complete, exhibited any adverse symptoms (pain or swelling) in the ipsilateral upper extremity.

The proportion of patients with a new stenosis was considerably lower than that reported by Da Costa and co-workers[8] in a prospective study based on digital subtraction venography at six months after PM implantation. A very high proportion (64 %) of their patients was found to have venous obstruction ranging from mild to complete. Severe obstruction (70 to 99 % stenosis) or complete occlusion was found in a total of 21 % of their venograms. In another study the incidence of venous obstruction (narrowing by at least 60%) was 32.9 % [7].

One of the strengths of our study was the inclusion of baseline venography in our protocol. There appeared to be a surprisingly wide inter-individual variation in the size and contour of the veins, and we classified 10 (7.3 %) baseline venograms as abnormal including 7 cases of stenosis, and one complete occlusion. In the study of da Costa and co-workers[8], no venography was performed at baseline, thus making it difficult to determine whether all of the noted abnormalities were actually induced by the PM leads. Oginosawa and Nakashima[7] incorporated a baseline venogram in their study revealing venous obstruction in 13.7 % of the patients prior to device implantation (60 % reduction in venous diameter). This criterion may, however, classify individuals with non-stenotic veins as stenotic due to some exceptionally large or ectatic segments in their veins.

In the study of da Costa [8] previous use of a transvenous temporary pacemaker (present in nearly half of their patients) and decreased left ventricular ejection fraction emerged as significant risk factors for the venous lesions. The former could explain some of the difference in findings compared to our study, as in our material only two

patients had a temporary lead prior to PM implantation. We found no significant association with ejection fraction and the development of stenosis.

In the present study, only baseline atrial fibrillation and biventricular PM emerged as significant independent predictors for the development of obstructive venous lesions. Although we have no certain information regarding the mechanisms responsible for our findings, earlier research provides helpful clues. Atrial fibrillation may be associated with a prothrombotic and proinflammatory state as well as plasma hyperviscosity [134-136], which in conjunction with lead-induced vessel wall trauma might potentially initiate stenosis development. Incidence of venous obstruction was more than two-fold higher among patients with implanted biventricular device. Implantation of a biventricular device can be challenging, and vessel wall damage during manipulation of a guiding catheter, as well as subsequent mechanical irritation by implanted leads, may indeed be crucial factors for stenosis development among these patients. Endothelial damage especially in the setting of reduced blood flow and elevated central venous pressures from left ventricular failure could increase propensity for thrombus formation and subsequent fibrosis. Furthermore, underlying heart failure by itself has been associated with a release of various cytokines leading to hypercoagulable state, inflammation, and endothelial damage [137-139]. Few previous investigations have included an assessment of baseline rhythm as a predictor for venous obstruction, and AF did not emerge as a risk factor in these studies [7, 44]. Several studies have included impaired left ventricular function as one of the candidate parameters potentially predisposing to obstruction [6-9, 25, 44], but only one found a reduced left ventricular ejection-fraction (< 40%) to be a significant risk factor [8], and the presence of dilated cardiomyopathy was a univariate, but not a multivariate predictor of obstruction in another study [44]. In our case-control study (study IV), AF and biventricular PM did not emerge as significant predictors of the combined VTE-end-point, which included other thromboembolic lesions in addition to venographic obstructions. This discrepancy in findings is discussed further in section 6.4.

The limitations of venous diameter measurements include potential variations in degrees of venous filling and tone, and the possibility of a spasm as opposed to structural stenosis in some of our patients cannot be excluded. We performed the venographies only in the anterior-posterior plane, but the inclusion of a lateral view is unlikely to provide meaningful additional information. The location of our measurement reference on body surface and not on the same plane with the veins can introduce a slight geometric distortion to the absolute diameter measurements, but is not crucial for the evaluation of obstructions. Our search for predisposing factors may have been hampered by the limited size of our study population, and other factors could potentially be found in a larger group of patients.

Prevention of the development of venous lesions is one important goal in pacemaker therapy. Unfortunately, neither our study nor earlier data provide any methods to accomplish this. The access site or techniques, operator experience, lead coating or antithrombotic therapy had no effect on the incidence of venous obstructions.

6.2. Progression of venous pathology

In order to evaluate venous changes during a time course longer than 6 months, a follow-up venographic study was conducted on a cohort of 50 patients (study III), whose 6-month venography showed new pathology in 23 (46 %) and normal findings in 27 (54 %). This patient cohort was prospectively followed for a mean of 2.4 years after PM or ICD implantation. The findings of this longer-term follow-up suggest that most of the venous irritation and damage leading to obstruction is set into motion relatively early in the post-operative phase. However, in some patients the process seems to continue longer or may even start later because late complete venous occlusion may occur in presumably normal veins at 6 months after implantation.

The development of late venous obstruction in patients with previously normal venograms obtained at shorter follow-up is a unique feature of our study. To our knowledge, the only other prospective venography-based study with serial short- and longer-term venographies (up to 18 months) showed no new obstructions after the first 6-12 months in 26 patients with previously normal venograms [7]. At the other end of the spectrum, the only patient in our series with a symptomatic early acute venous thrombosis was repeatedly found to have normal venograms during later follow-up. Most of the total venous occlusions were clinically silent, although pulmonary embolism was diagnosed in two of these patients based on careful symptom history during the follow-up visit. It was disappointing that no clinical predictors for the total venous occlusions could be revealed by a careful consideration of various clinical and procedure-related factors.

After late venography, the number of patients with TVO amounts to a total of 9 cases or 6 % in our entire series of 150 patients. This figure is lower than in previously published series, but is probably an underestimate of the true incidence of occlusions, because only one third of the original study group was included in the late follow-up. Should a similar relative rate of TVO occur among the 100 remaining patients not followed venographically beyond 6 months, approximately 10 additional cases of TVO would be expected to develop, yielding a hypothetical incidence of 13 %. There are only limited earlier data on the time course of lead-induced venous changes in the literature. In an early cross-sectional series of 100 patients from a pacemaker follow-up clinic, venographies were performed at 44 $\pm$ 10 months after pacemaker implantation and total occlusion was revealed in 15 % of the patients [36]. In a small prospective venography-based study of 40 patients with no baseline venography, an early (1 to 6 months) total occlusion was observed in 8 % with no further abnormalities discovered at 18-24-month follow-up [2]. Oginosawa et al [7] performed digital subtraction angiography prior to PM implantation on 131 patients, and after a mean follow-up of 44 months re-studied 60 % of the patients observing asymptomatic total occlusion in 10 (13 %) of 79 patients. In recent small cross-sectional studies,

where venograms were performed in conjunction with device or lead replacement at widely ranging time intervals from initial device implantations, the prevalence of total venous occlusion has ranged from 9 to 25 % [3, 29, 44, 66]. However, selection bias, wide variation in follow-up times, and e.g. pacemaker infection [66] are likely to have contributed to these figures.

One of the unique features of our study is that the changes in venous calibres were serially assessed in a quantitative fashion. A small, but clinically insignificant, reduction in the mean venous diameters from the pre-implantation phase to the 6-month follow-up was observed. Whether the slightly larger venous diameters at the time of PM implantation are due to pre-operative hydration by intravenous fluid administration, or whether the presence of transvenous leads alone could induce a mild decrease of the diameters during the ensuing months cannot be distinguished in the present study. In the late follow-up the venous diameters were measured in identical fashion at the same reference points, and no significant further changes in the mean venous diameters were found to have occurred in the group as a whole after the 6-month follow-up. Small filling defects suggestive of non-flow-limiting thrombi seen in 14 % of the 6-month venograms are likely to be clinically mostly insignificant as the majority of them exhibited no progression in the late venograms, and development into an obstructive lesion was seen in only one case.

Limitations of this study include the fact that only one third of the initial group of patients were followed beyond the first 6 months. Furthermore, the selection of patients with pre-existing lesions may affect the incidence venous lesions in the late follow-up. Thus, the incidence of TVO developing later than the first six months post PM implantation, as reported in the current study, should be interpreted with caution.

6.3. Transesophageal echocardiography

A total of 66 patients were included in the TEE study of central venous lead-related thrombi after PM implantation (study I). The main finding of this prospective study was that pacemaker lead-associated thrombosis in the RA and proximal SVC is not infrequent 6 months after implantation, and that TEE was superior in the diagnosis of these thrombi compared to peripheral intravenous contrast venography and TTE. At 6 months post-implantation the incidence of electrode-attached RA thrombus was 9 % as evaluated by TEE. Most of these thrombi were clinically silent, but symptomatic pulmonary embolism was found in some of the cases.

Peripheral intravenous contrast venography revealed subclavian or innominate vein thrombi in 20 % of our patients, but only one of the thrombi was completely occlusive, while the rest were small and nonocclusive. However, none of the RA thrombi visualized by TEE were seen in venography. These two methods could thus

be regarded as complementary diagnostic modalities. When the findings in TEE and venography were combined the overall incidence of lead associated thrombus was 27 % which is within the range previously reported in the literature [7, 9, 16]. However, assessment of the right ventricle can be difficult even with TEE and detection of thrombi within this chamber could potentially be missed even with this highly sensitive method. Important observations have come from autopsy data published in the recent years, which suggest that a significant portion of pulmonary emboli may arise within the right heart chambers especially in conjunction with right ventricular thrombi [43]. A significant proportion of the latter was diagnosed only post-mortem. A careful assessment of the right ventricle is thus warranted in a PM-patient suspected of having central venous thrombosis.

The echocardiographic appearance of a lead attached thrombus and infectious vegetation may be very similar. Differentiation of these diagnostic alternatives was not possible by echocardiographic means alone in our patients, but at the time of TEE or during subsequent follow-up none of the patients exhibited any symptoms or clinical findings of endocarditis rendering the diagnosis of endocarditis highly unlikely in these cases. The present findings that asymptomatic small thrombi mimicking vegetations are frequent in pacemaker leads should be kept in mind in the differential diagnosis when evaluating a febrile patient with permanent pacemaker leads. So-called fibrin strands attached to electrodes are not an infrequent finding at pacemaker lead extraction, although their frequency and clinical significance are not described in literature. Some of the lead attached lesions in our study may indeed have represented these types of strands, but the exact composition of lead attached lesions cannot be distinguished by TEE.

Routine utilization of TEE to evaluate PM leads is limited by its semi-invasiveness and cost. Some patients will not be able to tolerate the study, despite topical anesthesia and the availability of sedative medication. However, TEE would appear to be the method of choice to assess potential thrombi within the RA and proximal SVC when a clinical suspicion arises. Other methods such as TTE offer limited visualization and peripheral venography is hampered by inadequate contrast concentration in RA. Use of MRI is contraindicated by the PM itself.

We conclude that, in addition to previously reported common occurrence of subclavian vein thrombosis and stenosis, occult central venous thrombi associated with indwelling transvenous electrodes are surprisingly frequent. Although they mostly appeared to be asymptomatic, some of them gave rise to small symptomatic pulmonary emboli. Lead-attached thrombi should also be kept in mind in the differential diagnosis of endocarditis. In this study TEE was the best in the diagnosis of these lesions as they may be undetectable by TTE and conventional peripheral venography. Ours was a cross sectional study conducted at six months. Further investigations into this field are thus warranted to assess the progress of these lead-attached lesions over time, and to further evaluate their clinical significance.

6.4. Clinical and laboratory risk factors

To assess of the role of various potential background attributes in the development of venous complications after pacemaker implantation, a case-control study was conducted (study IV). All cases (n=47) that had been diagnosed with a venous obstruction, thrombosis and/or pulmonary embolism were included, and one matched control (n=47) without any venous obstruction or thromboembolism was assigned to each of the cases. This case-control study shows that although asymptomatic venous obstruction and thrombosis are common after pacing device implantation, the development of these complications cannot be predicted by any technical parameters of leads or implantation surgery. In our study, the relative frequency of end-point 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 cannot be used to screen for venous thromboembolism early after implantation.

Pacemaker lead associated thrombus formation is likely to be multifactorial and potentially involves all 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 [99]. Even an attempted pacemaker implantation may lead to venous occlusion[100]. 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 end-points neither in the current nor in the majority of previous studies [3, 7, 8, 41, 132].

In order to quantify 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 fibrin degradation products can be used as a measurement of both fibrin formation and breakdown [103]. It is well known, that a surgical procedure (e.g. PM implantation) and its consequent tissue destruction and acute phase reaction, by itself induces a

hypercoagulable state, even without apparent venous thrombosis [101]. This state is reflected in the elevation of plasma biomarkers, such as F1+2 and DD. It is further known that the more extensive the tissue destruction is the higher is the rise of these parameters. 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. Our findings are in agreement with 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. The fact that there was no difference in the degree of post-operative elevation of these biomarkers between the case and the control groups implicates that there was no significant difference in the extent implantation-related tissue destruction and in the resultant primary activation of the coagulation system between the groups. This is in accordance to the fact that there was no significant difference in the mean duration of the implant surgery and techniques employed in cases vs. controls. In other words, early implantation-related triggering conditions for thrombus-formation and venous lesions did not differ significantly in cases and controls as determined both by these plasma biomarkers and by clinical procedure-related parameters, such as duration of implantation surgery. It thus appears that the extent of early trauma from implantation may not be a major determining factor for subsequent development of venous obstruction and thrombosis. This emphasizes the importance of patients' individual characteristics (presence of risk factors including inherited and acquired persistent thrombophilic states) in the development of these lesions.

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 marker for endothelial activation, despite its poor specificity [105]. 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 [106, 107]. 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. 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 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, was not associated to the development of venous lesions. The lack of association between the number of pacemaker leads to the venous lesions is in agreement with the majority of the previously published (mostly cross-sectional) studies [3, 6-8, 132], with the exception of one [9]. 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 baseline vessel size was not associated with end-point events.

Congestive heart failure [140, 141] and atrial fibrillation [142, 143] 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. Indeed, in our study on venous obstruction (study II), AF and implantation of a biventricular PM (patients with heart failure) appeared to be associated with an increased risk for venographic obstructive lesions. However, the case-control study (study IV) did not reaffirm such a link between these two clinical background conditions and VTE. However, these two studies differed in the number study subjects with a smaller number in the case-control approach (study IV), and also in the definition of the end-points as in study IV all other forms of venous thrombosis and emboli were included in the end-point of VTE in addition to the venographic obstructions. Use of warfarin may have also had a diminishing effect on the association between AF and the combined VTE-end-point, although at the time of PM implantation the proportion of patients receiving therapeutic level anticoagulation (either warfarin with INR $\geq$ 2.0 or LMWH) was not significantly different (p=0.229) among patients with AF or sinus rhythm.

Some studies have suggested that anticoagulation with warfarin protects against pacemaker lead thrombosis [9, 25, 44]. 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. However, our study was not specifically designed to assess the effects of anticoagulation on venous lesions and the findings should therefore be interpreted with caution. Further investigations into the potential protective role (and into the possible contrary effects on the risk of bleeding) of anticoagulation are warranted, preferably in a randomized prospective study. Also, a PM-implanting clinician would anticipate future research into this field to provide more accurately defined criteria to identify a patient at-risk for clinically significant thrombosis and in whom the use prophylactic anticoagulation would be of benefit.

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 [2, 3, 7, 132]. 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, end-points appeared to be associated with clustering of classic VTE risk factors, as the occurrence of end-point 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 [9]. Similarly, systemic infection was a promoter of venous occlusion in a study using lead extraction experience [41].

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 [129, 144-147]. Of note however, 2 of 5 (40 %) patients with pulmonary embolism had thrombophilia (Table 15). Hereditary thrombophilia has previously been reported to be common in patients with pacemaker-induced superior vena cava syndrome [148], but Factor V Leiden/Prothrombin G20210A mutation and the activity of Factor VIII/C were not identified as independent risk factors for venous thrombosis after pacemaker implantation in another study [9].

There are certain limitations to this case-control study. Our study had limited power to assess the predictive value of potential risk factors with a low prevalence. 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 end-points, 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.

7. SUMMARY AND CONCLUSIONS

7.1. Summary of study findings

The venographies conducted before PM implantation and 6 months afterwards showed that the development of venous obstruction after permanent transvenous electrode implantation is not infrequent even with the modern thin PM leads as the incidence of obstruction was 14 %. Variations in implantation technique did not predict the development of these lesions, but obstructions were more common in patients with atrial fibrillation at the time of PM implantation and in those who received a biventricular PM. The majority of the obstructions in our study were non-occlusive and all were asymptomatic. However, lesions of this type could potentially cause difficulties in patients requiring an upgrade of the device or removal/replacement of leads in the future.

The two-year follow-up study showed the development of venous obstruction to be an ongoing process even after the first 6 months in some patients. This paper also presented the incidence (14 %) of minor non-obstructive venographic thrombi among those with a successful 6-month venogram (n=140), and described the symptoms related to venous obstruction and thromboembolism, as well as reported the incidence (5.3 %) of acute implantation-induced complications. Although most of the obstructive lesions and changes in venous calibres appear to develop during the first months of the post-implantation period, late and unpredictable complete venous occlusion may also occur. Unfortunately, no significant predictive factors for the development of total venous occlusions could be identified. One clinical implication from the study is that a venogram of the upper extremity should always be performed before upgrading or for other reasons implanting new leads to the same side of a previous pacemaker.

The TEE-study revealed that, in addition to previously reported common occurrence of subclavian vein thrombosis and stenosis, occult central venous thrombi associated with indwelling transvenous electrodes are surprisingly frequent. Although these thrombi mostly appear to be asymptomatic, one third of them gave rise to small pulmonary emboli and should also be kept in mind in the differential diagnosis of endocarditis. In this study TEE was the best method in the diagnosis of these lesions as they may be undetectable by TTE and conventional peripheral venography. Ours was a cross sectional study conducted at 6 months, and further investigations are thus warranted to assess the progression of these lead-attached lesions over time, and to further evaluate their clinical significance.

In the case-control study, none of the procedure-related variables were predictive of venous thromboembolism. Mean levels of vWF, F1+2, and DD increased significantly ($p<0.001$) and equally in both cases and controls suggesting a similar degree of procedure-triggered vascular and tissue damage and consequent induction of a hypercoagulative state. Thus, the degree early injury from implantation does not appear to be a major determinant of subsequent VTE or VO. 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 %). Thus, device implantation was shown to induce a definite hypercoagulable state, but no singular laboratory or clinical parameter predicted the development of venous thrombosis or obstruction. Therefore it is likely that the etiology of these lesions is multifactorial, and clustering of risk factors plays a role in the pathogenesis.

7.2. Conclusions

1. Venous obstructive lesions and thromboembolism are not uncommon after pacing device implantation as the overall incidence of such lesions amounted to 31.3 % at 6 months.
2. The incidence of venous obstruction was 14 % at 6 months after PM implantation and the majority (74 %) of these lesions was non-occlusive.
3. Total venous occlusion was encountered in 5 patients (3.6 %) at 6 months, and 4 additional cases were found in 50 late venograms conducted at approximately 2 years after PM implantation. Thus, the overall rate of total occlusion of the access vein extended into the entire series of 150 patients amounted to 6 % (a figure that is likely to be an under-estimation of the true incidence).
4. Most of the obstructive lesions and changes in venous calibres appear to develop during the first months of the post-implantation period, but late and unpredictable complete venous occlusion may also occur.
5. Transesophageal echocardiography was shown to be a feasible method to diagnose lead-attached thrombi within the central venous system as such thrombi were found in 6 (9 %) of the studied patients. Two of these patients were also found to have pulmonary embolism. TEE yielded additional pathologic findings unobtainable by venography or transthoracic echocardiography.
6. The vast majority of the venous lesions and thromboembolism induced by pacemaker placement are asymptomatic.
7. The majority of the end-point lesions are likely to remain clinically benign, but serious and even potentially life-threatening pulmonary embolism can develop in some patients.

8. Clustering of classic clinical risk factors in individual patients appears to predispose to venous lesions and thromboembolism after pacing device implantation, although none of these risk factors were significant univariate predictors when assessed separately in the case-control study.
9. The presence of atrial fibrillation at implantation and the placement of a biventricular device were significant independent predictors of the development of venographic obstructive lesions occurring during the first 6 months. However, in the smaller case-control study, these same clinical parameters were not significantly associated with the development of the combined end-point, which also included all other types of thromboembolic lesions in addition to the venographic obstructions.
10. Pacing device implantation induces a definite and measurable acute activation of coagulation post-operatively, which reflects the grade of initial tissue injury from the surgery. However, the degree of elevation in the biomarkers reflecting this injury and the consequent hypercoagulative state is not predictive of later development of venous lesions and thromboembolism.
11. The levels of plasma D-dimers become elevated in nearly all patients after pacemaker implantation, and thus, this test cannot be used for screening for pulmonary embolism in these patients during the early post-operative phase.

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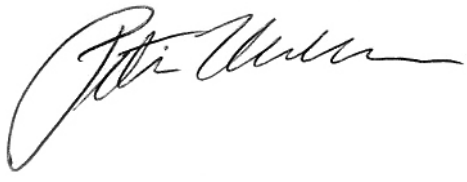

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