Risk assessment of thrombosis associated with central venous catheters

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Hold up
Hold on
Don't be scared
You'll never change what's been and gone

(Noel Gallagher)

Dedicated to my father
In memory of my mother

Contents

CHAPTER 1

Deep Vein Thrombosis Associated with Central Venous Catheters – a Review

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Introduction

Central venous catheters (CVCs) are frequently used in patients for a variety of indications such as cancer treatment, diagnostic monitoring, parenteral nutrition, haemodialysis, cardiac pacing, and administration of fluids, blood products or medication.[1] The benefit derived from a CVC may be offset by thrombosis and associated complications, such as pulmonary embolism (PE), CVC dysfunction, infection or loss of venous access. In the long term patients with thrombosis may suffer from a post thrombotic syndrome.[1,2]

The CVC-related thrombosis is an issue of importance to many clinicians, and insight into the different aspects is crucial to guide decisions in treatment in often vulnerable patients in daily practice. In medical literature, there is a lack of uniformity and uncertainty about several entities of CVC-related thrombosis. Firstly, two types of CVC-related thrombosis must be clearly distinguished: i.e. clinically manifest and subclinical thrombosis. Furthermore, the type of thrombosis and the incidence is defined by the diagnostic strategy in patients with a CVC. Secondly, anticipation of the risk of CVC-related thrombosis and the identification of certain "high-risk" patients, who are prone to develop thrombosis and secondary complications, is essential to initiate early preventive measurements such as prophylactic anticoagulation. The need for anticoagulant prophylaxis is however still a subject of discussion.[3,4] Finally, for the treatment of established CVC-related thrombosis, several therapeutic options were evaluated in literature. General recommendations of anticoagulant treatment, and whether CVC removal is necessary, or not, is warranted.

The primary aim of this review is to describe the diagnostic methods and their performance, the incidence and risk factors, complications, prevention and treatment of CVC-related thrombosis from a practical and clinical point of view. English medical literature studies were retrieved by an extensive Medline search (Pubmed®) and bibliographies of the obtained studies were cross-checked where necessary. For each subject, only those studies with the strongest level of evidence, as defined and discussed in the subsequent paragraphs, were selected and reviewed.

Diagnosis of CVC-related thrombosis

In view of diagnosis of CVC-related thrombosis, two types of thrombosis can be distinguished; clinically manifest thrombosis and subclinical thrombosis. Clinically manifest thrombosis is defined as thrombosis objectified by diagnostic imaging (ultrasound, venography) upon overt symptoms and signs, such as pain or tenderness, warmth, swelling or edema, bluish discoloration or visible collateral circulation. Subclinical thrombosis, defined as thrombosis in the absence of signs and symptoms, is demonstrated by screening diagnostic imaging. Most thrombotic events associated with CVCs remain subclinical, or complications such as PE are the first presenting symptom.[5-7]

Radiologically, thrombosis can have a typical appearance of enveloping sleeve surrounding the CVC (Fig. 1) or be characterized by mural thrombosis adherent to the venous vessel wall.[8] Mural thrombosis, present in approximately 30% of patients with CVCs, may cause subtotal stenosis (Fig. 2) or occlusion of the venous lumen and lead to clinically manifest thrombosis or associated complications.[6] Mural thrombosis is often found near the entry site of the CVC into the vessel or at the junction of large veins, although it may be extended or located into adjacent venous segments or the right atrium.

In the diagnostic work-up of CVC-related thrombosis, diagnostic imaging upon a clinical suspicion of thrombosis is mandatory. A diagnosis based solely on clinical symptoms and signs of thrombosis is non-specific, as in deep vein thrombosis (DVT) of the leg. In only about a third to a half of all patients in whom thrombosis is clinically suspected, the diagnosis is confirmed.[9-11]

Contrast venography is widely recognized as the reference standard in the diagnosis of thrombosis.[12] However, ultrasound is most often used clinically, because it is non-invasive, does not expose to ionizing radiation, can easily be performed at the bedside and is well accepted by patients. In modern ultrasonography, real time gray-scale images (B-mode) are obtained and the criteria of non-compressibility (compression ultrasound) and direct visualization of thrombotic material in the venous lumen can be used to establish the presence, or absence, of thrombosis. Besides, real time changes in vessel diameter due to respiration may detect occlusive thrombosis more centrally located. In addition, Doppler techniques can add the advantage of evaluation of blood-flow. With pulsed Doppler signals added to gray scale imaging (duplex ultrasound) qualitative and quantitative information of blood flow can be obtained. Color Doppler flow imaging (CDFI) displays blood flow in color in addition to gray scale imaging. A combination of all three modalities is known as color duplex ultrasound.

In symptomatic lower extremity DVT, compression ultrasonography has been validated in clinical practice,[13] but specifically for thrombosis associated with femorally insert-

ed CVCs no studies are available in which ultrasound was compared to venography. With regard to the upper-extremity DVT, venography has high to moderate inter-observer agreement rates (71 - 83%) and can be used as a reference test in clinical practice.[14] In several studies the diagnostic accuracy of ultrasound in upper extremity thrombosis compared with venography was evaluated.

For the purpose of this review, we selected those studies in which ultrasound was compared to routine contrast venography in the diagnosis of upper-extremity DVT in the entire cohort of reported patients, and which results were independently interpreted by blinded observers. Overall, six studies were retrieved (Table 1) in which patients with CVCs were included. The reported sensitivity of ultrasound in the diagnosis of upper extremity DVT among these studies ranged from 56% to 100%, whereas the specificity ranged from 77% to 100%.[10,11,15-18]

Reports specifically aimed at patients with CVCs are limited to three studies only.[16-18] Importantly, in patients with CVC-related thrombosis, thrombosis tends to be located more centrally than in patients with thrombosis not related to CVCs.[4] As a consequence, the diagnostic technique of ultrasound, and therefore the accuracy, in patients with suspected thrombosis because of CVCs is different than those without (history of) CVC. In one study continuous wave Doppler without gray scale imaging was used, a technique hardly applied nowadays.[18] Applying modern techniques, duplex ultrasound was reported to have an excellent specificity (100%), however the sensitivity was substantially lower (56%).[17] In another study, CDFI was found to be more sensitive (sensitivity 94%, specificity 96%).[16]

Summary

In summary, reliable data on the accuracy of ultrasound in CVC-related thrombosis are limited. In lower extremity CVC-related thrombosis no studies are available. In upper extremity CVC-related thrombosis specifically, only three studies are available, of which CDFI had the best performance (sensitivity 94%, specificity 96%). In view of the advantages of ultrasound mentioned, and the high specificity, patients with clinically suspected CVC-related thrombosis, should undergo ultrasound initially. However, the safety of withholding treatment in case of a negative ultrasound in patients suspected for thrombosis is uncertain.[19] As a consequence, in patients with normal ultrasound additional venography could be performed. Alternative strategies such as serially performed ultrasound, spiral computed tomography (CT) or magnetic resonance imaging (MRI) may be useful and of potential interest, but are not validated yet.

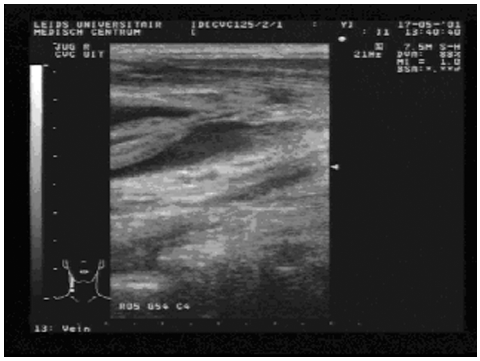

Figure 1. Ultrasonic appearance of a typical enveloping "fibrin sheath" demonstrated immediately after catheter removal (Jugular vein)

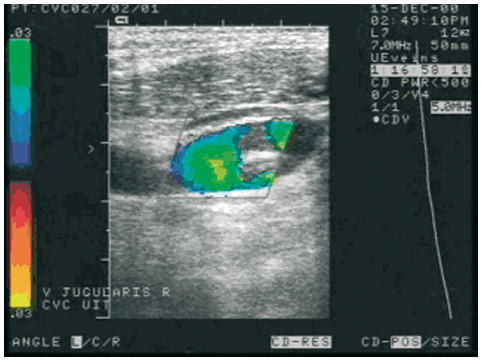

Figure 2. Nearly occlusive mural thrombosis visualised by a flow defect, detected by colour Doppler flow imaging, just after catheter removal

Table I. Diagnostic accuracy of ultrasound in the diagnosis of upper extremity thrombosis with routine contrast venography as the reference standard.

Study (Reference)	Patients	CVC†	Technique‡	Sensitivity	Specificity	Thrombosis-type*
Prandoni *et al.* (10)	n = 58	14%	CUS	96%	94%	Manifest
Prandoni *et al.* (10)	n = 47	N.I.	Duplex	81%	77%	Manifest
Prandoni *et al.* (10)	n = 34	N.I.	CDFI	100%	93%	Manifest
Baarslag *et al.* (11)	n = 99	N.I.	CDFI	82%	82%	Manifest
Baxter *et al.* (15)	n = 19	74%	CDFI	100%	100%	Manifest
Köksoy *et al.* (16)	n = 44	100%	CDFI	94%	96%	Mixed
Haire *et al.* (17)	n = 43	100%	Duplex	56%	100%	Mixed
Bonnet *et al.* (18)	n = 40	100%	Doppler	93%	93%	Mixed

† Percentage of patients with a central venous catheter (CVC). N.I. = Not Indicated

‡ Technique: CUS = compression ultrasound; CDFI = color Doppler flow imaging.

* For definition manifest/subclinical, see text.

Incidence and risk factors of CVC-related thrombosis

Incidence

In numerous studies the incidence of CVC-related thrombosis has been evaluated. In most studies, clinically manifest thrombosis was used as the primary endpoint. Among these studies incidences ranging from 0% to 28% were reported.[20,21] However, the decision to refer for diagnostic imaging upon clinical signs and symptoms for thrombosis lacks uniformity and may be subjective.
A more reliable estimate is given by studies in which routine diagnostic screening (ultrasound or venography) was used in consecutive patients with CVCs to determine thrombosis. For the purpose of this review these studies are selected and summarized in Table 2, according to the indication for the CVC, i.e. the underlying disease and the type of thrombosis (subclinical, clinically manifest and overall).[5,6,8,22-44]

Overall, the reported incidences of CVC-related thrombosis in these studies ranged widely from 2% to 67% (Table 2). The wide range in observed incidence may be partly caused by different diagnostic modalities (venography, ultrasound), the used criteria, and patient- and CVC characteristics. On average, a 30% cumulative incidence was found in hospitalized patients and the overall majority of thrombotic events remained subclinical.[6] The percentage of clinically manifest thrombosis in these studies ranged from 0% to 12% (Table 2).

In some specific populations, such as patients with hemophilia, prospective (screening) studies are not available. In cohort-studies with merely clinical manifest thrombosis as an endpoint incidences ranged from 0% to 3%.[45] Whether in patients with inherited bleeding disorders the risk of thrombosis is reduced as compared to other patients, is not known because of the lack of large studies in which all patients were screened systematically for thrombosis.

Risk factors

The individual risk of CVC-related thrombosis in a patient is the result of the interaction between patient characteristics, i.e. inherited and acquired risk factors; and the CVC (Fig. 3). There are numerous studies in which risk-factor analysis of CVC-related thrombosis was performed. For inherited and common acquired risk factors cohort studies were considered to represent the highest level of evidence (level 1); case control studies as level 2. For CVC characteristics, randomized trials were considered to represent level 1 of evidence; cohort studies as level 2.

Inherited coagulations disorders have been reported to contribute substantially to CVC-related thrombosis in large cohort studies (level 1). Factor V Leiden (FVL) was strongly associated with clinically manifest thrombosis in patients who underwent bone

marrow transplantation (n=277); i.e. 54% of patients with FVL developed thrombosis, in comparison to 10% of patients without (Cox proportional hazard ratio 7.7).[46] In a large hospital population of 252 patients, the presence of FVL and prothombin G20210A mutation increased the overall risk of CVC-related thrombosis almost threefold.[6] Two other recent performed studies also suggested a contribution of commonly inherited coagulations disorders.[47,48] In contrast to these studies, a case control study (level 2) reported no increased prevalence of FVL in patients with CVC-related thrombosis as compared to the general western population.[49] In children, similar risk estimates as in adults have been reported. In cohort studies, the risk of thrombosis in FVL carriers in pediatric patients was substantial in patients with acute lymphoid leukemia, as well in mixed populations.[43,50,51]

With regard to common acquired risk factors of venous thrombosis there are numerous studies of different level of evidence. In cohort studies, the presence of cancer or active cancer treatment, in both adults and children,[6,44] prior thromboembolism;[32] acquired (temporary) hypercoaguable state;[43,52] and a high platelet count at CVC insertion,[53] were associated with thrombosis. Age was also associated with CVC-related thrombosis, the risk was higher with increasing age, and in very young children.[24,44]

Many CVC characteristics have been associated with an increased risk of CVC-related thrombosis. The type of CVC may be an important factor in the development of CVC-related thrombosis. Catheters composed of silicon or polyurethane are less often associated with local thrombosis than CVCs made of polyethylene.[35,54,55] In addition, the risk of thrombosis tends to increase with the number of CVC lumina.[5,56] The role of the puncture-site of CVC insertion is still much debated. In two randomized trails (level 1) in intensive care unit patients insertion via the subclavian route had a low risk of thrombosis as compared to a femoral route (0% *vs.* 25%, respectively 6%).[57,58] A similar observation was found in a cohort (level 2) study in patients with subclavian vein CVC as compared to jugular CVCs (11% *vs.* 42%).[24] In both studies patients were routinely screened by ultrasound for CVC-related thrombosis. However, the methodology of comparing femoral with subclavian vein thrombosis associated with CVCs can

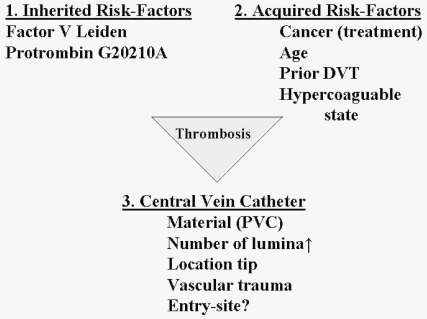

Figure 3. Interaction of inherited, acquired risk-factors of thrombosis with catheter characteristics play an important role the development of catheter-related thrombosis.

be debated since the technique and accuracy of ultrasound in asymptomatic upper and lower DVT differ. In a recent cohort study (level 2) in children, the subclavian route had an increased risk of thrombosis as compared to the jugular route as assessed by a combination of routine venography and routine ultrasound.[58] In cohort studies, a left insertion side has been reported to increase the risk of thrombosis,[37,53,58] and with a CVC tip position into the subclavian or innominate vein, thrombosis was more often observed in comparison to a superior caval vein or right atrial tip location.[39] Additional factors in cohort studies that have been reported to increase the risk of thrombosis are a percutaneous insertion procedure, prior CVC at the same puncture site and a prolonged stay of the CVC for over 2 weeks.[58,59]

Summary

In summary, CVC-related thrombosis is a multicausal disease. Prothrombotic factors (e.g. FVL) and the underlying disease (cancer) may play an important role in the development of CVC-related thrombosis. Some important CVC characteristics increase the risk of thrombosis, such as the type and material of the CVC, vascular trauma and the duration of stay of the CVC.

Complications

Central venous catheter-related thrombosis may be associated with several complications including PE, infection of the thrombus, CVC dysfunction and subsequent loss of intravenous access and post-thrombotic syndrome or recurrent thrombosis.

Pulmonary embolism

The reported incidence of PE as a complication of CVC-related thrombosis varies. In only one study, all patients with proven thrombosis systematically underwent screening for PE (ventilation-perfusion scan) and a 15% cumulative incidence was reported.[60] In other studies incidences of PE, using merely clinical endpoints, varied greatly. Whereas incidences of symptomatic PE up to 17% have been reported, others did not observe any PE.[61,62] Pulmonary embolism associated with CVC-related thrombosis has been reported to be the cause of death.[7,60]

Screening for PE if a diagnosis of CVC-related thrombosis is established, is usually not mandatory, since in most patients anticoagulant treatment is initiated, eventually with a removal of the CVC. A firm evidence regarding clinical outcome needs however to be established prospectively.

Table II. Incidence of catheter-related thrombosis amongst studies with routine diagnostic imaging performed in consecutive patients (ultrasound or venography).

Study (Reference)	Population*	n	Technique‡	Thrombosis	(manifest)	Location entry-site
Chastre *et al.* (22)	ICU	33	V	67%	(0%)	Jugular vein
Durbec *et al.* (23)	ICU	70	V	36%	(0%)	Femoral vein
Timsit *et al.* (24)	ICU	208	U	33%	(0%)	Subclavian & Jugular vein
Wu *et al.* (25)	ICU	81	U	56%	(0%)	Jugular vein
Joynt *et al.* (26)	ICU	124	U	10%	(2%)	Femoral vein
Martin *et al.* (27)	ICU	60	U	58%	(2%)	Axillary vein
Stoney *et al.* (28)	Cardiology	203	V	34%	(3%)	Cephalic & Jugular vein
Goto *et al* (30)	Cardiology	100	V	23%	(0%)	Cephalic & Subclavian vein
Lin *et al.* (29)	Cardiology	109	U	6%	(0%)	Cephalic & Subclavian vein
Antonelli *et al.* (31)	Cardiology	40	V	28%	(5%)	Cephalic & Subclavian vein
van Rooden *et al.* (32)	Cardiology	145	U	23%	(2%)	Cephalic & Subclavian vein
Valerio *et al.* (33)	Oncology	18	V	33%	(6%)	Subclavian vein
Brismar *et al.* (34)	Oncology	53	V	36%	(unknown)	Subclavian vein
Bozetti *et al.* (35)	Oncology	52	V	28%	(0%)	Subclavian vein
Haire *et al.* (5)	Haematology	35	V	63%	(9%)	Subclavian vein
Balesteri *et al.* (8)	Oncology	57	V	56%	(0%)	Subclavian vein
De Cicco *et al.* (37)	Oncology	95	V	66%	(6%)	Subclavian vein
Biffi *et al.* (38)	Oncology	302	U	4%	(2%)	Subclavian & Cephalic vein
Luciani *et al.* (39)	Oncology	145	U	12%	(3%)	Subclavian vein
Harter *et al.* (40)	Oncology	233	U	2%	(0%)	Jugular vein
Lordick *et al.* (41)	Haematology	43	U	30%	(0%)	Jugular vein
van Rooden *et al.* (42)	Haematology	105	U	28%	(12%)	Jugular & Subclavian vein
Nowak-Gottl *et al.* (43)	Pediatrics	163	U	11%	(11%)	Subclavian vein
Beck *et al.* (44)	Pediatrics	93	U	18%	(8%)	Jugular & Subclavian & Femoral vein
van Rooden *et al.* (6)	Mixed	252	U	30%	(7%)	Jugular & Subclavian vein

*Population: ICU = Intensive Care Unit

‡ Technique: V = Venography; U = ultrasound

Infection

CVC-related thrombosis and CVC-related infection have been reported to be associated.[24,41,63,64] The pathogenesis of CVC-related infection seems to depend on the development of thrombosis of the CVC. Several thrombo-proteins were shown to increase the risk of subsequent infection.[65,66] Results from a post-mortem study in 72 patients with a CVC at death revealed that in all patients with CVC-related sepsis (n=7) mural thrombosis after a CVC was present, out of a total number of 31 patients with thrombosis.[63] In a study in 265 critically ill patients the risk of infection and sepsis was 2.6-fold increased in patients with CVC-related thrombosis.[24] In 43 patients undergoing intensive chemotherapy, 13 patients had objectified subclinical thrombosis of whom 12 developed infection.[41]

In addition, CVC-related infection may also increase the risk of subsequent clinically manifest thrombosis. In one study CVC-related infection increased the risk of thrombosis (24%) markedly in comparison to those without infection (3%) (relative risk 17.6).[64]

In the presence of CVC-related infection, it may be useful to screen patients for thrombosis with ultrasound, even in the absence of other clinical overt signs and symptoms. Whether such a strategy is clinically beneficial, improves clinical outcome, and is cost-effective should be further investigated.

Early CVC removal and dysfunction

The CVC dysfunction due to clot formation may occur due to obstruction within the CVC lumina, or occlusion due to an enveloping sheath obstructing the CVC luminal tip. Clot formation of the CVC has been identified as the principal cause of CVC dysfunction in prospective follow-up studies. In a study in 85 CVCs placed for haemodialysis, 16 (19 %) clot formation occurred leading to CVC malfunctioning requiring removal of the CVC in all cases. [67] In another study in 92 CVCs inserted for haemodialysis, 11 CVCs had to be removed because of catheter complications.[68] In six (55%) of these cases, occlusion due to clot was the major reason for removal of the CVC. In a study of 949 CVCs placed for ambulatory chemotherapy in cancer patients, 152 (18%) of the catheters had to be removed due to complications.[69] In this study infection of the CVC was the leading cause of removal of the CVC, 47 (31%) out of 152 CVCs, but also 38 (25%), had to be removed due to CVC-related thrombosis or dysfunction due to clot. In a large study based on the Strategic Health Care Programs National Database, CVC complications that occurred in 45.333 CVCs used in an outpatient setting in a 17-month period between 1999 and 2000 were evaluated.[70] In 1.871 CVCs dysfunction occurred, and in 511 (27 %) cases dysfunction occurred as a consequence of clot formation. In this study different types of catheters were shown to carry a different complication rate but thrombosis

Table III. Studies in which the benefit from anticoagulant prophylaxis for catheter-related thrombosis was evaluated. Studies were classified into three categories: Randomized controlled trials with routine mandatory diagnostic imaging 2. Randomized controlled trials with clinically manifest thrombosis or associated complications, and 3. Observational studies with clinically manifest thrombosis or associated complications.

Randomized controlled trials – Mandatory diagnostic imaging

Study (Reference)	Population	n	Intervention	Patients	Controls	Endpoint
Bern *et al.* (74)	Oncology	82	Warfarin 1mg	9.5%	42%	Mandatory venogram
Monreal *et al.* (75)	Oncology	29	Dalteparin 2500 IU	6%	62%	Mandatory venogram
Abdelkefi *et al.* (76)	Haematology	128	UFH (100 IU/kg)	1.5%	12,6%	Mandatory ultrasound
Brismar *et al.* (34)	Nutrition	49	UFH (5000 IU q 6h)	21.7%	53.8%	Mandatory venogram
Rugerio *et al.* (80)	Nutrition	34	UFH (1000 IU/L)	53%	65%	Mandatory venogram
Fabri *et al.* (81)	Nutrition	46	UFH (3000 IU/L)	8.3%	31.8%	Mandatory venogram
Fabri *et al.* (82)	Nutrition	40	UFH (3000 IU/L)	0%	0%	Mandatory venogram
Mackoviak *et al.* (79)	Nutrition	37	UFH (1U/ml)	17.6%	15.6%	Mandatory venogram
Pierce *et al.* (78)	Pediatr. Crit. Ill	209	UFH bonded CVC	8%	0%	Mandatory ultrasound
Massicotte *et al.* (77)	Pediatr. Oncology	158	Reviparin 30-50 IU/kg	14.1%	12.5%	Mandatory venogram

Randomized controlled trials – Clinical endpoints

Study (Reference)	Population	n	Intervention	Patients	Controls	Endpoint
Heaton *et al.* (84)	Haematology	88	Warfarin 1 mg	17.7%	11.6%	Including PE & malfunction
Anderson *et al.* (85)	Oncology	255	Warfarin 1 mg	4.6%	4%	CMT only
Reichardt *et al.* (83)	Oncology	425	Dalteparin 5000IU	3,4%	3,7%	CMT only

Cohort studies - Clinical endpoints

Study (Reference)	Population	n	Intervention	Patients	Controls	Endpoint
Boraks *et al.* (86)	Oncology	223	Warfarin 1 mg	5%	13%	CMT only
Lagro *et al.* (87)	Oncology	323	Nadroparin 2850IU	7%	6%	CMT only
Lagro *et al.* (87)	Oncology	323	Nadroparin 5600IU	8%	6%	CMT only

UFH = unfractionated heparin; CMT = clinically manifest thrombosis; PE = pulmonary embolism.

was the most commonly reported cause of CVC dysfunction for peripherally and centrally inserted CVC with implantable ports.

Post-thrombotic syndrome and recurrent thrombosis

The incidence of the post-thrombotic syndrome, characterized by venous hypertension, swelling of the extremity and pain,[10] has been studied in patients without a CVC who experienced an episode of deep vein thrombosis. In such patients, an incidence of up to 80% of the post-thrombotic syndrome has been reported.[71] However, data on post-thrombotic syndrome occurring as a sequela of CVC-related thrombosis are scarce and show contradictory results. Hingorani *et al.* reported a cumulative incidence of 4%, whereas Hicken *et al.* found a much higher cumulative incidence of 50%.[63,72] In a prospective study of a large group of 405 children with various diseases who all developed thrombosis of the upper or lower extremity, 244 (60 %) had a CVC.[73] Of these 405 children, 40 % had thrombosis of the lower and 60 % had thrombosis of the upper extremity. Post-thrombotic syndrome was found to occur in fifty (12%) of the 405 children. Of the 50 children who developed a post-thrombotic syndrome, 23 had a CVC. In this study a CVC was not an indicator for post-thrombotic syndrome (OR 0.59; CI95% 0.28 – 0.94). There are no reliable data concerning recurrent thrombosis after an episode of proven CVC-related thrombosis.

Summary

In summary, PE is an understudied and probably underdiagnosed complication of CVC-related thrombosis and together with infection of the thrombus a serious life-threatening complication. In clinical practice, an established diagnosis of infection may render it worthwhile to screen for thrombosis with ultrasound. Besides, luminal clot is the most commonly reported cause of catheter malfunctioning and removal of the catheter. The post-thrombotic syndrome causes severe morbidity, however, whether a CVC is an important risk factor is unclear.

Prevention

In several studies among different patient populations the effectiveness of anticoagulant prophylaxis was evaluated. Basically, three groups of patients were distinguished: 1. Patients with haematological or solid tumor malignancies and 2. Non-cancer patients (usually patients with parenteral nutrition) and 3. Critically ill patients. For the purpose of this review three types of studies, according to level of evidence, are discussed subsequently (Table 3): 1. Randomized controlled trials (RCTs) with routine diagnostic imaging (venography or ultrasound) to define CVC-related thrombosis as an endpoint. Interpretation of data was blindly assessed. (level 1); 2. Randomized controlled studies (double blind) with clinically manifest throm-

bosis (or associated complications) as the primary endpoint (level 2) and 3. Observational studies which evaluated routine implementation of anticoagulant prophylaxis in a cohort of consecutive patients compared to historical controls without (level 3). Adult and pediatric populations are discussed separately.

Randomized controlled trials with routine diagnostic imaging

Three RCTs in which routine diagnostic imaging was used were performed in adult cancer patients, two in pediatric populations,[74-78] and five in patients receiving parenteral nutrition.[34,79-82]

Cancer patients. In cancer patients with subclavian CVCs, Bern *et al.* studied the benefit of a randomly allocated fixed low dose warfarin (1 mg once daily orally) compared to controls without.[74] Among patients on warfarin a substantially lower frequency of CVC-related thrombosis, as demonstrated by venogram, was observed (9.5% *vs.* 42% in controls). Monreal *et al.* observed a similar benefit from a low molecular weight heparin (LMWH) (Dalteparin 2500 IU subcutaneously) in cancer patients with subclavian inserted Port-a-Caths®.[75] In patients on Dalteparin a 6% rate in thrombosis was observed by routine venogram, as compared to 62% in patient without. In a recent study in 128 haemato-oncology patients a benefit from continuously administered unfractionated heparin (UFH) (100 IU/kg/daily) was observed.[76] In the heparin group a 1.5% of patients were diagnosed with thrombosis by routine ultrasound, in the controlgroup 12.6%. There were three events of severe bleeding in the heparin group, as compared to two in the controlgroup (p=NS). Combining the results of Monreal *et al.* and Abdelkefi *et al.* revealed a clear benefit from heparin as compared to placebo in adult cancer patients (RR 0.11; CI95% 0.03-0.45).

In a study of 158 children with haematological malignancies no substantial benefit was obtained with a LMWH as prophylaxis.[77] A total of 14% (11 of 78) of patients on LMWH and 13% (10 of 80) in control patients got thrombosis. In critically ill children, the effect of a heparin bonded catheter has been evaluated to reduce the risk of thrombosis.[78] A significant reduction in thrombosis from 8 of 103 (8%) to 0 of 97 was observed.[78]

Non-cancer patients/parenteral nutrition. In patients who received parenteral nutrition, only the benefit of UFH in various dosages added to the infusate has been assessed (Table 3). The statistically power of these studies was however limited, due to the small number of patients of each study. Combining the results of these studies, a trend in risk reduction of thrombosis by adding UFH to the infusate was calculated (RR 0.6; CI95% 0.34-1.06).

Randomized controlled trials with clinical endpoints

Cancer patients. In RCTs with clinically manifest thrombosis as a primary endpoint no clear benefit from anticoagulant prophylaxis was noticed in all three available studies (Table 3).[83-85] Remarkably, the absolute risk of clinically manifest thrombosis in the control group without anticoagulant prophylaxis was low in all these studies (4%), which might explain the lack of statistical power of these studies. The reason for the discrepancy with observational studies with incidences of up to 13% (Table 2) is unclear, but may be caused by selection of patients or referral criteria for diagnostic imaging. There have been no studies in non-cancer patients or critically ill patients or pediatric patients in this category of studies.

Observational studies

Cancer patients. In cancer patients two cohort studies were performed which evaluated the effect of LMWH (two regimens) or a fixed low dose warfarin on CVC-related thrombosis. (Table 3).[86,87] In a study among haematology patients a fixed low dose warfarin (1 mg orally) revealed a 5% clinically manifest thrombosis, as compared to 13% in historical controls without.[86] In another study with retrospective controls, a 7- (2850 IU) and 10- day (5700 IU) course of a LMWH in haematology patients was analyzed. Overall, there was no difference in the cumulative incidence of clinically manifest thrombosis between the groups who received Nadroparin (7% and 8% respectively) and those without (6%).[87] However, in this study most thrombotic events occurred after stopping prophylaxis while the CVC remained in place. It is unknown whether a prolongened course would have been effective.

Combining the results of RCT and cohorts-studies, neither an effect of warfarin or heparin was calculated, with regard to the risk of clinically CVC-related thrombosis. (warfarin: RR 0.72; CI95% 0.27-1.9/ heparin 0.92; CI95 0.57-1.49).

In order to reduce CVC the risk of intraluminal clotformation or dysfunction flushing or locking CVCs with UFH is performed routinely in many clinics. Whether such strategy is more beneficial as compared to saline is unsure. Currently there are no reliable data addressing this theme with clearly defined endpoints including routine assessment by contrast linogram, ultrasound or venography, response-rate to subsequent thrombolysis and safety.

Summary

In summary, the risk of thrombosis may be reduced by applying routine anticoagulant prophylaxis in patients with CVCs in cancer patients. However, a clear benefit was only demonstrated in cancer patients who underwent mandatory diagnostic imaging, including risk reduction of subclinical events. It is therefore debatable whether routine imple-

mentation of prophylaxis for CVCs is warranted. Besides, the safety of anticoagulant prophylaxis, a matter of serious concern especially with regard to patients with cancer, has not been studied well. In a recent survey, it was reported that a major reason for clinicians not to comply with consensus guidelines was the risk of bleeding due to thrombocytopenia, which presumably outweighed the risk of thrombosis, particularly in patients with cancer.[88-90] In this view, individualized strategies upon allocation of risk assessment in certain vulnerable patients with CVCs and a high risk of thrombosis, such as those with (chemotherapy induced) thrombocyptopenia, might be potentially useful to guide decisions on anticoagulant prophylaxis.

In non-cancer patients or critically ill patients no clear benefit from anticoagulant prophylaxis was observed. Available data consisted of small studies. With the improvement of CVC material no definite recommendations in these groups of patients can be made, until a large interventions study becomes available.

In critically ill children one study showed a risk reduction of CVC-related thrombosis using heparin bonded CVCs. These CVCs might be a safe alternative to systemic prophylactic anticoagulation, and this needs to be evaluated in other populations in need for short term catheterization.

Treatment

For the treatment of CVC-related thrombosis, various options are available. Anticoagulant treatment, removal or replacement of the CVC, or thrombolytic therapy may be used after a diagnosis of thrombosis is established. In this review randomized controlled intervention-trials evaluating the recurrence rate of thrombosis and complications, and safety of therapy are considered most convincingly (level 1), cohort studies as level 2, case series as level 3.

Currently, no randomized trials have appeared in the literature. In one cohort study, 112 cancer patients with CVC-related thrombosis, a diversity of therapeutic interventions (several anticoagulation strategies with or without CVC removal) were shown not to result in major differences in clinical outcome.[61] Treatment consisted of anticoagulation (n=39), anticoagulation with CVC removal or replacement (n=22), CVC removal or replacement (n=32), other therapy (n=7) or no therapy (n=8). In no patients recurrent thrombosis or secondary complications or death of unknown cause occurred within two weeks of diagnosis, while in four patients with CVC replacement only symptoms of edema were persistent. In a prospective case-series of 46 outpatients with upper extremity DVT, in whom 16 (35%) had a CVC showed that LMWH (Dalteparin 200 anti-Xa IU/kg) for a minimum of five days together with oral anticoagulants was shown to be safe and effective.[91] Evaluation after 12 weeks showed one recurrent thrombosis

(2%), no secondary complications of and one major bleeding event (2%). However, seven patients died, all presumably to underlying disease. Another study evaluated 36 patients with proven thrombosis of the upper extremity, mostly related to CVCs, up to one year after the diagnosis. With LMWH followed by oral anticoagulants (6 months), no recurrent thrombosis or secondary complications were noted. Nine patients died, presumably due to underlying disease (25%).[92]

A number of non-randomized studies of thrombolytic therapy in catheter related thrombosis have been carried out.[93-96] In a retrospective analysis of 95 patients with an upper-extremity DVT of whom 62 patients were treated with anticoagulants and 33 with systemic thrombolysis, it was shown that in 21 % of the patients, bleeding complications were observed after thrombolysis compared to no complications in the group of anticoagulants only.[97] Besides, in the long term no clinical differences with regard to recurrent thrombosis and post-thrombotic syndrome were observed between thrombolysis and anticoagulation.

For the treatment of fibrin sheaths or luminal occlusion which can lead to CVC dysfunction, the first choice of therapy is local thrombolytic therapy with low dose tissue plasminogen activator[98,99] or urokinase.[100,101] After 2-hour treatment with 2 mg per 2mL recombinant tissue plasminogen activator (Alteplase®), function was restored to 74% in the alteplase arm and 17% in the placebo arm ($P < 0.0001$ compared to placebo).[98] After another dose (2mg per 2mL), function was restored in 90% of patients. There were no serious study-drug-related adverse events, no intracranial hemorrhage, no major hemorrhage, and no embolic events.[98] Similar results were confirmed in a large randomized trial in over 1000 patients.[99]

Summary

In summary, the treatment of CVC-related thrombosis is controversial. There are no randomized designed studies on the best treatment of CVC-related thrombosis, but in most cohort studies anticoagulant therapy is given. The necessity to remove the CVC depends on the underlying diagnosis and need for vascular access. There is a definite need for well designed studies evaluating the optimal treatment in CVC-related thrombosis. Due to the high rate of complications during systemic thrombolysis, this therapy should be reserved to life- or extremity-threatening venous thrombosis.

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CHAPTER 2

Objective of the Thesis

Objective of the Thesis

Central venous catheters (CVCs) are frequently used in patients for a variety of indications such as cancer treatment, diagnostic monitoring, parenteral nutrition, haemodialysis, cardiac pacing, and administration of fluids, blood products or medication. The benefit derived from a CVC may be partially offset by thrombosis and associated complications, such as pulmonary embolism, CVC-related infection, CVC dysfunction or loss of central venous access. In the long term patients with thrombosis may suffer from a post thrombotic syndrome.

CVC related-thrombosis is an issue of importance to many clinicians of several specialties. Knowledge of the risk of thrombosis in patients who undergo catheterization, secondary complications and early identification and anticipation of thrombosis may be crucial in daily clinical practice.

The first aim of this thesis was to assess the incidence and contribution of genetic (Factor V Leiden, Prothrombin G21020A) and common acquired risk-factors (e.g. history of venous thrombosis) to CVC-related thrombosis in a large hospital population. Detailed knowledge of incidence and risk factors may help clinicians in decision making about preventive measures such as prophylactic anticoagulation. Therefore, in the present study over 250 patients were included, recruited from departments where central venous catheterisation is frequently performed (haematology, oncology, parenteral nutrition, ICU and post-operative patients). The contribution of common inherited risk factors in blood coagulation (factor V Leiden, prothrombin G20210A) and common acquired risk factors in venous thromboembolism was assessed (**Chapter 3**). In addition, the risk of upper-extremity deep vein thrombosis in patients with permanent pacemaker leads was assessed within the first year after implantation, and assessment of established risk factors in venous thromboembolism was performed (**Chapter 4**).

The second aim of this thesis was to evaluate the possibility of early identification of patients, who already have a CVC in situ, with a high risk of clinically manifest thrombosis. In this analysis, over 100 haematology patients who underwent intensive chemotherapy (cumulative incidence of CVC-related thrombosis in this population: 13%) were carefully monitored. We evaluated whether screening for subclinical thrombosis, performed by ultrasound (once weekly), could predict subsequent clinically manifest thrombosis (**Chapter 5**). In addition, we assessed whether, and to what extend, routine surveillance cultures of CVC lock fluid could predict or exclude clinically manifest CVC-related thrombosis later in follow-up (**Chapter 6**).

Finally, we investigated the clinicians' perception of risk of CVC-related thrombosis and his (or her) compliance with prophylactic anticoagulation by means of a nation-wide survey (**Chapter 7**).

In **Chapter 8** a summary is given and the results of this thesis are discussed and suggestions for future developments are given.

CHAPTER 3

The Contribution of Factor V Leiden and Prothrombin G20210A Mutation to the Risk of Central Venous Catheter-Related Thrombosis

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Abstract

Introduction. The purpose of this study was to assess the incidence of central venous catheter-related thrombosis and the contribution of two common inherited coagulation disorders (factor V Leiden, prothrombin G20210A mutation) to this complication in a large hospital population.

Patients and Methods. In a prospective setting, patients were assessed daily for signs and symptoms suggestive for thrombosis. Routine ultrasound was performed weekly in all patients until CVC removal. Ultrasound examinations were stored on videotape and assessed by two blinded observers. In case of clinically suspected thrombosis, physicians followed routine diagnostic and therapeutic procedures. In all patients the presence of factor V Leiden and prothrombin G20210A mutation and other potential risk factors were assessed.

Results. In 252 consecutive patients the cumulative incidence of central venous catheter-related thrombosis was 30% (clinically manifest thrombosis: 7%). The relative risk of factor V Leiden or prothrombin G20210A mutation for thrombosis was 2.7 (CI95% 1.9 - 3.8). In addition, a personal history of venous thrombosis was associated with central venous catheter-related thrombosis, whereas the severity of thrombosis was affected by the absence of anticoagulants and the presence of cancer.

Conclusions. Thrombosis is frequently observed after central venous catheterization. Common inherited abnormalities in blood coagulation contribute substantially to central venous catheter-related thrombosis. In view of physicians' reluctance of prescribing prophylactic anticoagulant treatment in vulnerable patients, the *a priori* determination of common inherited and acquired risk factors may form a basis to guide these treatment decisions.

Introduction

A central venous catheter (CVC) is commonly used for a variety of indications.[1] The benefit derived from these devices can be offset by thrombosis, which may be complicated by pulmonary embolism (PE) and CVC dysfunction.[2-4] Often, thrombosis may force premature CVC removal, which requires the insertion of a new CVC with the associated risk of complications (e.g. pneumothorax), and the need for anticoagulant treatment with associated bleeding risk.

Reliable estimates of the incidence of CVC-related thrombosis among a large hospital population are lacking. Besides, in contrast to a large number of studies on the association of factor V Leiden (FVL) and prothrombin G20210A mutation with deep vein thrombosis (DVT) of the leg and PE,[5] studies in which the relation of these risk factors with CVC-related thrombosis is investigated are scarce.[6-9] Such data are relevant, since they may indicate differences in the thrombotic risk in patients who need to undergo central venous catheterization. Moreover, it may assist clinicians in their decisions on anticoagulant prophylaxis.[10]

In a prospective setting we carefully assessed the incidence of CVC-related thrombosis in patients undergoing catheterization via the jugular or subclavian vein. We determined the contribution of the two most common prothrombotic inherited abnormalities in blood coagulation, FVL and prothrombin G20210A mutation, to CVC-related thrombosis in these patients. In addition all patients were assessed for other potential risk factors for CVC-related thrombosis.

Patients and Methods

Patients and study design

This prospective study was performed at the Leiden University Medical Center (LUMC), a university hospital, the Netherlands. The study protocol was approved by our local medical ethical committee and all participating patients gave written informed consent. Consecutive patients, aged 16 years or older, with a CVC in place for at least 48 hours were considered eligible to participate in the study. Central venous catheters could be inserted via the jugular or subclavian vein. Patients were recruited from the different departments throughout our hospital. Patients received a CVC for chemotherapy; for haemodynamic or perioperative monitoring, for fluid administration or for pharmacotherapy. Patients with abnormal ultrasound findings (performed within 48 hours after CVC insertion) were excluded if they had a history of a CVC at the same insertion-site, or a history of objectified thrombosis at the same insertion-side, since these were regarded as pre-existing thrombosis. Patients who were unable to undergo serial ultrasound were also excluded.

The decision to give anticoagulant prophylaxis and, if so, the dosage, were at dis-

cretion of the attending physicians. Postoperative patients, patients who were immobile or sedated, and patients with a long-term CVC (Port-a-cath®), who received prophylactic doses of Nadroparin subcutaneously in a dosage between 2850 IU and 7600 IU daily were classified as "prophylactic anticoagulant treatment". A higher daily dosage of Nadroparin, intravenous unfractionated heparin (target prolongation APTT by 2 - 2.5 fold) or oral vitamin K antagonist (target INR: 2.0 - 4.0) were classified as "therapeutic anticoagulant treatment".

Monitoring and follow-up

During their admission, all patients were examined daily by physicians for symptoms and signs suggestive for CVC-related thrombosis; i.e. pain, discoloration, local swelling or edema and visible collateral circulation. If patients were discharged from the hospital while their CVC was still in place, patients were seen at the (outpatient) clinic, at least every three to six weeks. Clinical follow-up ended six weeks after removal of the CVC, or one year after insertion if the CVC was still in place. Patients with clinically suspected thrombosis were referred to our department of Radiology for ultrasound. If no thrombosis was objectively identified by ultrasound, patients underwent unilateral venography.

Separate from the clinical follow-up, all patients were examined serially for CVC-related thrombosis by ultrasound by one ultrasonographer according to a standardized protocol. During admission, ultrasound was performed within 48 hrs after the insertion of the CVC, and at least once a week until CVC removal. Outpatients were examined by ultrasound every three to six weeks. Ultrasound examinations were performed bilaterally and the following venous segments were subsequently identified: the brachial, axillary, subclavian and jugular vein. All real-time examinations were coded and recorded on videotape. Recordings were assessed at least three months after discharge of the patient from follow-up by a panel of two blinded observers, experienced in ultrasound evaluation. A third expert opinion was asked for, when needed. The outcome of the screening ultrasound examinations were not made known to the attending physicians responsible for clinical follow-up, nor to radiologists who performed ultrasound or venography in case of clinical suspicion for thrombosis, since it is routine clinical practice to diagnose and treat CVC-related thrombosis based on clinical signs and symptoms.

Blood samples were taken from all patients within 48hrs after catheterization. Factor V Leiden and prothrombin G20210A mutation and factor VIII:C (IU/dl) were determined by standard techniques as described previously.[11-13] Factor V Leiden and prothrombin G20210A mutation were analyzed by comparing carriers of the mutation to homozygous wild-type individuals. Factor VIII levels were categorized in levels over and under the 90th percentile of the distribu-

Table I. Baseline characteristics for 252 patients with a central venous catheter

	Mean	(range)
Age (years)	54	(16 - 88)
Height (m)	1.73	(1.47 - 2.04)
Weight (kg)	75	(43 - 140)
Body mass index (kg/m2)	25	(16 – 41)
CVC in place (median days)	14	(2 - 365)
	n	**(%)**
Sex		
Male	149	(59.1)
Female	103	(40.9)
Underlying Disease		
Medical conditions	170	(67.5)
Solid tumor malignancy	39	(15.5)
Haematologic malignancy	97	(38.5)
Infectious disease	13	(5.2)
Cardiopulmonary disease	11	(4.4)
Inflammatory disease	8	(3.2)
Other	2	(0.8)
Postoperative condition	82	(32.5)
Anticoagulant treatment		
No anticoagulants	107	(42.5)
Prophylactic dose‡	127	(50.4)
Therapeutic dose‡	18	(7.1)
Type CVC*		
Single/Double lumen	61	(24.2)
Triple/Four lumen	86	(34.1)
Swan-Ganz catheter	69	(27.4)
Porth-a-cath®	35	(13.9)
Other	1	(0.4)
Location CVC*		
Right side	164	(65.1)
Jugular vein	143	(56.7)

‡ For definitions, see text

*CVC = central venous catheter

Table II. The risk of central venous catheter (CVC)-related thrombosis in the presence or absence of inherited coagulation disorders.

	CVC-related thrombosis		
	Yes	**No**	**Total**
Factor V Leiden or Prothrombin G20210A mutation			
Yes	16	7	23
No	59	170	229
Total	75	177	252

tion in this patient group. In addition, established risk factors for venous thrombosis and CVC characteristics were assessed in detail in each patient.

Outcome measures

The primary endpoint in this study was CVC-related thrombosis. Two types of thrombosis were distinguished; clinically manifest thrombosis and subclinical thrombosis. Clinically manifest thrombosis was defined as thrombosis objectified by ultrasound or venography following signs or symptoms suggestive for CVC-related thrombosis, as noticed by attending physicians. Subclinical thrombosis was defined as thrombosis demonstrated by screening ultrasound in the absence of signs or symptoms.

An ultrasound diagnosis of CVC-related thrombosis was made according to predefined criteria. For veins accessible to direct insonation, the criteria of non-compressibility, visualization of echogenic intravascular mass and absence of respiratory phasicity were used (jugular, axillary and subclavian vein).[14-17] For veins inaccessible to direct insonation the criterion of mono-phasic flow (spectral Doppler) was used (middle part of subclavian vein, brachiocephalic and superior caval vein) to detect occlusive thrombosis.[18]

Criteria for contrast venography included an intraluminal contrast filling defect of a venous segment or persistent non-filling of a venous segment in the presence of collateral circulation.[19] Possible complications associated with CVC-related thrombosis, PE and CVC dysfunction (occlusion), were carefully noted.

Statistical analysis

Cumulative incidences for subclinical thrombosis and clinically manifest thrombosis were calculated as the number of first events over the number of patients at baseline. The ratios of the cumulative incidences were the relative risks (RR). Ninety-five percent confidence intervals (CI95%) were based on standard errors for binominal dis-

tributions. The effects of risk factors that were likely to be associated were disentangled by restriction.

Results

Patients

In the 18-month study period, 368 patients with a CVC were considered for enrollment. Informed consent was not obtained in 88 eligible patients. In nine patients, the attending physician did not allow us to recruit the patient. Fourteen patients met one of the exclusion criteria: unable to undergo ultrasound (n=9), an abnormal ultrasound (performed within 48hours after CVC placement) in patients with a history of a prior CVC at the same insertion site (n=3), or a history of objectified thrombosis on the same side prior to CVC insertion (n=2). Thus, 257 patients enrolled the study protocol. In the end, five patients were excluded from analysis: in one patient the determination of FVL and prothrombin G20210A mutation had failed, in three patients it was not possible to perform scheduled ultrasound due to prior hospital discharge, and one patient withdrew informed consent. Thus, complete data were obtained for analysis from 252 patients. The main characteristics of these 252 patients are shown in Table 1.

CVC-related thrombosis

Overall, 29.8% (75 of 252) of patients developed CVC-related thrombosis (CI95% 24.1% - 35.4%). In 18 patients (7.1%) thrombosis was clinically manifest, while in 57 patients (22.6 %) subclinical thrombosis was demonstrated by routine ultrasound.

Four patients (1.6%) developed PE, objectifively diagnosed by a high probability ventilation perfusion scintigram (n=3) or abnormal spiral computed tomography (CT) (n=1). In 12 patients (4.8%) one or more lumina of the CVC became occluded. Pulmonary embolism and CVC occlusion were not associated with clinically manifest thrombosis. Subclinical thrombosis was diagnosed in one patient with PE and another patient with CVC occlusion.

Risk estimates for CVC-related thrombosis

Seventeen patients were heterozygous carriers of the FVL mutation (6.7%) and another 6 patients had heterozygous prothrombin G20210A mutation (2.4%). No patient was double heterozygous or homozygous. Thrombosis was diagnosed in 12 of the 17 patients with FVL (70.6%), as compared to 63 of 235 patients who did have no mutation (26.8%) (RR 2.6; CI95% 1.8 - 3.8).

Thrombosis was diagnosed in 4 of 6 patients (66.7%) with prothrombin G20210A mutation, whereas 71 thromboses were detected in 246 patients (28.9%) without the

mutation (RR 2.3; CI95% 1.3 - 4.2). For patients with CVC-related thrombosis who had at least one of both mutations the relative risk was 2.7 (CI95% 1.9 - 3.8) (Table 2). The population-attributable risk of the mutations to thrombosis was 13.4%.

The risk estimates of other factors for CVC-related thrombosis are summarized in Table 3. In univariate analysis, a personal history of venous thrombosis was associated with an increased risk of CVC-related thrombosis. If patients with an inherited coagulation disorder were excluded from the analysis, a personal history of a venous thrombosis was still associated with an increased risk of CVC-related thrombosis (RR 2.3; CI95% 1.6 - 3.4). When the risk factoranalysis was performed within the group of patients with inherited coagulation disorders (n=23) or within the different groups of patients according to the underlyingdisease (cancer *vs.* no cancer) or anticoagulant-status (absence *vs.* presence), no other substantial contributors to CVC-related thrombosis could be identified.

With regard to clinically manifest thrombosis, a similar trend in relative risk was observed for the inherited coagulation disorders and a personal history of thrombosis. Three out of 23 patients (13%) with an inherited coagulation disorder, in all cases heterozygous FVL, developed clinically manifest thrombosis, as compared to 15 of 229 (6.6%) patients without mutation, (RR 2.0; CI95% 0.6 - 6.4). The RR from a personal history of thrombosis was 2.3 (CI95% 0.8 - 6.5). Other factors were also associated with the occurrence of clinically manifest thrombosis. The lack of anticoagulant therapy was strongly associated with an increased risk of clinically manifest thrombosis (RR 4.7; CI95% 1.6 - 14), especially in cancer patients who underwent intensive chemotherapy. Among these patients, 14 of 98 without prophylaxis developed clinically manifest thrombosis (14.3%), whereas no patients among the group who received anticoagulants (n=35) did so.

Discussion

In a large cohort of prospectively followed patients, we found a clear relationship between two thrombophilic mutations, FVL and prothrombin G20210A, and CVC-related thrombosis. Overall, in the presence of one of the two mutations the risk of CVC related thrombosis increased almost threefold. Factor V Leiden or prothrombin G20210A contributed to 13.4% of the thrombotic events. In addition, a personal history of thrombosis was associated with CVC-related thrombosis.

Reliable data concerning the association between inherited coagulation disorders and CVC-related thrombosis are scarce and contradictory. In a study of patients undergoing bone marrow transplantation, a 54% frequency of clinically manifest thrombosis (seven of 13 patients) in patients who were heterozygous for FVL was reported, whereas in patients without mutation a 10% risk was

Table III. Risk estimates for central venous catheter-related thrombosis.

		Patients with thrombosis (%)	Relative Risk (CI95%)
Sex	Male	39/149 (26.2%)	
	Female	36/103 (35%)	1.3 (0.9 - 1.9)
Age (years)	< 75	66/226 (29.2%)	
	≥ 75	9/26 (34.6%)	1.2 (0.7 - 2.1)
Body mass index (kg/m2)	< 30	62/219 (28.3%)	
	≥ 30	13/33 (39.4%)	1.4 (0.9 – 2.2)
Personal history of venous thrombosis	No	60/224 (26.8%)	
	Yes	15/28 (53.6%)	2.0 (1.3 – 3.0)
Active cancer treatment/ intensive chemotherapy*	No	34/114 (29.8%)	
	Yes	41/138 (29.8%)	1.0 (0.7 – 1.5)
Major surgery / trauma**	No	47/153 (30.7%)	
	Yes	28/99 (28.3%)	0.9 (0.6 – 1.4)
Oral contraceptives / hormone therapy	No	61/218 (28%)	
	Yes	14/34 (41.2%)	1.5 (0.9 - 2.3)
Factor VIII: C (IU /dL)†	< 290	64/227 (28.2%)	
	≥ 290	11/25 (44%)	1.6 (1.0 - 2.5)
Family history of venous thrombo-embolism	No	64/223(28.7%)	
	Yes	11/29 (37.9%)	1.3 (0.8 – 2.2)
Insertion site	Jugular vein	42/143 (29.4%)	
	Subclavian vein	33/109 (30.3%)	1.0 (0.7 - 1.5)
Type of central venous catheter	Single/Double lumen	20/61 (32.8%)	
	Triple/Four lumen	29/86 (33.7%)	1.0 (0.6 - 1.6)
	Swan-Ganz	18/69 (26.1%)	0.8 (0.5 - 1.4)
	Port a cath®	8/35 (22.9%)	0.7 (0.3 - 1.4)
	Other	0/1	Not calculated
Absence of anticoagulant treatment	No	45/145 (31%)	
	Yes	30/107 (28%)	0.9 (0.6 – 1.3)

* Including all patients with haematological (n=97) or solid tumor malignancies (n=39) and two patients with a stem cell transplantation for rheumatoid arthritis.

** Including 82 patients with a primary postoperative condition and 17 patients with primary medical condition who became operated on in follow-up while the central venous catheter was in place.

† FVIII levels: cut off level is the 90th percentile.

found (26 of 264 patients). The reported relative risk (Cox proportional hazard model) from this study was 7.7 (CI95% 3.3 - 17.9).[6] In a smaller study in which 82 adult cancer patients with CVCs were evaluated, prothrombotic risk factors, including FVL, were not substantial predictors of clinically manifest thrombosis, although the data suggested that FVL increased the risk of thrombosis.[7] However, the statistical power of this study was limited because of the small numbers of patients with thrombosis and FVL.[7]

In one other study it was reported that FVL did not contribute to CVC-related thrombosis.[8] In this case control study, the prevalence of FVL in patients with thrombosis (7.4%; two of 27 patients) was not observed to be higher than the prevalence in Western general population (5%). The contribution of prothrombin G20210A mutation to CVC-related thrombosis was not assessed in these studies.[6-8]

In previous studies, clinically manifest thrombosis was used as a primary endpoint.[6-8] Due to systematic screening of our patients, we found a total of 75 cases with thrombosis (nearly 30%), which has clearly enhanced the statistical power of our study. This figure indicates that clot formation is a common phenomenon after CVC placement, while patients are at high risk for progression to clinically manifest thrombosis and associated morbidity. Our results emphasize the need for implementation of adequate prevention strategies.[20] Although the overall frequency of CVC-related thrombosis was not reduced by anticoagulants, the severity of thrombosis was. Clinically manifest thrombosis was observed substantially more often in patients who received no adequate anticoagulant prophylaxis, who were mainly patients with active cancer treatment.

Indeed, data from randomized controlled trials have supported the use of routine anticoagulant prophylaxis in patients with CVCs, which has resulted in consensus guidelines.[21-23] However, many clinicians are reluctant to prescribe anticoagulant prophylaxis routinely in patients with cancer and a CVC because of the low expected incidence of thrombosis and the fear of hemorrhage under anticoagulant prophylaxis.[10,24] Recently it was reported that only 10-20% of physicians routinely prescribe anticoagulant prophylaxis.[10,24]

Individual risk-assessment for CVC-related thrombosis, prior to the insertion of a CVC, could help clinicians in making decisions about prescribing anticoagulant prophylaxis in vulnerable patients who have a presumed increased risk of bleeding. From a clinical point of view, determination of FVL and prothrombin G20210A mutation may be useful in such individual risk assessment, since these risk factors can easily be determined before placement of the CVC. Future studies in which individualized anticoagulant prophylaxis, after determination of common inherited and established acquired risk factors, are clearly required to assess the effectiveness of such a policy.

Factor VIII levels were generally high in our patients, reflecting the acute phase reactive nature of this procoagulant factor. Patients with the highest levels appeared to

be at a slightly higher risk of thrombosis which further supports a prognostic role of a prothrombotic state in the occurrence of CVC-related thrombosis.

In this study, all patients were examined systematically for thrombosis with serial ultrasound. The reported sensitivity of criteria used with ultrasound in subclavian thrombosis ranged from 78 to 96%. [14-18] Thus the rate of thrombosis we found in patients with a subclavian CVC could be an underestimation, but this would not have materially affected our risk estimates for prothrombotic abnormalities. The reported specificity of ultrasound varied from 92 to 100%.[14-18] This precludes false labeling of patients with genetic abnormalities. Contrast venography, although the gold standard, is an invasive test and serial performance for screening is not feasible.

In conclusion, thrombosis occurs frequently after central venous catheterization. Common inherited coagulation disorders and a personal history of thrombosis contributed to CVC-related thrombosis and increased the risk almost three-fold. In vulnerable patients, the determination of these factors prior to CVC insertion could help clinicians to decide on anticoagulant prophylaxis. Future studies are needed to evaluate implementation of preventive strategies, including individual risk-assessment and subsequent anticoagulant prophylaxis of high-risk patients versus long-term routine anticoagulant prophylaxis in all patients.

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CHAPTER 4

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

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Abstract

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

Patients and Methods. One hundred forty-five consecutive patients underwent routine clinical and ultrasound evaluation for thrombosis before, and 3, 6 and 12 months after, lead implantation. Established risk factors for venous thrombosis were assessed in detail for all patients. Clinical outcome, including clinically manifest thrombosis, pulmonary embolism, associated pacemaker lead infection, complicated reinterventions and death was evaluated.

Results. Thrombosis was observed in 34 (23%) of 145 patients. Thrombosis did not cause any signs or symptoms in 31 patients but resulted in overt clinical symptoms in 3 patients. The absence of anticoagulant therapy, the use of hormone therapy and a personal history of venous thrombosis were associated with an increased risk of thrombosis. The risk of thrombosis increased in the presence of multiple pacemaker leads compared to a single lead.

Conclusion. Established risk factors for venous thrombosis and the presence of multiple pacemaker leads contribute substantially to the occurrence of thrombosis associated with permanent pacemaker leads. Risk factor assessment prior to implantation may be useful for identifying patients at risk for thrombotic complications. Preventive management in these patients may be warranted.

Introduction

Patients who undergo implantation of a pacemaker or defibrillator are at risk for thrombosis associated with transvenous leads.[1,2] Thrombosis may lead to severe local morbidity and can be a source for pulmonary embolism (PE).[3-5] Thrombosis may cause complications associated with reinterventions such as lead extraction or reimplantation, even when the thrombosis itself remains without overt clinical symptoms.

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

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

Patients and Methods

Patients and study design

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

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

Surveillance and Follow-up

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

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

Outcome measures

Two types of thrombosis were distinguished: clinically manifest thrombosis and subclinical thrombosis. Clinically manifest thrombosis was defined as thrombosis demonstrated by ultrasound or venography following signs or symptoms suggestive of upper limb thrombosis. Subclinical thrombosis was defined as thrombosis demonstrated by routine scheduled ultrasound assessed by a blinded panel, in the absence of signs or symptoms. An ultrasound diagnosis of thrombosis was made according to predefined criteria. For veins accessible to direct insonation, the criteria of non-compressibility (if possible and adequately performed), visualization of echogenic intravascular mass and absence of respiratory variation were used (jugular, axillary and subclavian vein)[14-17]

Table I. Baseline characteristics of the study patients

	Mean	**(Range)**
Age (years)	62.4	(19 – 940)
Height (m)	1.74	(1.42 – 2.04)
Weight (kg)	78.8	(45 - 130)
Body mass index (kg/m2)	25.9	(16 – 38)
Blood pressure systolic (mmHg)	132	(230 –80)
Blood pressure diastolic (mmHg)	77	(130 –50)
	Number of patients	**(%)**
Male sex	104	(71.7%)
Caucasian race	131	(90.3%)
Current smoker	30	(20.7%)
Diabetes mellitus	23	(15.9%)
Underlying disease		
Ventricular tachycardia/fibrillation	62	(42.8%)
Dilating cardiomyopathy	31	(21.4%)
Atrial fibrillation/flutter	18	(12.4%)
Atrio - ventricular block	17	(11.7%)
Sick sinus syndrome	13	(8.9%)
Other	4	(2.8%)
Device		
Pacemaker	70	(48.3%)
Internal cardiac defibrillator	75	(51.7%)
Number of implanted leads		
Single lead	28	(19.3%)
Double lead	82	(56.5%)
Triple lead	35	(24.1%)
Site of Implantation		
Subclavian vein	168	(56.6%)*
Cephalic vein	129	(43.4%)*
Left sided implantation	129	(89%)
Anticoagulant treatment	86	(59.3%)
Antiplatelet treatment	41	(28.3%)

* Based on the number of implanted pacemaker leads (n=297)

For veins inaccessible to direct insonation the criterion of mono-phasic flow (spectral Doppler) was used (middle part of subclavian vein, brachiocephalic and superior caval vein) to detect occlusive thrombosis.[18]

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

The primary study endpoint was pacemaker lead-related thrombosis as demonstrated by scheduled ultrasound examination. Secondary endpoints of this study were clinically manifest thrombosis as noticed by attending physicians between scheduled follow-up visits and possible complications of thrombosis (PE, infection, complicated re-interventions, death). Pulmonary embolism was diagnosed as the presence of an high-probability ventilation-perfusion lung-scintigraphy, a positive spiral computed tomography (CT) or pulmonary angiogram, based on overt clinical signs and symptoms. When PE was present, ultrasound of the upper and lower extremity was performed to identify the possible embolism source. Device-related infection was defined as a positive wound or device culture (local infection) with positive blood cultures (bloodstream infection) of identical types of micro-organisms. The decisions to obtain microbiological cultures was made by attending physicians based on clinical signs and symptoms.

Statistical analysis

Cumulative incidences were calculated as the number of first events over the number of patients at baseline. The ratios of the cumulative incidences were the relative risks (RR). Ninety-five percent confidence intervals (CI95%) were based on standard errors for binominal distributions. Factors associated with thrombosis in univariate analysis were analyzed by Mantel-Haenzel statistics, and corresponding CI95%s derived from the model were calculated.

Results

Patients

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

Table II. Observed incidence of pacemaker lead-related thrombosis assessed by routine ultrasound at different time-intervals.

Follow-up interval	3rd month	6th month	12th month
Patients before assessment	145	143	138
Available Recordings	143	138	129
Thrombosis (new events)	20 (14%)	8 (6%)	6 (5%)

thrombosis for 539 (96%) of 561 recordings (κ = 0.83).

Incidence of thrombosis

Overall, thrombosis was diagnosed in 34 of 145 patients, resulting in a one-year cumulative incidence of 23.4% (CI95% 16.6% - 30.3%). Most thrombotic events were subclinical (n=31). Thrombosis was clinically manifest in three patients (2.1%; CI95% 0% - 4.3%). These three patients suffered from multiple symptoms and signs of upper limb thrombosis, such as pain (n=2), arm edema (n=2), discoloration (n=1) or visible collateral circulation (n=1). Thrombosis was diagnosed by ultrasound in two of the patients, in and by additional venography in one patient. All three events were occlusive and confirmed by subsequent scheduled ultrasound.

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

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

Risk factors for thrombosis

The risk estimates for established risk factors for venous thrombosis are summarized in Table 3. In univariate analysis, a personal history of venous thrombosis, use of female hormones, and absence of anticoagulant treatment were associated with an increased risk of thrombosis (Table 3). The risk of thrombosis was increased in patients with multiple (two or three) pacemaker leads compared to a single lead (27.4% *vs.* 7.2%/ RR 3.8; CI95% 1.0 - 15.0). Analysis of other factors (including those as listed in Table 1, data not shown) did not reveal any other contributors to the risk of thrombosis. Congestive heart failure was inversely related to the risk of thrombosis. This finding was likely to be related to the protective effect of treatment with anticoagulants in these patients (Table 3). After multivariate analysis, the lack of anticoagulant treatment and hormone therapy still was associated with a substantially increased risk of thrombosis (Table 4). A personal history of thrombosis was slightly associated with pacemaker lead-related thrombosis (Table 4).

Secondary endpoints

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

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

Discussion

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

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

Table III. Risk of pacemaker lead-associated venous thrombosis for established risk factors in venous thromboembolism.

		Patients with thrombosis (%)	Relative Risk (CI95%)
Sex	Male	23/104 (22.1%)	
	Female	11/41 (26.8%)	1.2 (0.7 – 2.2)
Age (years) *	< 71.8	22/109 (20.2%)	
	≥ 71.8	12/36 (33.3%)	1.7 (0.9 - 3.0)
Body mass index (kg/m^2) *	< 27.9	24/109 (22.0%)	
	≥ 27.9	10/36 (27.8%)	1.3 (0.7 - 2.4)
History of venous thrombo-embolism	No	28/133 (21.1%)	
	Yes	6/12 (50%)	2.4 (1.2 – 4.6)
Active cancer	No	30/132 (22.7%)	
	Yes	4/13 (30.8%)	1.4 (0.6 – 3.2)
Major surgery / trauma	No	29/129 (22.5%)	
	Yes	5/16 (31.3%)	1.4 (0.6- 3.1)
Hormone therapy	No	28/137 (20.4%)	
	Yes	6/8 (75.0%)	3.7 (2.2 - 6.2)
Factor V Leiden / Prothrombin G20210A	No	31/135 (23.0%)	
	Yes	3/10 (30.0%)	1.3 (0.5 - 3.5)
Factor VIII: C (IU/dL)*	< 205.5	25/109 (22.9%)	
	≥ 205.5	9/36 (25%)	1.1 (0.6 – 2.1)
Family history of venous thrombo-embolism	No	30/124 (24.2%)	
	Yes	4/21 (19.0%)	0.8 (0.3 - 2.0)
Acute myocardial infarction	No	30/134 (22.4%)	
	Yes	4/11 (36.4%)	1.6 (0.7 - 3.8)
Congestive heart failure	No	29/101 (28.7%)	
	Yes	5/44 (11.4%)	0.4 (0.2 – 1.0)
Chronic obstructive pulmonary disease	No	27/113 (23.9%)	
	Yes	7/32 (21.9%)	0.9 (0.4 –1.9)
Upper limb paralysis	No	33/142 (23.2%)	
	Yes	1/3 (33.3%)	1.4 (0.3 – 7.3)
Lack of anticoagulant treatment	No	12/86 (14.0%)	
	Yes	22/59 (37.3%)	2.7 (1.4 – 5.0)

* The cut-off values of these parameters correspond with the 75th percentile.

Table IV. Risk factors for thrombosis associated with permanent transvenous pacemaker leads.

Risk Factor	RR* univariate (CI95%)	RR* multivariate (CI95%)
Age	1.7 (0.9 - 3.0)	not performed
Personal history of thrombosis	2.4 (1.2 – 4.6)	1.8 (0.6 – 5.5) [1]
Hormone therapy	3.7 (2.2 - 6.2)	3.2 (1.0 – 10.5) [2]
Absence of anticoagulant treatment	2.7 (1.4 – 5.0)	2.5 (1.1 – 5.5) [2]

*RR = Relative Risk

[1] Adjusted for age and hormone therapy

[2] Adjusted for age and personal history of thrombosis

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

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

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

The findings of our study also suggest a benefit from anticoagulant treatment on the thrombosis risk. One third of our study patients did not receive anticoagulant treatment, and no randomized trials have evaluated the effect of anticoagulant prophylaxis in such patients. A benefit of low-dose heparin

(5000 IE, 2 - 3 times daily for two weeks) in reducing the risk of PE after pacemaker implantation has been reported.[21] A 15% rate of PE was diagnosed by routine screening pulmonary scintigram at day 14 in patients who did not receive heparin, compared with no events in the group of patients who were given heparin prophylaxis. The source of PE was not determined, but was believed to be pacemaker lead-related. Based on our data, PE as a complication is infrequently observed. The present study determined clinically manifest PE. A "true incidence" estimate of PE would require systematic screening of all our patients by ventilation perfusion scan because embolic events may not be noticed clinically.[21] This was not the primary aim of our study and would require a different design.

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

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

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CHAPTER 5

Central Venous Catheter-Related Thrombosis in Haematology Patients and Prediction of Risk by Screening with Ultrasound

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Abstract

Introduction. Patients with a central venous catheter who receive intensive chemotherapy or a stem cell transplantation for haematological disease are at risk for developing central venous catheter-related thrombosis. To study the incidence of thrombosis, 105 consecutive patients underwent serial ultrasound and we evaluated whether clinically manifest thrombosis could be predicted by screening with ultrasound.

Patients and Methods. Patients with subclavian or jugular inserted catheters were clinically assessed each day for signs and symptoms of thrombosis. Additional screening ultrasound was performed weekly by an independent physician in all patients until catheter removal. Ultrasound recordings were assessed by a panel of two blinded observers. In case of clinically suspected thrombosis, attending physicians followed routine diagnostic and therapeutic procedures.

Results. The overall cumulative incidence of central venous catheter-related thrombosis was 28.6% (30 of 105 patients). Of the 30 patients with thrombosis, 26 had subclinical thrombosis by screening ultrasound. Nine of whom developed clinically manifest thrombosis later. Four patients had clinically manifest thrombosis without prior abnormal ultrasound. In case of subclinical thrombosis the risk of developing symptomatic disease increases sevenfold (34.6% *versus* 5.1%).

Conclusions. Screening ultrasound may be useful to identify patients at high and low risk for clinically manifest central venous catheter-related thrombosis.

Introduction

Central venous catheters (CVCs) are frequently used in patients undergoing intensive chemotherapy or a stem cell transplantation for haematological disease. The benefit derived from these devices can be offset by thrombosis, which may force premature removal of the CVC and necessitates anticoagulant treatment with associated risk of bleeding in patients who often have thrombocytopenia.[1] In addition, thrombosis could lead to pulmonary embolism (PE) and also chemotherapy may have to be postponed.[2,3]

Two types of CVC-related thrombosis can be distinguished, i.e. clinically manifest and subclinical thrombosis. For clinically manifest thrombosis, a cumulative incidence of 12% in patients with haematological malignancies has recently been reported.[4,5] For subclinical thrombosis, reliable estimates are scarce in patients with haematological disease. A cumulative incidence of 33% for subclinical thrombosis was found in recent studies of critically ill patients admitted to the intensive care unit.[6]

The use of anticoagulant prophylaxis in cancer patients with a CVC to reduce the risk of thrombosis and associated complications has been proposed in consensus guidelines, but remains debatable.[7-9] Many physicians are reluctant to prescribe anticoagulant prophylaxis for the prevention of CVC-related thrombosis due to a low expected incidence of clinically manifest thrombosis and a presumed high-risk of bleeding in these patients.[7,8]

In order to individualise anticoagulant prophylaxis, it would be worthwhile to identify patients at high-risk for clinically manifest thrombosis.[5,8] Screening with ultrasound for thrombosis before signs and symptoms or complications become manifest, may be potentially useful. The purpose of this study was twofold. Firstly, we evaluated the overall incidence of CVC-related thrombosis, clinically manifest and subclinical by ultrasound, in patients undergoing intensive chemotherapy or a stem cell transplantation for haematological disease. Secondly, we evaluated the value of screening ultrasound findings in predicting or excluding an event of clinically manifest thrombosis.

Patients and Methods

This study was a prospective cohort study performed at the department of Haematology of the Leiden University Medical Center (LUMC), the Netherlands. The study protocol was approved by the local medical ethical committee. All consecutive patients, aged 16 years or older, who had a CVC indwelling for over 48 hours, were considered eligible to participate in the study. All participating patients gave written informed consent.

Patients with abnormal ultrasound findings (performed within 48 hours after insertion) were excluded if they had a history of a CVC at the same insertion-site, or if they had proven thrombosis in history at the same

insertion-side. Patients who were unable to undergo serial ultrasound were also excluded.

Central venous catheters were inserted via the subclavian or jugular vein and were used for administering cytotoxic drugs, supporting therapy, blood products, parenteral feeding or antimicrobial therapy. Nurses were allowed to use the CVC to withdraw blood for diagnostic purposes and monitoring. The lumina of the CVC were rinsed once daily with a urokinase-lock (3750 IU in 1.5cc saline) according to a local protocol. The decision to give unfractionated heparin intravenously (100 IU per kilogram/24 hours continuously) for the prevention of veno-occlusive disease of the liver was at discretion of the attending physician, but was carefully recorded.

Screening ultrasound for CVC-related thrombosis

All patients were examined serially for subclinical CVC related thrombosis by ultrasound with a 7.5MHz linear transducer (Aloka® SSD 1400, Tokyo, Japan, or ACUSON® XP128, Mountain View, CA, USA). Ultrasound was performed at least once a week until CVC removal, always by one ultrasonographer according to a standardised protocol. Examinations were performed bilaterally and the following venous segments were identified subsequently: the brachial, axillary, subclavian, and jugular vein.

All real-time examinations were coded and recorded on videotape (S-VHS, Sony® SVO-9500MDP, Tokyo, Japan). Recordings were assessed at least three months after discharge of the patient from follow-up by a panel of two blinded observers that were experienced in ultrasound evaluation. In case of disagreement between these two, a third expert-opinion was sought. The outcome of the ultrasound examinations were not made known to the attending physicians responsible for clinical follow-up, or to the radiologists who performed ultrasound or venography in case of clinical suspicion of CVC-related thrombosis, as it is routine clinical practice to diagnose and treat thrombosis on the basis of clinical signs and symptoms.

Clinical follow-up for CVC-related thrombosis

During admission, all patients were examined routinely each day by attending physicians for signs and symptoms suggestive of CVC-related thrombosis including pain, swelling, discoloration, the presence of collaterals or CVC dysfunction. Discharged patients were seen at the outpatient clinic weekly by attending physicians. Clinical follow-up took place until six weeks after CVC removal.

Patients with clinically suspected thrombosis were referred to the department of Radiology for ultrasound and, if indicated, additional venography. Primary endpoint was the number of clinically suspected CVC-related thrombosis confirmed by ultrasound or venography.

Ultrasound criteria for CVC-related thrombosis

The criteria used for diagnosis of both types of CVC-related thrombosis, subclinical and clinically manifest, were similar. A diagnosis of CVC-related thrombosis by ultrasound was made according to predefined criteria. For veins accessible to direct insonation, the criteria of non-compressibility, visualisation of echogenic intravascular mass and absence of respiratory variation (jugular, axillary or subclavian vein) were used.[10-14] For veins inaccessible to direct insonation (middle part of the subclavian vein, brachiocephalic vein and superior caval vein) the criterion of monophasic flow to detect occlusive thrombosis was used.[15]

Venographic criteria for CVC-related thrombosis

Contrast venography, using a standardised protocol, was used in patients with clinically suspected thrombosis in whom ultrasound findings were apparently normal or inconclusive. A diagnosis of thrombosis was made in case of presence of an intraluminal filling defect of a venous segment (axillary, subclavian, brachiocephalic and superior caval vein) or persistent non-filling of a venous segment in the presence of collateral circulation.[16]

Statistical analysis

Cumulative incidences for thrombosis were analysed through Kaplan-Meier time to event analysis. Endpoints were "subclinical thrombosis" and "clinically manifest thrombosis" respectively. Patients were censored if they died or reached the end of follow-up; i.e. CVC removal for follow-up with ultrasound for subclinical thrombosis and six weeks after CVC removal for clinical follow-up for clinically manifest thrombosis.

Diagnostic accuracy indices for ultrasound to predict clinically manifest thrombosis with 95% confidence intervals (CI95%) were calculated: i.e. sensitivity, specificity, positive predictive and negative predictive values. Confidence intervals were based on standard errors for binomial distributions (cumulative incidence) and Poisson distributions (incidence rates).

Results

Patients

A total of 136 consecutive patients were eligible for this study during the 18-month study period. Informed consent was not obtained in 26 eligible patients and two patients were excluded because they met exclusion criteria. Overall, 108 patients were enrolled on the study protocol. Three patients were excluded from the analysis: in

Table I. Baseline characteristics of the study patients

	n	(%)
Sex		
Male	63	(60)
Female	42	(40)
Disease		
Acute myeloid leukaemia	46	(44)
Acute lymphoblastic leukaemia	13	(12)
Chronic myeloid leukaemia	11	(10)
Multiple myeloma	11	(10)
Non-Hodgkin lymphoma	9	(9)
Other	15	(14)
Therapy		
Intensive chemotherapy	48	(46)
Stem cell transplantation (Allogeneic)	36	(34)
Stem cell transplantation (Autologous)	21	(20)
Central venous catheter		
Double lumen	44	(42)
Triple lumen	56	(53)
Other	5	(5)
Insertion-site central venous catheter		
Jugular vein	11	(10)
Subclavian vein	94	(90)
Anticoagulant treatment		
None	92	(88)
Prophylactic dose (VOD*)	12	(11)
Therapeutic dose (atrial fibrillation)	1	(1)

* VOD = veno-occlusive disease of the liver

two patients it was impossible to perform ultrasound at CVC removal due to early hospital discharge and one patient withdrew informed consent after the start of the study. Ultimately, complete data were obtained for 105 patients. The main characteristics of the 105 patients and the types of CVCs used are shown in Table 1. The average age of the patients was 48 years (range 16-77). The average time of the CVC being in place was 21.7 days (range 5-64 days).

Subclinical thrombosis

In 105 patients, 422 scheduled ultrasound recordings were performed. At evaluation 20 (4.7%) were not interpretable. From the remaining 402 recordings, 377 were of good quality (89.3%) and 25 were of poor (5.9%), but interpretable, quality. In 380 of 402 interpretable recordings (94.5%) there was agreement between the two observers ($\kappa = 0.82$).

The cumulative incidence of subclinical thrombosis was 24.8% (26 of 105 patients) (CI95%; 16.5% - 33%). The time from CVC insertion to subclinical thrombosis is shown in Figure 1. The 26 events of subclinical thrombosis took place in a total of 2096 days of follow-up (incidence 12.4/1000 days (CI95%; 6.2/1000 to 21/1000 days). In 9 of 26 events (34.6%), subclinical thrombosis was observed within the first week after CVC insertion. The remaining 17 events (65.4%) were observed later during follow-up.

None of the patients with subclinical thrombosis on the ultrasound screen underwent initiation of anticoagulant treatment or CVC removal, as the attending physicians were kept unaware of the results of the ultrasound screen.

Clinically manifest thrombosis

The cumulative incidence of clinically manifest thrombosis in our patients was 12.4% (13 of 105 patients) (CI95% 6.1% - 18.7%). In another 12 patients (11.4%) thrombosis was clinically suspected, but excluded by diagnostic imaging. Most patients with thrombosis had multiple signs or symptoms, including pain (n=12), oedema (n=7), discoloration (n=6) or superficial collateral circulation (n=4). The time from CVC insertion to clinically manifest thrombosis is shown in Figure 2. The 13 events of clinical manifest thrombosis took place in 5901 days of clinical follow-up (incidence 2.2/1000; CI95% 0.2/1000 - 7.2/1000 days). The median number of days between insertion of the CVC and time of diagnosis was 17 days (range 9-54 days). In 10 of the 13 patients (76.9%) thrombosis was diagnosed within the second and third week after CVC insertion.

Interestingly, in five of the 13 patients (38.5%) the episode of clinically manifest thrombosis occurred after removal of the CVC (range 3 - 40 days). All events were diagnosed upon clinical suspicion by the attending physician and subsequently confirmed by ultrasound or additional venography.

In all patients who still had a CVC at the time of diagnosis of thrombosis, the CVC was removed. All patients with clinically manifest thrombosis received initially unfractionated heparin intravenously or a low molecular weight heparin (LMWH) subcutaneously, followed by oral anticoagulant treatment for a period of six weeks. During anticoagulant treatment, plateletcounts were monitored and maintained at a level above 30 $x10^9$/L.

Diagnostic value of screening ultrasound (Table 2)

Of 13 patients with clinically manifest thrombosis, there were nine in whom subclinical thrombosis was identified earlier by screening ultrasound (sensitivity 69.2%, CI95%; 44.1% to 94.3%), whereas in the 92 patients without clinically manifest thrombosis, 75 patients had persistent normal screening ultrasound tests and 17 had abnormal ultrasound findings (specificity 81.5%; CI95% 73.6% - 89.4%).

Of 26 patients with subclinical thrombosis, nine developed clinically manifest thrombosis later during follow-up (positive predictive value 34.6%; CI95% 16.3% - 52.9%). The clinical diagnosis was made within a week after the diagnosis of subclinical thrombosis in eight patients. In the other patient the interval between subclinical and clinically manifest thrombosis was longer (6 weeks). However, in this patient an occluded CVC led to extravasation of infusate, followed by pain and swelling of the shoulder which may have mimicked the signs and symptoms of thrombosis as seen on screening ultrasound the day after CVC withdrawal.

In 79 patients in whom the ultrasound screen remained normal throughout clinical follow-up, four patients developed clinically

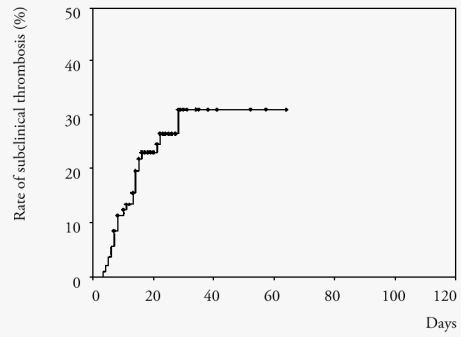

Figure 1. Time to event analysis for the group of patients with subclinical central venous catheter-related thrombosis

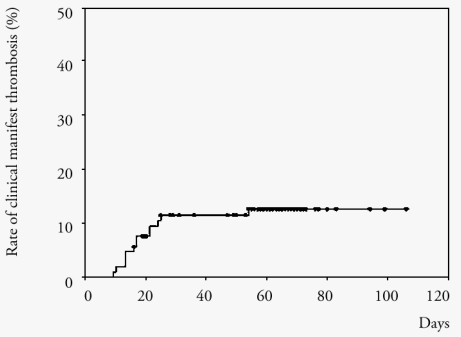

Figure 2. Time to event analysis for the group of patients with clinically manifest thrombosis

manifest thrombosis (negative predictive value 94.9%; CI95% 90.1% - 99.8%). In three of these patients ultrasound remained normal until signs and symptoms of manifest thrombosis became apparent, and clinically manifest thrombosis could only be demonstrated in another patient by additional venography.

From the 17 patients (16.2%) with subclinical thrombosis only, nine in whom subclinical thrombosis was diagnosed by scheduled screening ultrasound within 48 hours from CVC removal. In the other eight patients the CVC remained in place for at least three more days. As CVC removal could have had effect on the outcome of clinically manifest thrombosis, we performed an analysis with the classification "subclinical thrombosis" limited to patients with subclinical thrombosis with prolonged catheterisation. This increased the positive predictive value to 52.9% (CI95% 29.3% - 76.7%), whereas the negative predictive value was slightly increased to 95.5% (CI95% 91.1% - 99.8%).

Discussion

Central venous catheter related thrombosis is frequently observed in patients undergoing intensive chemotherapy or a stem cell transplantation for haematological disease. In this prospective cohort study we observed a 12% cumulative incidence of clinically manifest thrombosis, which confirms previously reported findings.[4,5] In addition, we found subclinical thrombosis in 16% of the patients. Thrombosis therefore occurred in over a quarter of our patients.

In this study, we show that screening ultrasound in this population might be valuable for two reasons. Firstly, the presence of subclinical thrombosis increased the risk of

Table 2. The risk of clinically manifest and subclinical thrombosis by screening ultrasound

	Clinically manifest thrombosis		
	Yes	**No**	**Total**
Screening ultrasound			
Subclinical thrombosis	9	17	26
No subclinical thrombosis	4	75	79
Total	13	92	105

developing clinically manifest thrombosis to 35%. Secondly, in patients with normal screening ultrasound findings the risk of clinically manifest thrombosis was reduced to 5%. Thus, the presence of subclinical thrombosis, as seen on ultrasound, increased the risk of clinically manifest thrombosis sevenfold compared to negative ultrasound findings (relative risk 6.8; CI95%; 2.3 - 20.3).

Anticoagulant prophylaxis might be useful, to reduce the rate of CVC-related thrombosis. However, it should be noted that evidence-based data on anticoagulant prophylaxis in haematology patients with CVCs is very limited. In one study with 223 patients undergoing bone marrow transplantation a reduction (from 13% to 5%) clinically manifest thrombosis was reported by when 1 mg warfarin once daily was administered.[17] In this non-randomized study, a group of historical controls (n=115) without warfarin was used as a reference population. In another retrospective study with 382 patients, two regimens of a short-term course of prophylaxis using a LMWH were given during the first 7-10 days after CVC insertion.18 Both regimens, 7 days 2850 IE (n=123) and 10 days 5700 IU of Nadroparin (n=98), did not reduce the rate of clinically manifest thrombosis (8%, respectively 7%) as compared to a group of historical controls (n=161) without Nadroparin (6%). In our view, continued prophylaxis with a LMWH over a prolonged period might be needed to prevent the overall majority of events, as thrombotic events in the study by Lagro *et al.* mainly occurred after stopping Nadroparin-prophylaxis (median 22 days).[18] In our study, three quarters of clinically manifest thrombosis occurred within the second and third week after CVC placement. Interestingly, clinically manifest thrombosis occurred at a median-interval of 17 days after CVC placement, a finding strikingly similar to the observation by Lagro *et al.*[18]

The use of routine anticoagulant prophylaxis to prevent CVC-related thrombosis is, however, still debated. It was shown that clinicians are very reluctant to prescribe anticoagulant prophylaxis routinely, because of a low expected incidence of thrombosis and a concern for bleeding complications in this vulnerable population.[7,8] Alternatively, identifying patients at high-risk for thrombotic complications may help haematologists to individualise anticoagulant prophylaxis, i.e. making decisions in which patient anticoagulant prophylaxis might be warranted or not.[5,8] In patients with persistent normal screening ultrasound tests, which represent the overall majority of our patients, our data suggest that anticoagulant prophylaxis might be withheld. Anticoagulant prophylaxis, (low dose)

therapy or other interventions like timely CVC removal could be restricted to high-risk groups, e.g. such as our patients with subclinical thrombosis on ultrasound. However, the effects of these interventions in patients are currently uncertain and further studies, including individualised based anticoagulant prophylaxis versus prolonged routine anticoagulant prophylaxis, are needed to evaluate which is the best strategy to prevent clinically manifest thrombosis. Furthermore, our data suggest that CVC removal upon diagnosis of subclinical thrombosis could reduce the risk of a manifest event; this observation clearly needs prospective validation.

Implementation of our findings warrants comment. Screening ultrasound performed weekly is labour-intensive. It may be possible to reduce the number of patients and examinations performed by selecting patients at high-risk for CVC-related thrombosis based on clinical risk assessment prior to the insertion of a CVC. Currently, reliable studies in which common risk factors for venous thrombosis that contribute to CVC-related thrombosis are scarce.[5] Interestingly, in one study of patients with factor V Leiden who underwent bone marrow transplantation, a cumulative incidence of clinically manifest thrombosis of 54% was reported.[5] Clearly, more studies are needed to identify common acquired and genetic risk factors in venous thrombosis to identify those patients in whom screening with ultrasound might be advantageous.

Venography is currently the reference standard in the diagnosis of upper limb vein thrombosis, however it is clearly not acceptable as a screening procedure in this vulnerable patient group. Ultrasound has the advantage that it is non-invasive, gives no radiation exposure, and can easily be performed serially at the patients' bedside. The accuracy of ultrasound is highly dependent on the criteria used for detecting thrombosis. With the criteria used for upper limb thrombosis with ultrasound, a high specificity in literature has been reported (92-100%).[10-15] The reported sensitivity ranges from 78 to 96%, which means that our reported incidence of thrombosis could be an underestimation. In our study, 5% of patients with clinically manifest thrombosis had persistent normal screening ultrasound examinations. Whether venography would have identified these patients is unknown, as it was not used routinely. In addition, the accuracy of ultrasound is likely to be operator dependent. In the present study, all of the scans were performed by a single, experienced, ultrasonographer. Although we observed a high interobserver agreement in ultrasound evaluation, the accuracy of ultrasound is rather dependent on a reliable real-time investigation, which is enhanced by an experienced operator.

In conclusion, we observed a high incidence of CVC-related thrombosis in patients undergoing intensive chemotherapy or a stem cell transplantation for haematological disease. Screening with ultrasound in haematology patients enabled discrimination between a high- and a low-risk group for clinically manifest thrombosis. Further studies are needed to identify those patients for

whom screening would be advantageous and what preventative strategy, including risk-calculation based individualised anticoagulant prophylaxis, timely CVC removal, and prolonged routine anticoagulant prophylaxis is most likely to safely prevent clinically manifest thrombosis.

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CHAPTER 6

Infectious Complications of Central Venous Catheters Increase the Risk of Catheter-Related Thrombosis in Haematology Patients: a Prospective Study

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Abstract

Purpose. We studied whether the risk of central venous catheter-related thrombosis increased after an episode of catheter-related infection in haematology patients undergoing intensive chemotherapy. Secondly, we determined whether thrombosis can be predicted or excluded by catheter lock fluid surveillance cultures.

Patients and Methods. In a prospective setting, 105 consecutive patients were carefully examined for central venous catheter-related infection and thrombosis. In all patients microbial surveillance cultures of catheter lock fluid were taken every other day. All patients with clinical suspicion of central venous catheter-related thrombosis underwent ultrasound, or additional venography.

Results. The cumulative incidence of central venous catheter-related infection was 24% (25 of 105 patients). Clinically manifest thrombosis occurred in 13 (12%) of 105 patients. In patients with central venous catheter-related infection, the risk of thrombosis increased markedly in comparison to those without infection (relative risk 17.6; CI95% 4.1 - 74.1). In patients having two or more positive subsequent catheter lock fluid cultures with identical micro-organisms, 71.4% developed thrombosis, as compared to 3.3% in patients with negative or a single positive culture.

Conclusions. The risk of clinically manifest thrombosis is increased after an episode of central venous catheter-related infection in haematology patients. Surveillance culturing of catheter lock fluid may be clinically useful in estimating the risk for thrombosis and the instigation of focused early intervention.

Introduction

In patients who undergo intensive chemotherapy or a stem cell transplantation, central venous access is often needed. The use of a central venous catheter (CVC) may be complicated by thrombosis and associated complications such as pulmonary embolism, which may lead to premature removal of the CVC and anticoagulant treatment.[1,2] These patients, who often suffer from thrombocytopenia, are particularly vulnerable for bleeding complications.

An association of CVC-related infection with CVC-related thrombosis has been suggested previously.[3-5] However, the reported thrombotic events were subclinical and often diagnosed at CVC removal. Whether CVC-related infection increases the risk of clinically manifest thrombosis while the CVC remains in place is unknown. It is highly relevant to investigate this association, since early determination and intervention upon the diagnosis of infection in these patients could lead to CVC salvage and may prevent thrombotic complications. We undertook a prospective study to evaluate whether, and to what extent, CVC-related infection increases the risk of subsequent clinically manifest thrombosis. In addition, we assessed the predictive value of surveillance CVC lock cultures in the diagnosis of thrombosis, which gives information on the potential benefits of prevention of thrombotic complications.

Patients and Methods

Patients and study design

This study was performed at the department of Haematology of the Leiden University Medical Center (LUMC) from October 2000 until May 2002, a tertiary referral center for haematological disease in the Netherlands.[6] The study protocol was approved by the local medical ethical committee, and all participating patients gave written informed consent. All consecutive patients 16 years or older with a CVC inserted for over 48 hours were considered for enrollment.

CVCs were inserted via the subclavian or jugular vein and used for administering cytotoxic drugs and supporting treatment (i.e., fluids, blood products, parenteral feeding and antimicrobial therapy). Nurses were allowed to withdraw blood from the CVC for diagnostic purposes and monitoring. The lumina of the CVC were rinsed daily with urokinase (3750 IU in 1.5 ml sodium chloride). The use of urokinase for the prevention of CVC-related complications was based on local experience (not yet published), as well as other studies, the data of which suggest that urokinase may reduce the risk of (serious) infectious CVC complication as compared to heparin and saline alone.[7,8] No antibiotic prophylaxis specifically for CVC-related infections were given. All patients were treated according to a local protocol to prevent infections with aerobic

Table I. Definitions of the different types of CVC-related infection adapted to earlier studies

Descriptions
1. Local CVC-related infection
a). Insertion-site infection. The CVC insertion-site exhibits clinical signs of inflammation with the swab Gram stain > 20 micro-organisms per field of vision (1000x) and a positive culture within 48 hours. The CVC lock fluid and blood cultures remain negative.
b). Significant CVC colonization. At least two consecutive CVC lock cultures become positive within 48 hours or the CVC tip culture is positive. Blood cultures by venipunture are negative; CVC drawn blood cultures may yield identical micro-organisms.
2. Systemic CVC-related infection
CVC-related bacteraemia. Presence of fever (body temperature > 38.5 °C) or clinical signs or symptoms of infection, and blood cultures are positive. The insertion-site swab, CVC tip culture or a positive CVC lock culture yields growth of identical micro-organisms. A systemic CVC-related infection with positive blood cultures* at least 24 hours after adequate antimicrobial therapy is considered as a major systemic CVC-related infection.

* In case of *coagulase-negative staphylococci*, at least two drawn bloodcultures are positive.

CVC = central venous catheter

Gram negative rods, *viridans streptococci* and *Candida spp*.[9] Prophylactic treatment included neomycin (250 mg), polymyxin B (1.10^6 IU) orally q.d., pipemidic acid 400 mg orally b.i.d., amphotericin B 200/10mg q.d.. After 10 days of treatment, the dosage of the regime was reduced (half of the dosage in mg), except for the pipemidic acid.

Patients with abnormal ultrasound findings (performed within 48 hours after insertion) were excluded if they had a previous CVC at the same insertion-site, or if they had a proven thrombosis at the same insertion-side. Patients who were unable to undergo ultrasound were also excluded.

Microbiological surveillance and treatment

Starting the day after the insertion of the CVC, lock fluid was cultured routinely each second day as described previously.[10] If a surveillance CVC lock fluid culture yielded growth of micro-organisms (positive lock culture), lock cultures were drawn daily. At each episode of onset of fever (body temperature >38.5 °C) or other symptoms or signs of infection (hypotension, chills, hypothermia, unexplained tachycardia) blood cultures were drawn, at least one via the CVC and one by standard venipuncture. At least two blood cultures were drawn on each consecutive day in all patients with clinical symptoms or signs of infection, until a causative

micro-organism was isolated. In the presence of clinical signs of inflammation at the insertion site (i.e. erythema, exudation, tenderness, warmth or swelling) swab cultures were taken. Catheter tip cultures were not performed routinely, only to support the diagnosis of CVC-related infection. Micro-organisms were identified by current tests (DNAse testing), additional commercial ID 32 STAPH biochemical test strips (API, bioMerieux®) and anti-microbial sensitivity patterns.

The criteria for establishing a diagnosis of CVC-related infection were adapted to previous studies.[10,11] Two entities were distinguished: "local CVC-related infection" and "systemic CVC-related infection" (Table 1).[11] In case of a proven insertion-site infection or CVC colonization, appropriate antimicrobial therapy was started. The CVC was left in place. If a single CVC lock fluid culture was positive, no treatment was started. In case of fever or other symptoms or signs of systemic infection empirical therapy was started (ceftazidime 500 mg intravenously t.i.d. and teicoplanin 200 mg intravenously b.i.d. on day one, q.d. on consecutive days). Empirical therapy was discontinued if blood cultures remained negative after 72 hours. If a systemic CVC-related septicemia was diagnosed, empirical therapy was adjusted to the most appropriate small-spectrum regimen.[7] The CVCs were not removed routinely.

Outcome: CVC-related thrombosis

During admission, all patients were routinely examined each day for symptoms and signs of CVC-related thrombosis; pain, swelling, discoloration, visible collateral circulation or CVC dysfunction. Discharged patients were seen once weekly at the outpatient clinic by attending physicians. Patients with a clinical suspicion of CVC-related thrombosis were referred to the department of Radiology for ultrasound. If ultrasound findings appeared normal or were inconclusive, additional venography was performed. In addition, for this study, all patients with clinically suspected thrombosis were examined by an independent examiner who performed ultrasound. These examinations were coded and assessed by a panel of two blinded physicians experienced in ultrasound evaluation. If needed, a third expert opinion was asked. A diagnosis of thrombosis was made when ultrasound recordings were abnormal, or when normal or inconclusive, by an abnormal venogram. Follow-up for CVC-related thrombosis took place until 6 weeks after CVC removal.

A diagnosis of CVC-related thrombosis was made according to predefined criteria. For veins accessible to insonation, the criteria of non-compressibility, visualization of echogenic intraluminal mass and absence of respiratory variation (jugular, axillary or subclavian vein) were used.[12-15] For veins inaccessible to direct insonation (middle part of the subclavian vein, brachiocephalic vein and superior caval vein), the criterion of

Table II. Baseline characteristics of the study patients

	Mean (range)	
Age (years)	48 (16 – 77)	
Central venous catheter in situ (days)	22 (5 – 64)	
	n	**(%)**
Sex		
Male	63	(60)
Female	42	(40)
Disease		
Acute Myeloid Leukaemia	46	(43.8)
Acute Lymphoblastic Leukaemia	13	(12.4)
Lymphoma	13	(12.4)
Chronic Myeloid Leukaemia	11	(10.5)
Multiple Myeloma	11	(10.5)
Other	11	(10.5)
Therapy		
Intensive Chemotherapy	48	(45.7)
Stem Cell Transplantation		
Allogeneic	36	(34.2)
Autologous	21	(20)
Central venous catheter		
Double or Triple lumen	100	(95.2)
Subclavian vein	94	(89.5)
Left insertion-side	71	(67.7)

monophasic flow to detect occlusive thrombosis was used.[16] A diagnosis of thrombosis by contrast venogram was made in case of intraluminal filling defects of a venous segment (axillary, subclavian, brachiocephalic or superior caval vein) or persistent non-filling of a venous segment in the presence of collateral circulation.[17]

Statistical analysis

Cumulative incidences for infection and thrombosis were calculated as number of first events over the number of individuals at baseline and Kaplan-Meier statistics were performed. Patients were censored if they died or reached the end of follow-up. Relative risks (RR) and 95% confidence intervals (CI95%) were calculated and based on standard errors for binominal distributions. The relation of infection and thrombosis was assessed by applying Fisher's exact test, ($p < 0.05$ was considered statistically significant).

Results

CVC-related thrombosis

The main patient and CVC characteristics have been described in detail elsewhere.[6] Briefly, from 136 consecutive patients, 110 consented to participate. Two patients were excluded before the start of the study and three patients were excluded from the analysis based on exclusion criteria. Ultimately, for 105 patients complete data were obtained and evaluated. The main characteristics for these 105 patients are shown in Table 2. None of the pre-treatment parameters in Table 2 predisposed for CVC-related infection or thrombosis.

In 25 patients CVC-related thrombosis

was clinically suspected upon symptoms and signs. In 13 out of these 25 patients clinically manifest thrombosis was objectified (cumulative incidence 12.4%; CI95% 6.1% -18.7%). In the other 12 patients thrombosis was excluded by diagnostic imaging. There was no disagreement between the real time diagnosis and the diagnosis as judged by our blinded panel.

CVC-related infection and risk of clinically manifest thrombosis

The cumulative incidences for CVC-related infections and the absolute and relative risks of subsequent clinically manifest thrombosis are summarized in Table 3. Overall, CVC-related infection was observed in 25 of 105 patients (cumulative incidence 23.8%; CI95% 15.7% - 32%). In 11 patients (10.5%) CVC-related infection was classified as a local CVC infection, i.e. CVC colonization (n=1), a local insertion-site infection (n=6) or both (n=4) in the absence of associated bacteraemia. Swab and CVC lock-fluid cultures yielded mainly *coagulase-negative staphylococci* (CoNS; n=6) or multiple types of micro-organisms including CoNS (n=3). Other isolated pathogens were *Enterobacter spp.* (n=1) and *Acinetobacter spp.* (n=1). Another 14 patients (13.3%; CI95% 6.8% - 19.8%) suffered from systemic CVC-related infection. In these patients blood cultures yielded CoNS (n=10), multiple types of micro-organisms including CoNS (n=3), and *Corynebacterium spp.* (n=1).

In the group of patients with a CVC-related infection the frequency of subsequent clinically manifest thrombosis was 44% (11 of 25 patients), compared with 3% thrombosis in the patients without CVC-related infection (two of 80 patients; $p < 0.05$). This yields a relative risk of 17.6 (CI95% 4.1 - 74.1). Our findings suggest that the absolute risk of clinically manifest thrombosis increases with the severity of infection, since thrombosis was observed in 57.1% of patients with systemic CVC-related infection as compared to 27.3% in patients with a local CVC infection (Table 3).

The frequency of CVC-related infection in the group of patients with objectified CVC-related thrombosis was higher than in the group of patients in whom thrombosis was clinically suspected but ruled out (84.6% *vs.* 16.7%), indicating that the observed association of infection with thrombosis was not affected by the knowledge of infection among attending physicians who had decided on referral for diagnostic imaging for thrombosis.

Fifteen patients had a systemic infection (14.3%; CI95% 7.6% - 21%) classified as unrelated to the CVC. Blood cultures in these patients yielded CoNS (n=4), *Streptococcus spp.* (n=3), multiple types of micro-organisms (n=3), *Candida albicans* (n=2) or other micro-organisms (n=3). From these patients only one suffered from clinically manifest thrombosis (6.7%).

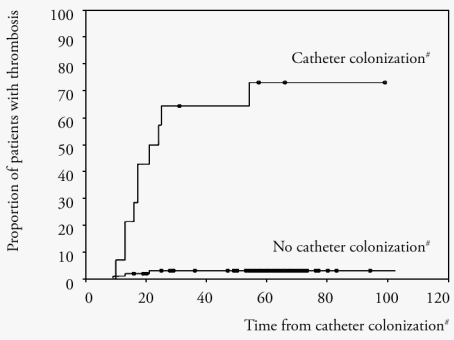
Table III. Observed cumulative incidences of central venous catheter-related infections and the absolute and relative risks of subsequent clinically manifest thrombosis.

	Number (%)	Risk of thrombosis *
No CVC-related infection	80 (76.2)	2.5%
CVC-related infection‡		
1. Local CVC-related infection	11 (10.5)	27.3% (10.9)
Insertion-site	6	
CVC colonization	1	
Insertion-site and CVC colonization	4	
2. Systemic CVC-related infection	14 (13.3)	57.1% (10.4)
Overall	25 (23.8)	44.1% (17.6)

* Absolute risks of thrombosis in percentages, between braces the relative risks.

‡ For definitions of CVC-related infection, see Table 1.

CVC = central venous catheter



#Colonization, as defined by at least two consecutive catheter surveillance culturess

Figure 1. The risk of clinically manifest thrombosis based on at least two surveillance central venous catheter lock fluid cultures.

Accuracy for CVC lock fluid cultures to predict clinically manifest thrombosis

During follow-up, 30 of 105 patients had at least one positive surveillance CVC lock culture (28.6%). Of 13 patients with clinically manifest thrombosis, 11 had at least one prior positive culture (sensitivity 84.6%; CI95% 65% - 100%). In 73 of 92 patients without clinically manifest thrombosis, a negative culture was obtained for a specificity of 79.3%; CI95% 71.1% - 87.6%). In 75 patients with serially negative CVC lock fluid cultures, thrombosis occurred in 2 patients (negative predictive value 97.3%; CI95% 93.7

% - 100%), whereas 11 out of 30 patients with a positive CVC lock fluid developed thrombosis (positive predictive value 36.7%; CI95% 19.4% - 53.9%). If two or more subsequent positive cultures with identical strains of micro-organisms were used to predict symptomatic thrombosis the positive predictive value increased to 71.4%, whereas the negative predictive value decreased only slightly (96.7%). As illustrated in Figure 1, the risk of thrombosis increased markedly in patients with two or more consecutive positive cultures, compared with only one positive followed by negative cultures or consecutive negative cultures.

The time interval between the first positive surveillance culture and the clinical diagnosis in 11 patients with clinically manifest thrombosis ranged from 1 to 39 days (mean 9 days).

Discussion

In the present study, we show a clear temporal association of CVC-related infection and thrombosis. After an episode of CVC-related infection the risk of clinically manifest thrombosis increased markedly (RR 17.6). Besides, our findings suggest that the absolute risk of developing a symptomatic thrombotic event increases with the severity of CVC-related infection; a 57% thrombosis risk was observed after an episode of CVC associated septicemia, *versus* 27% in patients with a local CVC infection.

Previously, a direct association of CVC-related infection and thrombosis has been suggested in autopsy studies.[3] Reliable prospective data in which a direct relationship of CVC-related infection and thrombosis has been reported are scarce.[4,5] In a study of critically ill patients (n=208), the presence of subclinical thrombosis detected by routine ultrasound performed at CVC removal was associated with a three-fold increased rate of systemic CVC-related septicemia.[4] In haemato-oncology patients only one small study (n=42) has been performed, in which a direct association of infection and thrombosis was reported.[5] In this study, daily screening using ultrasound for (subclinical) thrombosis was used to estimate the risk of subsequent CVC-related infection. From 13 patients with documented subclinical thrombosis, CVC-related infection occurred in 12 (92%), whereas in 29 patients without thrombosis, the number of infections was only two (7%).[5] The main difference between our and these studies is that we have used clinically manifest thrombosis as the primary endpoint and that CVC-related infection was used as a parameter to predict symptomatic thrombotic events.

Based on our findings, as well as results from earlier studies, it could be argued that the relationship of thrombosis and infection is bi-directional. Thrombus formation, which is commonly observed after catheterization, may play an important role in the development of certain CVC related infections.[4,5,18,19] The composition of CVC-associated thrombi consists of several proteins such as fibrin,

fibronectin, collagen, laminin and several types of immunoglobulins.[20-22] Micro-organisms, especially *Staphylococcus aureus* and certain types of CoNS, easily adhere to thrombin sheaths, which could explain the clinical observation of a close association of CVC-related infection and thrombosis.[20-23] Besides, CVC-related infection might induce an inflammatory response,[24] that could induce or lead to further progression of excessive thrombus formation. Thrombosis and infection might also just be two separate entities occurring simultaneously in patients being severely ill, but this hypothesis is not likely, since the molecular basis of thrombosis suggests a direct relationship.[20-24] We can not, however, exclude that thrombosis may be induced by a local chemical phlebitis caused by antibiotics in patients treated for CVC-related infection.

From a clinical point of view, surveillance cultures of CVC lock fluid may be valuable to assess the risk of clinically manifest thrombosis in individual patients, particularly if this risk assessment is based on serially determined cultures. Such a strategy could allow early intervention in addition to adequate antimicrobial therapy. Timely CVC removal at the first sign of thrombosis or infection, or individualized anticoagulant prophylaxis, may be beneficial. Such individualized risk assessment for clinically manifest thrombosis might be an alternative for routine anticoagulant prophylaxis in haematology patients with CVCs, especially after intensive chemotherapy.[25] However, this study was an observational study, and whether early intervention would have changed clinical outcome and whether this such a strategy is cost-effective is unknown and should be investigated. Although anticoagulant prophylaxis is recommended in consensus guidelines, there is great reluctance amongst clinicians to prescribe anticoagulant prophylaxis routinely because of fear of bleeding complications and a low expected incidence of thrombosis.[25-27] In addition, since the seems to be a strong association of infection and thrombosis, the use of antibiotic impregnated CVCs may be of clinical benefit as well. However, the outcome of intervention(s) based on surveillance cultures is currently unknown and this clearly needs prospective evaluation before routinely implemented. Whether such intervention is based on a single or multiple subsequent positive lock cultures is uncertain. However, as in CVC-related infection, the accuracy-indices of surveillance cultures to predict clinically manifest thrombosis improved with more subsequent cultures (two or more) that were positive for identical types and strains of micro-organisms. Serially positive cultures are likely to reflect a more significant colonization of the CVC, or less frequently, contamination as compared with a single positive surveillance culture.

In conclusion, we have shown a close association of CVC-related infection with thrombosis. The risk of developing clinically manifest thrombosis increases substantially after an episode of CVC-related infection (RR 17.6) and is enhanced by the severity of the infection. Routine culturing of CVC lock

fluid is clinically useful to monitor the risk of clinically manifest thrombosis, which might allow early intervention. However, the outcome of such a strategy is currently unknown and clearly needs to be explored prospectively.

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CHAPTER 7

Low Physician Compliance of Prescribing Anticoagulant Prophylaxis in Patients with Haematological or Solid Tumour Malignancies and Central Venous Catheters

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Abstract

Introduction. Patients with a central venous catheter who are treated with chemotherapy for haematological or solid tumour malignancies have a high risk of developing thrombosis. There is consensus on anticoagulant prophylaxis in cancer patients with a central venous catheter, but incidental findings suggested a poor physician compliance.

Materials and Methods. We performed a large survey of medical departments of Dutch hospitals (General Internal Medicine, Haematology and Oncology) to assess the policy of physicians in prescribing anticoagulant prophylaxis for central venous catheter-related thrombosis in patients with haematological or solid tumour malignancies.

Results. Central venous catheters were used in most medical departments of Dutch hospitals (Haematology 84%, Oncology 85%). A minority of the physicians responded to prescribe anticoagulant prophylaxis routinely (10% Haematology, 21% Oncology) according to the American College of Chest Physicians or national Dutch consensus. The most important reasons for not prescribing prophylaxis were a low perceived risk of clinically manifest thrombosis and the fear of haemorrhage.

Conclusions. For most physicians the perceived increased risk of bleeding outweighs the benefit of anticoagulant prophylaxis, i.e. reducing the rate of manifest thrombosis.

Introduction

Thrombosis is a well-recognised complication of a central venous catheter (CVC), especially in haematology and oncology patients. In cancer patients an incidence-rate of thrombosis of 42% has been reported.[1] The thrombus may be a source for pulmonary embolism and associated infection.[2,3] Subsequent anticoagulant treatment of thrombosis may be associated with haemorrhage in this vulnerable population and may delay chemotherapy.

The use of anticoagulant prophylaxis for CVC-related thrombosis has been studied with unfractionated heparin (UFH), low molecular weight heparin (LMWH) and low dose warfarin.[4-6] In the American College of Chest Physicians (ACCP) consensus on anticoagulant prophylaxis it is suggested that warfarin (1 mg daily) or LMWH should be given to cancer patients with a CVC.[7] The Dutch consensus is in concordance with this.[8] Data on the implementation of these consensus guidelines are limited. One report from a single hospital in the United States suggested that physicians are reluctant to prescribe anticoagulant prophylaxis in cancer patients with CVCs.[9]

The aim of this survey was to assess the physician compliance with consensus guidelines at medical departments in the Netherlands where haematology and oncology patients are treated with chemotherapy.

Materials and Methods

We conducted a survey of all hospital-departments of General Internal Medicine, Haematology or Oncology in the Netherlands. In April 2001, a postal questionnaire was sent to a member of staff of the eligible hospitals. A reminder was sent to all non-respondents after 8 weeks.

The questionnaire contained three topics:

1) Use of CVCs for chemotherapy

2) Systematic use of anticoagulant prophylaxis in patients with CVCs

3) Rationale for the absence of systematic use of anticoagulants. Options given in the questionnaire included:

a. A low expected rate of clinically manifest thrombosis

b. A high perceived risk of bleeding

c. Preference of other regimes or policy (UFH-locks or flushes)

d. No awareness of consensus-guidelines

e. Other reasons

In addition, questions were asked about the type of anticoagulant prophylaxis (UFH, LMWH, coumarin derivatives) and the dose; about the influence of platelet counts on this treatment, as well as of the expected duration of the CVC.

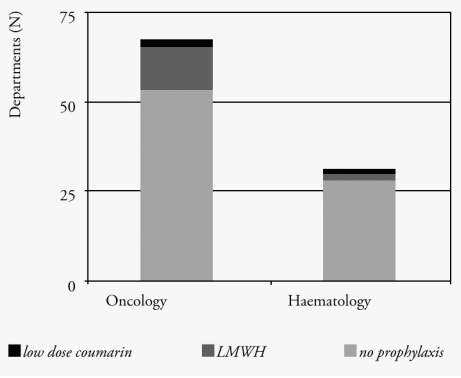

Figure 1. The policy of prescribing anticoagulant prophylaxis (no prophylaxis, LMWH or low dose coumarin) for central venous catheter related-thrombosis amongst centres involved in treatment of oncology and haematology patients.

Results

We sent 157 questionnaires to medical, Haematology and Oncology departments involved in the treatment of cancer patients, of which 116 were returned (response-rate 74%). The response was similar for departments where haematology (37 of 51) and oncology patients were treated (79 of 106 questionnaires). In most departments CVCs were used to administer chemotherapy and supporting treatment for haematology (84%) and oncology patients (85%). The results of the questionnaire are summarised in Figure 1.

Overall, in three of 31 (10%) of Haematology and in 14 of 67 (21%) of the Oncology departments , prescription of anticoagulant prophylaxis for CVC-related thrombosis was routine policy. The most frequently used type of anticoagulant prophylaxis was a LMWH (88%), at a low dose of 2850 anti-Xa units, although in some centres a therapeutic dose (up to 7500 anti-Xa units) was given. Low-dose coumarin derivatives (1 mg acenocoumarol once daily) were used at two departments where anticoagulant prophylaxis was prescribed as a standard policy.

The platelet count was an important parameter in the decision on prescribing prophylaxis. In nine clinics (53%) where anticoagulant prophylaxis was used, prophylaxis was not given if the platelet count dropped below $50x10^9$/L. The expected duration of stay of the catheter was not a major factor; in only two (12%) of the departments, anticoagulant prophylaxis was not started when the expected duration of stay of the CVC was less than 14 days.

The two most important reasons given for not having a routine policy of anticoagulant prophylaxis were a low expected incidence of clinically manifest thrombosis or the fear for haemorrhage (62%). This was also reflected by the preference for heparin locks or flushes (38%), which some respondents considered to give less systemic anticoagulant effects. Several physicians mentioned spontaneously that they did not feel the consensus guidelines to be sufficiently convincing to prescribe anticoagulant prophylaxis (29%). Only a minority of contacted physicians responded not to be familiar with the national or international ACCP consensus (18%).

Discussion

This survey reveals that in a minority of the Dutch clinics where chemotherapy is given, anticoagulant prophylaxis for CVC-related thrombosis is prescribed according to national and international guidelines, in spite of general awareness of consensus guidelines. In the ACCP consensus, it is suggested that 1 mg warfarin daily or LMWH can be administered in cancer patients with a CVC.[7] This advice is based on two randomised trials. In the first trial there was a reduction from 38% to 10% of venogram documented thrombosis in patients with malignancies by 1 mg Warfarin daily.[4] In the second trial a reduction from 62% to 6% of venogram documented thrombosis was observed by administering Dalteparin 2500 IU subcutaneously once daily.[5]

The low compliance among physicians to prescribe anticoagulant prophylaxis in this large survey is similar to an incidental finding.[9] In the tudy by Carr and Rabinowitz, an initial 10% compliance was observed, which increased to only 20% after notification of the physicians about the policy and benefits of anticoagulant prophylaxis.[9] However, reasons for a poor compliance remained unclear from this study. In our survey, the most important reasons given for not prescribing anticoagulant prophylaxis were the fear for bleeding under anticoagulant prophylaxis and a low expected incidence of clinically manifest thrombosis.

According to our survey, the presumed increased risk of bleeding in patients treated with chemotherapy depended largely on the occurrence of thrombocytopenia, which is commonly observed in patients undergoing chemotherapy. Available data from randomised trials concerning the safety of anticoagulant prophylaxis are mainly restricted to patients with normal baseline or only slightly decreased platelet counts (over $100x10^9$/L).[4,5] In our view, the contribution of anticoagulant prophylaxis to an increased risk of bleeding cannot be extrapolated to groups of patients with lower platelet counts.

The incidence of clinically manifest thrombosis in the contacted clinics of our survey is unknown. The observed incidence of clinically manifest CVC-related thrombosis varies widely between studies. The average overall incidence of clinically manifest thrombosis in patients with solid tumour and haematological malignancies from recently performed studies was 6-12%.[9-11] Selecting patients with a high risk profile for developing manifest thrombosis might help clinicians to decide in whom anticoagulant prophylaxis is warranted or not.[10] For example, in patients undergoing bone marrow transplantation and carriers of factor V Leiden, the incidence of clinically manifest thrombosis may be as high as 54%.[10]

In conclusion, despite an evidence-based recommendation of anticoagulant prophylaxis for CVC-related thrombosis, routine use it is not generally implemented. We think that this survey shows that more evidence is needed to firmly establish the risk-benefit ratio for broader implementation of consensus guidelines.

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CHAPTER 8

Summary

Discussion and Future Developments

Summary

Venous thrombosis is a well-known complication of central vein catheters (CVCs), which may cause serious morbidity and may result in potentially lethal complications such as pulmonary embolism (PE). In this thesis the general risk of CVC-related thrombosis has been assessed, i.e., what is the overall risk of developing CVC-related thrombosis? Which patients are prone to develop thrombosis with its associated morbidity? Are we able to predict this risk by routine surveillance in patients? Better knowledge of the incidence of CVC-related thrombosis and identification of high-risk groups will assist clinicians in decision making about CVC use in the various patient groups and in whom anticoagulant prophylaxis may be warranted.

The best moment to identify patients with a high risk and those at lesser risk is before CVC introduction. The incidence of CVC-related thrombosis and the contribution of common inherited coagulation disorders (Factor V Leiden (FVL), prothrombin G20210A) to it, studied in a large hospital population, were described in **chapter 3**. Overall, the cumulative incidence of CVC-related thrombosis (clinically silent and manifest) in our patients was 30%. The presence of heterozygous FVL or prothrombin G20210A mutation increased the risk of thrombosis nearly three-fold (relative risk 2.7; CI95% 1.9 - 3.8). In addition, a personal history of venous thrombosis was positively associated with CVC-related thrombosis. Clinically manifest thrombosis was observed in 7% of our patients. Clinically manifest thrombosis clearly occurred more often in the absence of anticoagulants and in patients who received intensive chemotherapy.

The characteristics of patients with permanent pacemaker leads differ from patients with CVCs used for infusion. Many patients receive anticoagulant treatment at a high (therapeutic) intension , the leads are permanent in situ (lifelong), and there is a closed device-system (less manipulation and risk of infection). Risk assessment of a group of 145 patients who underwent pacemaker-implantation is described in **chapter 4**. Although thrombosis was observed in 23% of patients, most events did not cause signs or symptoms (clinically manifest thrombosis 1.5%). Thrombosis was observed mostly within the first three months after lead-implantation. The absence of anticoagulant therapy increased the risk of thrombosis substantially. Analogous to what we observed in patients with a CVC, established risk factors in venous thrombosis (use of hormone therapy and a personal history

of venous thrombosis) were associated with an increased risk of thrombosis in patients with pacemaker leads. In addition, the risk of thrombosis increased in the presence of multiple pacemaker leads as compared to one single lead.

Obviously, clinically manifest CVC-related thrombosis may result in severe morbidity or associated complications such as PE or infection. In clinical practice it may be worthwhile to screen certain high-risk patients by frequent monitoring. Patients who received intensive chemotherapy or stem cell transplantation for haematological disease had a substantial risk of manifest thrombosis (13%). Both serially performed ultrasound (**Chapter 5**) and surveillance CVC lock cultures (**Chapter 6**) were evaluated as predictors of clinically manifest thrombosis. Both techniques were shown to be clinically useful in predicting or excluding manifest thrombosis in those high-risk patients.

In **chapter 5** we evaluated whether screening with ultrasound for subclinical thrombosis could predict clinically manifest thrombosis later in follow-up. In this study, a positive ultrasound screening test for subclinical thrombosis increased the relative risk of developing subsequent clinically manifest thrombosis substantially (positive predictive value 34%; negative predictive value 5%; relative risk 6.7).

In **chapter 6**, we show the clear relation of CVC-related infection and -thrombosis. When routine surveillance cultures of CVC lock fluid are performed (cultures drawn each second day), the risk of clinically manifest thrombosis, in the presence of a single positive culture, was 33%. This predictive value increased to 71 % in patients with two or more positive subsequent CVC lock fluid cultures with identical microorganisms.

As outlined in **Chapter 7**, implementation of anticoagulant prophylaxis for CVC-related thrombosis is still under debate, especially in (haemato-)oncology patients. In a national survey, we investigated the compliance rate of prescribing anticoagulant prophylaxis amongst oncology (n=67) and haematology departments (n=31) where patients with a CVC were treated with chemotherapy. Prescription of anticoagulants was used to prevent CVC-related thrombosis in only 10% (Haematology departments), to 21% (Oncology departments) of the Dutch medical departments. Important reasons for not complying with consensus guidelines were a low expected incidence of CVC-related thrombosis, and a presumed high risk of bleeding in these patients.

In conclusion, in view of physicians' reluctance of prescribing prophylactic anticoagulant treatment in vulnerable patients, the *a priori* determination of common inherited and acquired risk factors may form a basis to guide (prophylactic) treatment decisions. Vulnerable patients may benefit the most, i.e. those who have a high risk of clinically manifest thrombosis, and who are at risk of haemorrhage, such as patients who undergo intensive chemotherapy. Besides, surveillance of these patients with screening

by ultrasound, or alternatively surveillances cultures, may be useful to identify patients at high- or low- risk for clinically manifest CVC-related thrombosis, and focused early intervention may be initiated.

Discussion and Future developments

The potential benefit from our studies, concerning risk assessment and early identification of patients at high-risk of CVC-related thrombosis, needs still to be defined. Clearly, in patients who receive routine anticoagulant prophylaxis (i.e. postoperative or intensive care unit patients, patients with therapeutic anticoagulants due to cardiac disease) additional risk stratification or screening is not beneficial. The risk of thrombosis and secondary complications is too low to justify additional measures. In addition, in patients with a low-risk of thrombosis, anticoagulant prophylaxis may be safely withheld. The groups who may benefit most from individualized preventive measures are those who have a substantial risk of manifest thrombosis or complications (e.g. a risk > 10%), and those with substantial bleeding risk (e.g. due to chemotherapy induced thrombocytopenia). The clinical value, benefit and safety of risk stratification of CVC-related thrombosis and subsequent individualized prophylaxis or surveillance needs to be further explored.

An important issue in performing risk stratification is which risk factors to include. Those are preferably factors already known before CVC insertion. In an ideal setting, such parameters are also easy to determine, of low-cost, safe and binary. Established risk factors in venous thrombosis are commonly known in the clinical field and are usually easily determined by the history of patients, e.g. oral contraceptives, obesity, personal history of thrombosis. FVL and prothrombin G20210A (5-7% in the general population) may also be included, since they clearly enhance the risk of thrombosis. However, measuring such factors should be carefully implied, since they are genetic determinants of blood coagulation and "labeling" patients of heritable disease may have psychological and social disadvantages. Firstly, knowledge of the presence of thrombophilia should not affect future treatment decisions in thromboembolic disease; i.e. a patient might develop proximal deep vein thrombosis of the leg in the future. Secondly, patients should be protected against unjustified legal and insurance issues. Other factors that influence decisions on the initiation of prophylaxis and surveillance could be the type of CVC, the degree of vascular trauma, manipulation, and the expected duration of catheterization. Since the majority of adverse clinical complications occur after the first 10 days of catheterization, anticoagulant prophylaxis may only be necessary in prolonged catheterization.

After insertion of a CVC, routine surveillance may identify patients at increased risk of clinically manifest thrombosis. However,

several issues are still to be clarified. Firstly, it should be investigated whether routine surveillance affects clinical outcome. Serially drawn surveillance cultures may be used to identify patients at high-risk of manifest thrombosis and to initiate early intervention. Important issues in this strategy are the cut-off point (number) of positive identical cultures and the type of intervention (anticoagulants, early CVC removal or replacement, or both) possibly after additional diagnostic imaging. Although screening ultrasound has potential benefits, it is labor-intensive and costly when performed on a weekly basis. Ultrasound screening may therefore be reserved for patients with CVC related infections, or to determine whether a CVC should be removed, or to decide whether anticoagulants should be started, in patients in whom these interventions are (relatively) contra-indicated. Ultrasound screening may also be reduced to a limited single observation, to reduce labor and costs. Whether a limited screening-schedule is still beneficial is however unknown.

Finally, the assessment of the true incidence of pulmonary embolism in CVC-related thrombosis and the treatment of CVC-related thrombosis were beyond the scope of this thesis and are largely understudied. Clearly, there is a clinical need for well-designed studies addressing both issues.

CHAPTER 9

Nederlandse Samenvatting (Dutch Summary)

Samenvatting

Bij patiënten die zijn opgenomen in het ziekenhuis bestaat vaak de noodzaak tot het inbrengen van een centrale infuuslijn. Deze "centrale lijnen" kunnen worden gebruikt voor verschillende indicaties: het toedienen van vloeistoffen en medicatie (bijv. chemotherapie), reguleren van het hartritme, voor dialyse en voor serieel bloedafnames bij de patiënt. Tevens kan bij patiënten met hartritmestoornissen een pacemaker worden ingebracht, waarbij geleidingsdraden via de aderen worden geïmplanteerd. Hierbij kunnen complicaties optreden in de vorm van trombose (stolselvorming). Naast het feit dat trombose de functie kan belemmeren, kunnen patiënten ernstige klachten krijgen (trombose-arm). Soms ontstaat een levensbedreigende situatie als er een infectie ontstaat of wanneer een stolsel losschiet en zich verplaatst door de bloedsomloop naar de longen (longembolie).

Met betrekking tot trombose bij centrale lijnen bestaat nog een groot aantal vragen, waarop in het huidige onderzoek wordt ingegaan. In dit onderzoek wordt het vóórkomen en het risico van centrale lijnen trombose beschreven. Daarnaast wordt inzicht gegeven in de bijdrage van genetische en verworven risicofactoren van trombose. Het goed kunnen schatten van het risico van trombose is belangrijk in de dagelijkse praktijk. Bij patienten met een "hoog-risico" op het krijgen van een trombosearm kunnen preventieve maatregelen genomen worden om trombose en complicaties daarvan te voorkomen. Dit kan in de vorm van profylaxe met antistollingsmidel. Echter, bij sommige patiënten wordt het risico van bijwerking van deze antistolling te hoog geacht (bloedingsrisico), bijvoorbeeld bij patiënten die net een kuur chemotherapie hebben ondergaan en daarom een laag gehalte aan bloedplaatjes hebben. In de praktijk kan dit een reden zijn van profylaxe met antistolling af te zien.

Uit het huidige onderzoek blijkt dat bij patiënten met een centrale lijn, trombose in ongeveer 30% van alle patiënten met een centrale lijn voorkomt. Vaak leidt trombose echter niet tot klachten of complicaties. Van alle patiënten met een centrale lijn blijkt 7% klachten te krijgen (25% van de patiënten met trombose). Tevens blijkt dat bij patiënten met een zogenaamde erfelijke afwijkende stollingsfactor in het bloed (factor V Leiden, protrombine mutatie) het risico van trombose 2 tot 3 keer meer toeneemt (van ongeveer 30% naar 70%). Daarnaast is het eerder gehad hebben van een trombose (bijvoorbeeld trombosebeen) een belangrijke

risicofactor. Kankerpatiënten die chemotherapie krijgen blijken een grotere kans te hebben op symptomen van trombose (ernstige pijnklachten of zwelling van de arm) dan andere patiënten.

Patiënten met pacemakers of defibrillators kunnen ook te maken krijgen met trombose. Deze ontstaat als gevolg van het inbrengen van een geleidingsdraad, ingebracht via de ader onder het sleutelbeen. In vergelijking met patiënten met een centrale lijn hebben patiënten met pacemakers minder kans op trombose (22%). Ook zijn complicaties van trombose bij deze patiënten zeer zeldzaam. In deze groep patiënten zijn de twee belangrijkste risicofactoren: het niet krijgen van antistolling en hormoongebruik (bijv. "de pil"). Zeer waarschijnlijk speelt het volledig onderhuids plaatsen van het systeem ook een beschermende rol (minder manipulatie en minder infectiegevaar).

Na het inbrengen van een centrale lijn kan bij patienten die een hoog risico hebben op het krijgen van een trombose-arm het nuttig zijn te screenen met echografie op vroege stolselvorming of routinematig te kweken van vloeistof afgenomen vanuit de centrale lijn. In het geval dat er sprake is van vroege stolselvorming blijkt het risico van klachten of complicaties van trombose een factor 7 toe te nemen. Ook bestaat er een nauwe relatie tussen centrale lijn gerelateerde trombose en infectie. Routinematig kweken van vloeistof uit de centrale lijn blijkt soms een trombose-arm te kunnen voorspellen in 33-71% van de gevallen (afhankelijk van de hoeveelheid positieve kweken). Of vroegtijdige behandeling gebaseerd op screenen met echo of routinematig kweken van catheter vloeistof, bijvoorbeeld door antistolling of door vroegtijdige lijn verwijdering of wisseling, ook effectief is, kan op dit moment niet worden gezegd en zal in de toekomst verder moeten worden onderzocht.

Curriculum Vitae

The author was born on the 1st of January 1972 in Doetinchem. In 1990 he graduated from high-school (VWO), at the Thij-College in Oldenzaal. The same year he started his medical-school at the University Leiden. During the third and fourth year of medical-school, he was a student-assistant at the department of Medical Statistics (Dr. J. Hermans) and performed research on the outcome of renal artery revascularisation at the department of Vascular Surgery of the Leiden University Medical Center (Prof. dr. J.H. van Bockel). In 1995 he started with his internships, which he completed in 1997 after an elective internship at the department of Gynaecology and Oncology, Westmead Hospital in Sydney (G.V. Wain, MD), and a four- month training period at the Royal Flying Doctor Services of Australia and Broken-Hill Base Hospital in Broken Hill (A. Sexton, MD). In December 1997 he graduated from medical-school.

From February 1998 until December 1999 he worked at the St. Clara Hospital, Rotterdam, at the department of Surgery (Dr. T.I.Yo), and at the department of General Internal Medicine (Dr. A.F. Grootendorst). In January 2000 he started with a research program at the department of General Internal Medicine (Prof. dr. A.E. Meinders) at the Leiden University Medical Center, which resulted in the studies described in this thesis. From June 2001 until December 2003 he worked at the "Stichting Trombosedienst Leiden en Omstreken", Leiden (Dr. F.J.M. van der Meer). Since December 2003 he is a resident at the department of Radiology (Drs. W.M.C. Mallens), Hagaziekenhuis-Leyenburg, the Hague.

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