available at http://ajws.elsevier.com/tcmj

Tzu Chi Medical Journal

Review Article

Evidence-Based Review on Catheter-Related Thrombosis of the Implantable Venous Access Device

*Chien-Yu Chen[1], Chih-Chung Liu[2], Wei-Zen Sun[2]**

[1]*Department of Anesthesiology, Taipei Medical University Hospital, Taipei, Taiwan*
[2]*Department of Anesthesiology, National Taiwan University Hospital, Taipei, Taiwan*

Article info:

Article history:
Received: March 26, 2007
Revised: April 4, 2007
Accepted: May 15, 2007

Keywords:
Catheter-related thrombosis
Central vein thrombosis
Evidence-based analysis
Implantable venous access device (IVAD)
Right atrial thrombosis

Abstract

An implantable venous access device (IVAD) is routinely implanted for long-term intravenous access. Despite its reliability and safety, catheter-related thrombosis remains the most common complication leading to irreversible dysfunction. Thrombosis incidence is underestimated because clinical manifestation is usually asymptomatic. In this evidence-based review, we compared the distinct natural courses of four thrombosis locations with respect to the vessel (right atrium/central vein) or the catheter (intraluminal/fibrin sheath). Practical management recommendations are also proposed. Specifically, right atrial thrombus is a rare but life-threatening complication possibly leading to pulmonary embolism and cardiac arrest. Prompt surgical thrombectomy is strongly recommended, while medical treatments may be tried for pediatric patients with small to moderate-sized thrombi. Central vein thrombosis is usually unnoticeable but, when left untreated, may progress to extensive obstruction of the superior vena cava. An antithrombotic agent, such as unfractionated or low-molecular-weight heparin, is the first choice, while surgical intervention is not recommended due to lack of benefits. Intraluminal thrombotic occlusion (2–3%) and fibrin sheath formation (42–100%) are common etiologies associated with device malfunction. Both conditions are minor and can be readily resolved by fibrinolytic agents. Surgical removal of the device should only be considered after fibrinolytic agents have failed or therapy has been terminated because of its minor severity and high success rate of medical treatment. In conclusion, while IVAD is a durable and sustainable device that can provide a long-term intravenous route, identification of the exact thrombosis location will lead to rational treatment strategies and thereby avoid unnecessary surgical intervention. (*Tzu Chi Med J* 2007;19(4):207–219)

*Corresponding author. Department of Anesthesiology, National Taiwan University Hospital, 7, Chung-Shan South Road, Taipei, Taiwan.
E-mail address: wzsun@ntu.edu.tw

1. Introduction

Implantable venous access devices (IVAD) have been widely used for cancer patients for long-term intravenous access. In past decades, an IVAD has not only provided a safe, convenient, cosmetic and reliable system for access needs but has also improved the quality of life of oncologic patients. An IVAD opens up the possibilities of frequent, multiple and long-term intravenous injections, as well as blood aspirations. Such benefits allow patients to receive multiple treatments, such as chemotherapeutic agents, antibiotics, total parenteral nutrition and blood products.

Despite its well-documented benefits, between 10% and 50% of patients with an IVAD experience complications during treatment. Major complications, such as infection, thrombosis, occlusion, extravasation, migration and mechanical malfunction, may restrict the use of the device and thereby interrupt treatment courses. Of these complications, catheter-related thrombosis (CRT) is known to be the most frequent complication. The clinical manifestations of CRT may range from asymptomatic vessel thrombosis to venous access failure or even symptomatic obstruction of major vessels, depending on the location of the thrombus. When thrombi are located around the catheter tip or within the lumen, symptoms usually go unnoticed until injection difficulty or injectate extravasation occurs. However, if the thrombus extends to the superior vena cava (SVC) or the right atrial (RA) wall, life-threatening complications may occur. Although CRT is a complex problem with divergent outcomes, the incidence and management guidelines are unclear. The reported incidence of CRT varies from 2% to 20% because standard diagnostic tools and criteria are lacking. As shown in Table 1, most studies used apparent clinical symptoms and signs as their diagnostic tool without the aid of any objective evidence. Consequently, the specific type or location of the thrombosis was not documented [1]. In most of these CRT cases, thrombotic devices were removed without aggressive medical treatment [2–4] or with inappropriate treatment [2,5,6]. Without scientific evidence for CRT management, once a thrombus occurs, most physicians will choose to remove the device to avoid complications. This high removal rate incurs treatment delay and limits the therapeutic options of cancer patients. Only a few researchers have applied a scientific tool to investigate the etiology of CRT systematically. In these studies, there were higher occurrence rates and more variable CRT outcomes than in studies without standard diagnostic criteria.

To date, we have yet to find any evidence-based review comparing IVAD CRT based on the specific location of thrombosis: RA thrombus, central vein thrombus, intraluminal thrombotic occlusion and fibrin sheath (Fig. 1). In this review, we undertook a systematic survey of the etiology and incidence of CRT, and primarily focused on issues related to the diagnosis and management of such thromboses. We systematically searched for reports in MEDLINE, EMBASE and the Cochrane Library, and classified each study into one of five levels of evidence (I to V) according to its importance and reliability. Based on this classification, we further investigated the risk and benefit analysis of medical management and traditional surgical revision.

2. Levels of evidence

Five levels of evidence were modified from the Oxford Centre and *The Journal of Bone and Joint Surgery* with respect to therapeutic, prognostic or diagnostic studies [7,8]. In order to identify the importance and reliability of the references, we noted the levels of evidence in each reference in our tables.

2.1. Therapeutic studies

- Level I: high-quality systematic review, randomized controlled trial with narrow confidence interval;
- Level II: lesser-quality systematic review of cohort studies (e.g., <80% follow-up, no blinding or improper randomization);
- Level III: retrospective comparative study or case-control study;
- Level IV: case series;
- Level V: expert opinion.

2.2. Prognostic studies

- Level I: high-quality prospective (all patients were enrolled at the same point in their disease with >80% follow-up) systematic review study;
- Level II: lesser-quality prospective (patients enrolled at different points in their disease or <80% follow-up) retrospective study or untreated control from a randomized controlled trial;
- Level III: absent in prognostic studies;
- Level IV: case series;
- Level V: expert opinion.

2.3. Diagnostic studies

- Level I: systematic review of prospective cohort studies with good follow-up;
- Level II: retrospective cohort study or poor follow-up;
- Level III: non-consecutive cohort study or very limited population;

Table 1 — Catheter-related thrombosis of implantable venous access devices

	Incidence (Ref)	*n*	Diagnostic tools	Level of evidence	Systematic survey	Symptomatic survey	Symptoms and signs	Etiology	Complications
RA thrombus	12.5% (13)*	48	TEE	I	√		Often asymptomatic & combined with infection	Catheter tip position in right atrium	Pulmonary embolism Cardiogenic shock Cardiac arrest Death
	3.8% (12)†	156	TTE	II	√				
CVT	2.6% (26)	379	Cavography	II		√	Catheter malfunction	Endothelial damage caused by catheter tip	DVT (61%)
	2.6% (4)	230		II		√	Local inflammation & tenderness		Thrombus recurrence (4–19%)
	2.9% (2)	169		II		√			Postphlebitic syndrome (5–25%)
	13.8% (25) 10% (right IJV) 20–23% (others)	412	Doppler US	II§	√		Face, neck & upper limb swelling Venous dilatation		Pulmonary embolism (8–15%) Death (2–4%)
	50% (24)‡ 43% (asymptomatic)	24	Venography	I	√		SVC syndromes		
	16% (3)	92	Venography	II		√			
ITO	1.9% (5)	1500	PPT	II		√	Total catheter occlusion	Inadequate volume or frequency of heparin installed Retrograde blood flow	Catheter malfunction
	1.8% (2)	169	PPT	II		√			
	1.7% (4)	230	PPT	II		√			
	3.0% (6)	707	PPT	I		√			
FS formation	Most common (42–100%) (33)		Contrast venography	IV	√		PWO	Unknown	Catheter malfunction Extravasation (2.6%)

*Data from Hickman catheter; †data from pediatric patients and Level II in prognosis; ‡data from oncologic children; §Level IV in therapy but Level II in prognosis. RA=right atrial; CVT = central venous thrombus; ITO = intraluminal thrombotic obstruction; FS = fibrin sheath; IJV = internal jugular vein; TEE = transesophageal echocardiography; TTE = transthoracic echocardiography; US = ultrasonography; PPT = push-pull technique; SVC = superior vena cava; PWO = persistent withdrawal occlusion; DVT = deep vein thrombosis.

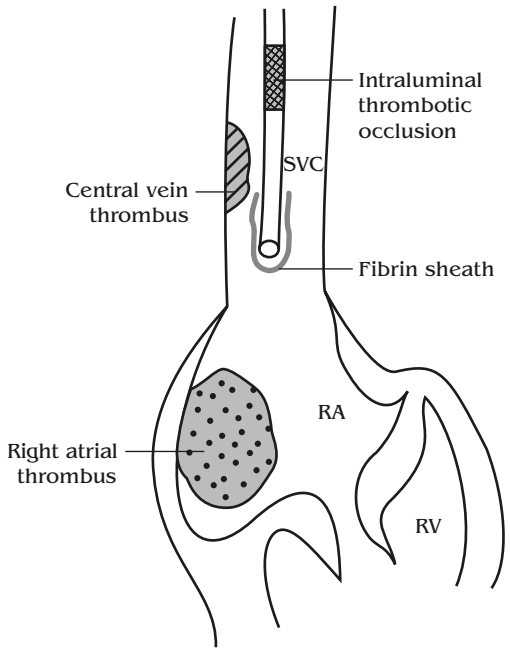

Fig. 1 — Four locations of implantable venous access device-related thromboses. SVC = superior vena cava; RA = right atrium; RV = right ventricle.

- Level IV: case-control study or study with poor reference standards;
- Level V: expert opinion.

3. Etiology and incidence

3.1. RA thrombus

IVAD-induced RA thrombus is clinically rare and silent but, when left untreated, will lead to life-threatening catastrophe. RA thrombus complicated with cardiogenic shock, pulmonary embolism or cardiac arrest may result in a high mortality rate ranging from 28% to 31% [9–11]. Most patients with RA CRT had a high association with the catheter tip position in the RA [10,12–15]. In Gilon et al's prospective study, all the RA thrombi were in the group with the catheter tip in the RA and 46% of this group developed RA thrombus within 6 months [13]. When the catheter tip is located within the RA, it may repeatedly brush against the atrial wall and induce intimal damage. The endothelium injury results in adherence of platelets, initiation of the coagulation cascade and thrombus formation. The severity of RA thrombus is much less in pediatric patients, leading to less hemodynamic compromise and pulmonary embolism [12]. The size of the thrombus was not significantly altered by the type of line or sepsis but showed a weak correlation with line age [16]. RA CRT may also be closely associated with infection [16–21]. *Staphylococcus* and *Candida albicans* infection were often noted in patients with RA thrombus [16,19,20].

3.2. Central vein thrombus

Catheter-related central vein thrombosis (CVT) is a common, early-occurring and extensive complication, although it is usually asymptomatic and is an underestimated thrombotic complication in patients with IVAD. It is believed that the etiology of CVT is also related to endothelium injury. The movement of the catheter tip may cause intimal damage, which results in the formation of a mural thrombus that is attached to the wall of the vessel. In such conditions, the catheter tip may sometimes become inlayed within this thrombus, inhibiting the function of the IVAD [22]. Most of these types of thrombus are silent and are not recognized until malfunction of the device or the occurrence of SVC syndromes.

The incidence of CVT ranged from 2% to 50%. The subclavian vein, which most catheters passed through, had the highest thrombosis rate [5,22]. Episodes may also occur in the internal jugular, axillary, brachiocephalic and azygous veins [23]. To investigate the actual incidence of CVT, Glaser et al evaluated the vessel patency of 24 oncologic children by contrast venography, which showed abnormalities in 12 patients (50%) [24]. Only three children had physical findings consistent with thrombosis, so the prevalence of silent thrombosis without signs or symptoms was nine out of 21 (43%). Therefore, the reported incidence appears to depend on whether the thrombosis is searched for systematically or only when it becomes symptomatic. It is clear that symptomatic CVT is less common than asymptomatic CVT [4,24,25]. On average, 2.6–16% of patients with IVAD develop symptomatic CVT and 13–66% are asymptomatic. For this reason, CVT is probably underreported (Table 1). Several predisposing factors may influence the occurrence rate of CVT: the accelerated coagulation system, the duration of the infusion time, the position of catheter insertion and its tip, the choice of chemotherapeutic agents, and the diagnostic tools used [4,5]. Higher platelet counts and blood hemoglobin levels >12.5g/dL are also suspected to be risk factors. The catheter material and thickness may also determine the pathogenesis [23]. Catheters made of polyethylene have a higher thrombosis rate than those made of silicon, and it is believed that the thicker the catheter used, the greater the incidence of thrombosis [4]. There is evidence that indicates that there is a relationship between the thrombotic and infectious complications of catheters [23]. The site of implantation and the position of the catheter tip also have a strong correlation with the thrombosis rate. In Puel et al's prospective trial, left-implanted

IVAD with the catheter tip in the upper half of the vena cava appears highly dangerous because the catheter tip knocks against the vessel wall at every heartbeat and can cause chronic microtrauma, resulting in thrombosis occurring in up to 28.6% of patients [26,27]. Besides mechanical attack, another reason is toxicity and chemical attack by the infused drugs themselves. Advanced damage may also occur when the delivered drugs are in close contact with the injured vessel wall, progressing the mural thrombus to CVT. Therefore, right-implanted IVAD is safer than left-implanted IVAD; the catheter tip is located in the lower portion of the SVC and this is safer than being in the upper portion. Peripheral-implanted IVAD had a higher incidence than central-implanted IVAD [27]. CVT may be associated with deep venous thrombosis (DVT) and SVC syndrome [4,24]. Clinically symptomatic thrombosis can present in various ways, including catheter malfunction in association with arm swelling, neck or arm pain, and jugular venous distension. Subsequent symptoms include fever in the absence of infection, skin temperature changes and skin discoloration [23]. It is believed that CVT can also contribute to recurrence of the thrombus (4–19%), postphlebitic syndrome (5–25%), pulmonary embolism (8–15%) and death (2–4%) [23,24].

3.3. *Intraluminal thrombotic occlusion*

Obstruction, with resultant loss of ability to withdraw and/or infuse material, is another complication related to IVAD. Such occlusion may lead to potentially significant delays in necessary treatment regimens as many of the patients are receiving medication that can only be administered via central access. This complication may be due to a variety of conditions, including mechanical obstruction, fibrin sheath formation, drug precipitation and intraluminal thrombosis occlusion [28–30]. Mechanical obstructions may include kinking of the catheter, malposition of the tip and the catheter being pinched against the first rib or clavicle [28,31]. The occurrence of fibrin sheath formation is another reason for intraluminal obstruction. Fibrin may migrate into the lumen causing catheter obstruction. This topic will be discussed later in the paper. Deposition of either lipid or crystal may also cause catheter occlusion. Total parenteral nutrition is the major source of lipid precipitates, which can be cleared by instillation of 70% ethyl alcohol. Etoposide, calcium, diazepam, phenytoin and heparin may cause mineral drug precipitates, which can be treated with 1 mL of 0.1% hydrochloric acid [28,32]. However, over 60% of catheter obstruction is due to thrombotic occlusion, which leads to the removal of the device in 60–100% of cases before the development of effective therapy [2,4]. IVAD intraluminal thrombotic occlusion is caused by blood components in 1.7–3% of cases [4,6,28]. Without adequate volume or frequency of heparin injection, retrograde blood clots will develop inside the lumen, resulting in total occlusion.

3.4. *Fibrin sheath*

Fibrin sheath formation is an insidious problem that can plague essentially all central venous catheters. The formation may start as early as 24 hours after insertion and between 42% and 100% of catheters in place over 1 week may generate fibrin sheaths [33,34]. The term *fibrin sheath* refers to a sleeve of fibrin that surrounds the catheter from the tip to where it enters the vein. A fibrin sheath can form and encase the outside surface of the catheter. The sheath may cause a sac in the distal tip initially and extend downward closing over the tip of the catheter. A flap-valve will be formed, allowing entry but preventing withdrawal of blood and fluid, resulting in partial occlusion [33,34]. This partial occlusion is also called persistent withdrawal occlusion (PWO) and typically manifests at the occurrence of fibrin sheath. This is of particular importance when large-bore catheters are used for hemodialysis. However, its influence is trivial when IVADs are used for chemotherapy. Complete occlusion may occasionally occur if the fibrin adhering to the catheter migrates into the lumen. Although most fibrin sheaths are clinically silent, their formation may promote and mediate bacterial attachment and infection. Therefore, a catheter with a fibrin sheath may cause an increase in IVAD infection rate. Consequently, infected catheters can be the source of positive blood cultures and fibrin sheath can enhance the propensity for persistent bacteremia [18,35]. In a few cases (2.6%), extravasation of fluid into the surrounding tissues can occur if a sheath solidly encases the IVAD from its tip to its venous entry point [33].

4. Diagnosis

4.1. *RA thrombus*

RA thrombi may be underdiagnosed because most of them are asymptomatic and a small thrombus is difficult to recognize by transthoracic echocardiography [36]. Most RA thrombi were found by accident while evaluating heart function by echocardiography [14,17]. One case was noted on routine chest computed tomography (CT) scan [37]. Transesophageal echocardiography (TEE) is a simple and effective diagnostic technique, which provides an unobstructed view of the cardiac structures and the great vessels [13,17,36]. Cohen et al evaluated the superiority of

TEE for detecting catheter-related RA thrombus in 19 patients, while transthoracic echocardiography only found five (26%) of them. TEE not only better defined the size and mobility of the thrombus, it also provided a superior image of masses located in or near the SVC, inferior vena cava or in the RA appendage [16]. A similar outcome was also reported by Schwartzbard et al [38]. In their investigation, transthoracic echocardiography had a 60% false-negative rate for the evaluation of RA thrombi and 100% misdiagnosis of RA appendage thrombi. Therefore, evaluation using TEE is needed whenever RA thrombus is suspected.

4.2. CVT

Although the occurrence of thrombotic symptoms is the best way to identify CVT, diagnosis is usually delayed after the patient develops symptoms of complete occlusion or infusional difficulties. This is because the clinical presentation of CVT is insidious in evolution and is usually characterized by nonspecific symptoms [23]. Catheter-related CVT patients did not consistently demonstrate venous dilation or develop clinically recognizable venous collaterals, nor was regional swelling a uniform clinical feature [5]. In such a situation, recognition of early signs or symptoms of CVT does not seem to be easy.

There are several available modalities, such as chest radiography, contrast venography, ultrasonography, CT, magnetic resonance imaging (MRI) angiography and TEE, for evaluating suspected cases [23]. Chest radiography can rule out the possibility of catheter tip malposition, kinking or fracture. Contrast venography is used as the standard for diagnosis of large vessel occlusion in the upper venous system. It helps to assess the size and location of intramural thromboses accurately, and gives excellent visualization of collaterals [3,24]. Although contrast venography is a great tool for evaluating CVT, it is still too invasive for general survey such as TEE. CT and MRI provide excellent visualization and are noninvasive, although their high costs limit their use [23]. Although ultrasonography, especially color flow Doppler and compression ultrasonography, provides a convenient and noninvasive method for thrombosis diagnosis, its high sensitivity and specificity are only particular for upper-extremity DVT. Therefore, we can conclude that different tools have different advantages and limitations, and none of them can be widely used as the standard method at present.

4.3. Intraluminal thrombotic occlusion

To identify whether the device is occluded, a push-pull technique can be used [29]. In this procedure, normal saline is used in an attempt to gently irrigate the catheter to see if installation of normal saline and/or blood aspiration is successful. If infusion of fluids and aspiration of blood is impossible, complete occlusion has occurred and is generally caused by clotted blood. If fluids can be infused but no blood can be aspirated, this is called partial occlusion or PWO, which is usually caused by fibrin sheath formation [39,40]. A more precise definition of "cannot aspirate" is the inability to withdraw 3 mL of blood from the device [31,41]. To rule out the possibility of malpositioning of the catheter, recent chest X-rays should be reviewed to verify the catheter tip location [29,41]. In addition, occlusion caused by nonhematologic factors, such as deposition of either lipids or crystal, should also be considered. Check the medication administration to see whether any infusate has been infused that may cause a precipitate [29]. Although Ponec et al believed radiographic contrast material injection is useful in determining the cause of obstruction and the type of therapy necessary, contrast injection studies are often not readily available in clinical practice [31]. As a result, clinical catheter dysfunction is still the most popular way to diagnose device obstruction.

4.4. Fibrin sheath

Diagnosis of fibrin sheath formation is usually manifested by catheter malfunction, especially PWO. To exclude anatomical obstruction, various physical maneuvers should be performed, such as changing the position of the patient's arm and/or head while attempting aspiration. Fluoroscopy, a tool for seeking catheter kinks or leaks, can be used if mechanical cause is highly suspected. However, if definite diagnosis needs to be proven, contrast venography should be performed [34].

5. Management

5.1. RA thrombus

5.1.1. Surgical approach

For a symptomatic patient with a large mobile thrombus or persistent infection, surgical thrombectomy is strongly recommended (Table 2) [12,17]. These thrombi may threaten atrial or ventricular inflow and cause sudden death. Further, large-sized thrombi can be organized and contain calcifications, suggesting that they are usually old and hard to resolve [12]. In some cases, with additional infection, antibiotics alone are not sufficient. These thrombi should be surgically removed and the catheter should also be explanted [16–20]. Compared with medical

Table 2 — Surgical approach to catheter-related thrombosis

	Methods	Authors (Ref)	Level of evidence	Percentage of all thrombosis cases
RA thrombus	Thrombectomy + explantation	Kentos et al (19)	IV	
		Cohen et al (16)	IV	
	Thrombectomy	Paut et al (17)	IV	
		Horner et al (18)	IV	
		Hollingsed et al (20)	IV	
		Wilimas et al (45)	IV	
		Ellis et al (15)	IV	
	Thrombectomy after rt-PA failed	Ozimek et al (14)	IV	
	Thrombectomy after Actylise failed	Gadomski et al (21)	IV	
	Thrombectomy	Schwartzbard et al (38)	III	7/20 (35%)
	Thrombectomy	Korones et al (12)	IV†	2/6 (33%)
CVT	Explantation after fibrinolytics failed	Kock et al (5)	II	
		Poorter et al (2)	II	4/5 (80%)
	Explantation	Lokich et al (3)	II	10/15 (67%)
	Explantation	Barrios et al (4)	II	3/6 (50%)
ITO	Explantation after fibrinolytics failed	Kock et al (5)	II	
	Explantation after urokinase failed	Schwarz et al (6)	I	12/20 (60%)
	Explantation	Poorter et al (2)	II	3/3 (100%)
	Explantation	Barrios et al (4)	II	3/4 (75%)
	Replacement after fibrinolytics failed	Jacobs et al (39)*	IV	9/320 (2.8%)
FS formation	—	—	—	—

*Data from central venous catheter; †Level II in prognosis but Level IV in therapy. RA = right atrial; CVT = central venous thrombus; ITO = intraluminal thrombotic obstruction; FS = fibrin sheath.

management, surgical thrombectomy and explantation not only remove the thrombus and control the infection but also prevent the possibility of life-threatening complications (17).

5.1.2. Medical approach

Due to morbidity and mortality, only a few cases of RA thrombosis, most of them in children, have been treated by medical management (Table 3). A completely dissolved case without side effects was reported by Adamovich et al in a neonate after 5 days' infusion of urokinase and prophylactic intravenous heparin with subcutaneous low-molecular-weight heparin (LMWH) (42). Another successful pediatric case reported by Cesaro et al was treated with recombinant tissue plasminogen activator (rt-PA) (0.1 mg/kg/hr for 12 hours) and heparin (10IU/kg/hr for 24 hours) for 6 days without significant side effects (43). Korones et al believed that a small-sized thrombus did not need any intervention, even though no regression was seen after 1 year, and that a moderate-sized thrombus only needed medication, such as warfarin, instead of surgical thrombectomy (12). Although RA thrombus is less menacing in pediatric patients, there were still several cases of failure that eventually needed surgical intervention (14,21). In adults, medical treatment has been tried in only a few reported cases because it is believed that, even though antithrombotic agents may stabilize or regress catheter-related RA thrombi, anticoagulated patients remain at risk of pulmonary embolism and need to receive surgical thrombectomy eventually (10,11,44).

5.1.3. Summary

Catheter-related RA thrombosis is a life-threatening complication that may not be as rare as we previously thought if the catheter tip is inserted into the RA. Medical management may be indicated in pediatric patients with small- to moderately-sized thrombi. However, surgical thrombectomy is still considered the safest and most effective treatment for adults and also for children with large-sized thrombi.

5.2. CVT

5.2.1. Surgical approach

The handling of IVAD after CVT varies in the literature. Although medical antithrombotic treatment was widely applied, most of the devices were still explanted; some were removed before treatment (5,6) and some were explanted after fibrinolytic, antithrombotic or anticoagulant

Table 3 — Medical approach to catheter-related thrombosis

	Authors (Ref)	Methods	Success rate or outcome (thrombus regression or device recovery)	Level of evidence
RA thrombus	Korones et al (12)*	Warfarin (moderate-sized) or no intervention (small-sized)	1/4 (25%)	IV
	Ozimek et al (14)*	rt-PA	Failed	IV
	Adamovich et al (42)*†	5 d of local urokinase 3000–4500 IU/kg/hr, heparin 100 IU/kg/hr iv, LMWH sc	Successful case report	IV
	Gadomski et al (21)*	14 d of fibrinolytics (Actylise)	Failed	IV
	Cesaro et al (43)*†	6 d of rt-PA (0.1 mg/kg/hr) and heparin (10 I U/kg/hr)	Successful case report	IV
	Huraib et al (44)	Heparin iv for 10 wk	Successful case report	IV
CVT	Kroger et al (22)	Heparin iv or LMWH sc with anticoagulants for 6–12 wk	42/56 (80%)	IV
	Breddin et al (47)‡	UFH iv bolus 5000 IU and continuous 1250 IU/hr	129/321 (40.2%)	I
		LMWH sc bid 5–7 d	175/328 (53.4%)	
		LMWH sc qd 28 d	167/312 (53.5%)	
	Pucheu et al (25)	Systemic fibrinolytics	16/32 (50%)	IV
		LMWH 3 wk + warfarin	1/25 (4%)	
	Lokich et al (3)	Streptokinase, heparin or coumadin	5/7 (71.4%)	II
ITO	Atkinson et al (55)†	Twice rt-PA 2 mg/2 mL into occluded device	5/6 (83.3%)	IV
	Haire et al (54)†§	Twice rt-PA 2 mg/2 mL into occluded device	25/28 (89.3%)	I
		Twice urokinase 10,000 U into occluded device	13/22 (59.1%)	
	Timoney et al (29)†	Alteplase 2.5 mL/1 mg/mL inserted into occluded device for 30 min	136/168 (81%)	I
			36/44 (82%) – IVAD	
	Semba et al (41)†	Alteplase 2 mg/2 mL injected into occluded device for 120 min. If failed, another dose may be tried.	798/1064 (75%) – 1st dose	I
			905/1064 (85.1%) – 2nd dose	
			234/309 (75.7%) – IVAD	
	Chesler et al (56)*†	Alteplase 0.5 mg/1 mL injected for 30–60 min. If failed, repeat the same dose.	29/42 (69%) – 1st dose	III
			37/42 (88%) – 2nd dose	
	Ponec et al (31)†	Alteplase 2 mg/2 mL injected for 2 hr. If failed, repeat the same dose.	51/69 (74%) – 1st dose	I
			63/69 (90%) – 2nd dose	
FS formation	Davis et al (40)†§||	Alteplase 0.5 mg/1 mL injected for 60 min. If failed, tried 1 mg/1 mL, then 2 mg/mL.	50/58 (86.2%) – 1st dose	II
			55/58 (94.8%) – 2nd dose	
			56/58 (96.5%) – 3rd dose	
	Whigham et al (34)	tPA 1 mg/mL installed for 15 min 3 times. If failed, repeat the same dose overnight.	52/56 (92.9%)	II

*Pediatric patients weighing <30 kg; †data from patients with central venous access devices; ‡non-catheter-related study; §both pediatric and adult patients; ||included both partial and complete occlusion. RA = right atrial; CVT = central venous thrombus; ITO = intraluminal thrombotic obstruction; FS = fibrin sheath; rt-PA = recombinant tissue plasminogen activator; LMWH = low-molecular-weight heparin; iv = intravenous; sc = subcutaneous; UFH = unfractionated heparin; IVAD = implantable venous access device.

treatment failed [4,5,8]. The most common reason for explantation of IVAD is prevention of thrombosis progression, especially in the case of SVC syndrome. Other reasons are persistent pain, combined with a documented infection and extravasation. However, does SVC syndrome or any other complication related to CVT definitely disappear after explantation? A negative answer was first noted in Lokich et al's study, when they noticed that withdrawal of IVAD rarely resolved the vascular occlusion [3]. Recently, to determine whether CVT can be self-limiting after explantation, 24 oncologic children undergoing port removal because of completion of therapy were enrolled in the study of Glaser et al [24]. Vessel patency was evaluated by contrast venography, which showed abnormalities in 12 patients (50%), including three severe occlusions and nine occult. This trial revealed that the obstructed vessels may not recanalize even after IVAD removal. Wilimas et al followed up the catheter-related CVT by contrast-enhanced CT at least 2 months after catheter removal [45]. Surprisingly, the thrombus in several patients persisted as long as 30 months after catheter removal and did not recanalize. This result shows that the thrombotic lesions may be long-lasting or permanent. Therefore, surgical explantation may not consequentially solve the problems of CVT but may influence usability with respect to the advantages of IVAD in the treatment of cancer patients.

5.2.2. Medical approach

Antithrombotic treatment is necessary for all CVT patients with or without IVAD explantation. Removal of the device should be decided by clinical necessity for venous access or by evidence of pulmonary embolism [5]. Although pulmonary embolism is considered a morbid complication, no case has been documented in the ongoing use group of IVAD with catheter-related CVT [5,22,25]. In a *Letter to the Editor* from Kroger et al, 42 patients (80%) with CVT received only heparin intravenously, with effective prolongation of the partial thromboplastin time, or LMWH subcutaneously without explantation [22]. The results showed that the devices could still be used for further application of chemotherapy and possible complications, such as pulmonary embolism, infections, or bleeding associated with the anticoagulation or caused by the puncture of subcutaneous collateral veins, were not observed. They suggested that anticoagulation should be maintained for 6–12 weeks. Recently, unfractionated heparin (UFH) and LMWH have been the most popular antithrombotic agents used for the treatment of catheter-related CVT.

5.2.2.1. UFH

Intravenous UFH is the initial treatment of choice for acute CVT. UFH can prevent clot propagation but cannot dissolve it. Therefore, recanalization may not develop. It can be given by continuous intravenous infusion for 5–10 days, starting with a bolus of 5000 IU followed by 30,000–35,000 IU/day, adjusted to achieve an activated partial thromboplastin time of 1.5–2.5 times the control [46]. Patients who achieved therapeutic plasma concentrations of heparin had recurrence rates 15 times lower than those who did not reach the therapeutic range [46]. Long-term vitamin K antagonists and warfarin may also be given with UFH to prevent the propagation of thrombi [47]. However, UFH has a number of limitations that have restricted its use: unpredictable anticoagulant effects, inhibition of platelet aggregation, augmentation of vessel wall permeability, thrombocytopenia and potential bleeding complications.

5.2.2.2. LMWH

Recently, LMWHs have been used in the treatment of acute DVT and acute pulmonary embolism. LMWHs have theoretical advantages over UFH, including higher bioavailability, longer half-life and a more predictable antithrombotic effect. The antithrombotic activity of LMWHs is mainly based on the inactivation of factor Xa because of a reduced ability to inactivate factor IIa when compared with UFH.

To assess the efficacy of LMWHs, several randomized trials have taken place since the early 1990s comparing LMWHs with standard heparin in the initial treatment of acute proximal venous thrombosis. In six recent studies, there were obvious reductions in the rate of recurrent venous thromboembolism between LMWH groups and UFH groups (Table 4) [48–51]. LMWHs not only prevented the recurrence of thrombosis but also helped with thrombus regression [48].

In addition to efficacy, LMWHs have many advantages compared to UFH. Firstly, LMWHs can be administered subcutaneously in weight-adjusted, once or twice daily, doses without the need for laboratory monitoring [46,47]. Due to their properties, most patients with CVT can be given LMWHs safely and accurately at home without hospitalization, increasing the convenience for the patient and reducing the cost to the health care system [51,52]. Secondly, LMWHs have minimal interaction with platelets and have potentially more antithrombotic rather than hemorrhagic activity compared with UFH. Further, the incidence of heparin-induced thrombocytopenia is less with LMWHs [46]. Thirdly, the major bleeding rate and mortality rate associated with LMWHs were significantly lower than those associated with UFH, and LMWHs may exert an inhibitory effect on tumor growth in cancer patients [48,53]. Therefore, we can conclude that LMWHs have better effectiveness than UFH in the prevention of recurrent episodes of DVT, better safety with respect to the occurrence of major bleeding, and better cost-effectiveness and convenience facilitating outpatient management of catheter-related CVT.

Table 4 — Comparison of the efficacy and safety of treatment of central vein thrombosis with low-molecular-weight heparins (LMWHs) and unfractionated heparin (UFH)

Authors (Ref)	LMWHs/UFH		
	Rate of recurrent venous thromboembolism (%)	Rate of major bleeding (%)	Rate of death (%)
Hull et al (48)	2.8/6.9	0.5/5.0*	4.7/9.6*
Prandoni et al (49)	7/14	1.1/3.5	7/14
Dolovich et al (50)	4.3/5.1	1.5/2.5	4.9/6.5*
Levine et al (51)	5.3/6.7	1.2/2.0	5.3/6.7
Koopman et al (52)	6.9/8.6	0.5/2.0	6.9/8.1

*$p<0.05$.

5.2.2.3. Fibrinolytic agents

Fibrinolytic agents, such as streptokinase, urokinase and rt-PA, are usually effective for the lysis of fresh thrombi. Therefore, resolution of thrombi is more significant in acute occlusions than in CVT, which is always detected after a period of time. Although some studies mentioned their usage, antithrombotic agents are still the first choice (5,25).

5.3. Intraluminal thrombotic occlusion

5.3.1. Surgical approach

It is certain that surgical explantation of the device should only be considered after fibrinolytics have failed or therapy has been terminated because of its minor severity and the high success rate of medical treatment (5,6,39).

5.3.2. Medical approach

Fibrinolytic agents, such as rt-PA, urokinase and streptokinase, have been used in recent decades to lyse intraluminal thrombi, to restore device patency and to avoid catheter removal. Although some complications, such as bleeding, hypersensitivity reactions, arrhythmias, hypotension, fever, nausea or vomiting, may be associated with their usage, intraluminal installation of fibrinolytic agents is still considered the safest and most effective therapy for the treatment of IVAD intraluminal thrombotic occlusions.

5.3.2.1. rt-PA

Alteplase is the most popular and effective rt-PA used in the treatment of thrombotic occlusion. It is a serine protease that activates plasminogen to plasmin in the cleavage of thrombus-bound fibrin. Alteplase was primarily used for the treatment of acute myocardial infarction, pulmonary embolism and acute ischemic stroke, and has recently been used in the therapy of occluded IVAD. In adult patients, 2 mg alteplase in 2 mL sterile water may be injected into the occluded catheter. Restoration of function is assessed 30–120 minutes later (29,31,41,54,55). If function is not restored, a second attempt with the same dose is performed (31,41,54–56). Surprisingly, the proportion of patients in whom successful treatment was achieved after a single dose ranged from 64% to 86%, and success was achieved in 81–94% after two doses (Table 3). Alteplase can also be used in pediatric oncologic patients with dysfunctional IVAD. Indwelling 0.5 mg/1.0 mL alteplase once or twice obtained an 88–97% success rate without significant adverse events (56,57). Alteplase not only converts the entrapped plasminogen to plasmin, resulting in local fibrinolysis, but also provides better efficacy in restoring occluded IVAD function and faster dissolving of thrombi than urokinase (29,41,54,55). In addition, alteplase has the advantages of a low incidence of allergic reactions (<0.02%) and no documented reports of sustained antibody formation after administration (5).

Although small dose alteplase is so far not commercially available, large dose alteplase can be split into unit doses and cryopreserved at –20°C for 30 days (29). Reconstruction to small dose aliquots makes this a cost-effective solution without compromising safety and efficacy (29,40,41,56). However, the production of a single-dose rt-PA vial is still needed, not only for small institutions but also as a convenient and safe agent for oncologic patients.

5.3.2.2. Urokinase

Previously, urokinase, a product from primary cell cultures of kidney cells harvested after death from human neonates, was suggested by the United States Food and Drug Administration (FDA) as a clinical pathway for IVAD occlusion. However, in January 1999, the FDA identified problems with the manufacturing process of urokinase. Like all human-based biological products, it has the potential to spread infectious disease (40). In 1999, the FDA reported on microorganism contamination of urokinase and issued a warning about variations in quality control during manufacture, recommending that urokinase be restricted to specific patients in whom the physician has judged urokinase to be critical to the clinical situation (58).

5.3.2.3. Streptokinase

Although streptokinase can resolve occlusions without hemorrhagic side effects or coagulation changes, allergic reactions and the induction of antibody formation limits its usefulness. Fever and shivering (1–4%), and anaphylactic reactions (0.1%) occurred when intravenous streptokinase was given (29). In addition, inactivated antibodies resulting from patients' prior exposure to streptokinase or streptococcal infections may potentially increase the risk of allergic response (40). An initial (1.5 million IU) dose of streptokinase may produce neutralizing antibodies that persist for up to 12 weeks that could preclude prolonged or follow-up administration. These risks/issues led to the restriction of its usage (29,59). Therefore, the producers of streptokinase, AstraZeneca, released an *Important Safety Information* letter on streptokinase in December 1999. They warned that there is a risk of significant allergic reactions and that streptokinase is not indicated for restoration of IVAD patency (59).

5.4. Fibrin sheath

5.4.1. Surgical approach

Although fibrin sheath formation is the most common type of catheter-related thrombosis, life-threatening complications rarely occur. Fibrin sheath formation without device malfunction needs no treatment. If PWO or complete occlusion is exhibited, most of the problems can be solved by fibrinolytics. In contrast, device removal is not only high in cost but also delays the patient's treatment (33). In addition, a near-fatal case of air embolism was reported after surgical explantation of the device. It is speculated that fibrin sheath formation might provide a channel for air embolism after catheter removal (60). Therefore, surgical management is not suggested for fibrin sheath treatment.

5.4.2. Medical approach

PWO, complete occlusion and extravasation of the device caused by fibrin sheath formation can all be lysed by fibrinolytics (32,40). The formation of the fibrin that causes PWO may take a longer period of time than fresh thrombi that induce complete occlusion. Therefore, clearance of PWO may be more difficult than clearing complete occlusion. Davis et al suggested that alteplase be used in partially blocked catheters, at a dosage of 0.5 mg/mL, 1 mg/mL and 2 mg/mL (40). Whigham et al used 1 mg/mL tPA injected into the catheter followed by 0.4 mL sterile saline for 15 minutes three times until successful (34). If catheter clearance was not achieved after the third dose, a fourth dose was infused and allowed to remain overnight: 92.9% of fibrin sheath with PWO were dissolved and confirmed by contrast venography, requiring an average dose of 2.29 mg.

5.4.3. Summary

Catheter-related IVAD fibrin sheath formation needs no invasive treatment. However, fibrinolytic agents are the best choice for a non-functioning device.

6. Conclusion

Without proper diagnosis of the exact etiology, IVADs with related thromboses have been removed before attempting any medical treatment. However, our evidence-based review clearly demonstrates that use of fibrinolytic agents through the device is the best practice for the two most common etiologies of IVAD-related thromboses, i.e. fibrin sheath formation and intraluminal thrombotic occlusion. Device explantation is obviously not indicated. Furthermore, antithrombotic agent infusion is undoubtedly essential for the management of CVT, while the benefit of removing the device is still in question. Among the four locations of IVAD-related thromboses, RA thrombus is an absolute surgical indication due to its potentially life-threatening outcome. Prompt thrombectomy is considered the safe and effective treatment for adults and for children with large-size thrombi. In conclusion, our review suggests that an exact diagnosis of the location of the IVAD-related thrombosis is indispensable so that a proper treatment strategy can be implemented to prolong the lifespan of the IVAD and reduce the complications associated with thrombosis.

References

1. Koonings PP, Given FT Jr. Long-term experience with a totally implanted catheter system in gynecologic oncologic patients. *J Am Coll Surg* 1994;178:164–6.
2. Poorter RL, Lauw FN, Bemelman WA, Bakker PJ, Taat CW, Veenhof CH. Complications of an implantable venous access device (Port-a-Cath) during intermittent continuous infusion of chemotherapy. *Eur J Cancer* 1996;32A: 2262–6.
3. Lokich JJ, Bothe A Jr, Benotti P, Moore C. Complications and management of implanted venous access catheters. *J Clin Oncol* 1985;3:710–7.
4. Barrios CH, Zuke JE, Blaes B, Hirsch JD, Lyss AP. Evaluation of an implantable venous access system in a general oncology population. *Oncology* 1992;49:474–8.
5. Kock HJ, Pietsch M, Krause U, Wilke H, Eigler FW. Implantable vascular access systems: experience in 1500 patients with totally implanted central venous port systems. *World J Surg* 1998;22:12–6.
6. Schwarz RE, Groeger JS, Coit DG. Subcutaneously implanted central venous access devices in cancer patients: a prospective analysis. *Cancer* 1997;79:1635–40.

7. Centre for Evidence-based Medicine, Oxford, UK. *Oxford Centre for Evidence-based Medicine Levels of Evidence*. Available at: http://www.cebm.net/levels_of_evidence.asp#levels (Date accessed: May 2001)
8. The Journal of Bone & Joint Surgery. *Levels of Evidence for Primary Research Question, Instructions to Authors*. Available at: http://www2.ejbjs.org/misc/instrux.shtml
9. Alhaddad IA, Soubani AO, Brown EJ Jr, Jonas EA, Freeman I. Cardiogenic shock due to huge right atrial thrombus. *Chest* 1993;104:1609–10.
10. Kingdon EJ, Holt SG, Davar J, et al. Atrial thrombus and central venous dialysis catheters. *Am J Kidney Dis* 2001;38:631–9.
11. Forauer AR, Bocchini TP, Lucas ED, Parker KR. Giant right atrial thrombus: a life-threatening complication of long-term central venous access catheters. *J Vasc Interv Radiol* 1998;9:519–20.
12. Korones DN, Buzzard CJ, Asselin BL, Harris JP. Right atrial thrombi in children with cancer and indwelling catheters. *J Pediatr* 1996;128:841–6.
13. Gilon D, Schechter D, Rein AJ, et al. Right atrial thrombi are related to indwelling central venous catheter position: insights into time course and possible mechanism of formation. *Am Heart J* 1998;135:457–62.
14. Ozimek W, Wroblewska-Kaluzewska M, Gadomski A, et al. Echocardiographic assessment of right atrial thrombus related to the implanted port device in patient receiving chemotherapy for non-Hodgkin's lymphoma. *Med Sci Monit* 2000;6:1013–7.
15. Ellis PK, Kidney DD, Deutsch LS. Giant right atrial thrombus: a life-threatening complication of long-term central venous access catheters. *J Vasc Interv Radiol* 1997;8:865–8.
16. Cohen GI, Klein AL, Chan KL, Stewart WJ, Salcedo EE. Transesophageal echocardiographic diagnosis of right-sided cardiac masses in patients with central lines. *Am J Cardiol* 1992;70:925–9.
17. Paut O, Kreitmann B, Silicani MA, et al. Successful treatment of fungal right atrial thrombosis complicating central venous catheterization in a critically ill child. *Intensive Care Med* 1992;18:375–6.
18. Horner SM, Bell JA, Swanton RH. Infected right atrial thrombus—an important but rare complication of central venous lines. *Eur Heart J* 1993;14:138–40.
19. Kentos A, Dufaye P, Jacobs F, De Smet JM, Serruys E, Thys JP. *Candida albicans* septic thrombosis of the right atrium is associated with a central venous catheter. *Clin Infect Dis* 1995;21:440–2.
20. Hollingsed MJ, Morales JM, Roughneen PT, Burch KD. Surgical management of catheter tip thrombus: surgical therapy for right atrial thrombus and fungal endocarditis (*Candida tropicalis*) complicating paediatric sickle-cell disease. *Perfusion* 1997;12:197–201.
21. Gadomski A, Jaranowska D, Ebinger K, Ozimek W, Brzewski M. Right atrial thrombus complicating chemotherapy by central venous catheterization in a child with Hodgkin's disease. *Wiad Lek* 1998;51(Suppl 4):266–9.
22. Kroger K, Grutter R, Rudofsky G, Fink H, Niebel W. Follow-up after Port-a-Cath-induced thrombosis. *J Clin Oncol* 2002;20:2605–6.
23. Cobos E, Dixon S, Keung YK. Prevention and management of central venous catheter thrombosis. *Curr Opin Hematol* 1998;5:355–9.
24. Glaser DW, Medeiros D, Rollins N, Buchanan GR. Catheter-related thrombosis in children with cancer. *J Pediatr* 2001;138:255–9.
25. Pucheu A, Dierhas M, Leduc B, et al. Fibrinolysis of deep venous thrombosis on implantable perfusion devices. Apropos of a consecutive series of 57 cases of thrombosis and 32 cases of fibrinolysis. *Bull Cancer* 1996;83:293–9.
26. Puel V, Caudry M, Le Metayer P, et al. Superior vena cava thrombosis related to catheter malposition in cancer chemotherapy given through implanted ports. *Cancer* 1993;72:2248–52.
27. Kuriakose P, Colon-Otero G, Paz-Fumagalli R. Risk of deep venous thrombosis associated with chest versus arm central venous subcutaneous port catheters: a 5-year single-institution retrospective study. *J Vasc Interv Radiol* 2002;13:179–84.
28. Rauthe G, Altmann C. Complications in connection with venous port systems: prevention and therapy. *Eur J Surg Oncol* 1998;24:192–9.
29. Timoney JP, Malkin MG, Leone DM, et al. Safe and cost effective use of alteplase for the clearance of occluded central venous access devices. *J Clin Oncol* 2002;20:1918–22.
30. Hooke C. Recombinant tissue plasminogen activator for central venous access device occlusion. *J Pediatr Oncol Nurs* 2000;17:174–8.
31. Ponec D, Irwin D, Haire WD, Hill PA, Li X, McCluskey ER. Recombinant tissue plasminogen activator (alteplase) for restoration of flow in occluded central venous access devices: a double-blind placebo-controlled trial—the Cardiovascular Thrombolytic to Open Occluded Lines (COOL) efficacy trial. *J Vasc Interv Radiol* 2001;12:951–5.
32. Lawson M. Partial occlusion of indwelling central venous catheters. *J Intraven Nurs* 1991;14:157–9.
33. Mayo DJ. Fibrin sheath formation and chemotherapy extravasation: a case report. *Support Care Cancer* 1998;6:51–6.
34. Whigham CJ, Lindsey JI, Goodman CJ, Fisher RG. Venous port salvage utilizing low dose tPA. *Cardiovasc Intervent Radiol* 2002;25:513–6.
35. Mehall JR, Saltzman DA, Jackson RJ, Smith SD. Fibrin sheath enhances central venous catheter infection. *Crit Care Med* 2002;30:908–12.
36. Crowley JJ, Kenny A, Dardas P, Connolly DL, Shapiro LM. Identification of right atrial thrombi using transoesophageal echocardiography. *Eur Heart J* 1995;16:708–10.
37. Oh WK, Lee BH, Sweitzer NK. Nonmalignant diagnoses in patients. Case 3. Right atrial thrombus associated with a central venous catheter in a patient with metastatic adrenocortical carcinoma. *J Clin Oncol* 2000;18:2638–9.
38. Schwartzbard AZ, Tunick PA, Rosenzweig BP, Kronzon I. The role of transesophageal echocardiography in the diagnosis and treatment of right atrial thrombi. *J Am Soc Echocardiogr* 1999;12:64–9.
39. Jacobs BR, Haygood M, Hingl J. Recombinant tissue plasminogen activator in the treatment of central venous catheter occlusion in children. *J Pediatr* 2001;139:593–6.
40. Davis SN, Vermeulen L, Banton J, Schwartz BS, Williams EC. Activity and dosage of alteplase dilution for clearing occlusions of venous-access devices. *Am J Health Syst Pharm* 2000;57:1039–45.
41. Semba CP, Deitcher SR, Li X, Resnansky L, Tu T, McCluskey ER. Treatment of occluded central venous catheters with alteplase: results in 1,064 patients. *J Vasc Interv Radiol* 2002;13:1199–205.
42. Adamovich K, Tarnok A, Szauer E. Successful treatment of a right atrial thrombus secondary to central venous catheterization. *Orv Hetil* 1999;140:1467–70.

43. Cesaro S, Paris M, Corro R, et al. Successful treatment of a catheter-related right atrial thrombosis with recombinant tissue plasminogen activator and heparin. *Support Care Cancer* 2002;10:253–5.
44. Huraib S. Right atrial thrombus as a complication of subclavian vein catheterization—a case report. *Angiology* 1992; 43:439–42.
45. Wilimas JA, Hudson M, Rao B, Luo X, Lott L, Kaste SC. Late vascular occlusion of central lines in pediatric malignancies. *Pediatrics* 1998;101:E7.
46. Ageno W, Huisman MV. Low-molecular-weight heparins in the treatment of venous thromboembolism. *Curr Control Trials Cardiovasc Med* 2000;1:102–5.
47. Breddin HK, Hach-Wunderle V, Nakov R, Kakkar VV. Effects of a low-molecular-weight heparin on thrombus regression and recurrent thromboembolism in patients with deep-vein thrombosis. *N Engl J Med* 2001;344:626–31.
48. Hull RD, Raskob GE, Pineo GF, et al. Subcutaneous low-molecular-weight heparin compared with continuous intravenous heparin in the treatment of proximal-vein thrombosis. *N Engl J Med* 1992;326:975–82.
49. Prandoni P, Lensing AW, Buller HR, et al. Comparison of subcutaneous low-molecular-weight heparin with intravenous standard heparin in proximal deep-vein thrombosis. *Lancet* 1992;339:441–5.
50. Dolovich LR, Ginsberg JS, Douketis JD, Holbrook AM, Cheah G. A meta-analysis comparing low-molecular-weight heparins with unfractionated heparin in the treatment of venous thromboembolism: examining some unanswered questions regarding location of treatment, product type, and dosing frequency. *Arch Intern Med* 2000;160:181–8.
51. Levine M, Gent M, Hirsh J, et al. A comparison of low-molecular-weight heparin administered primarily at home with unfractionated heparin administered in the hospital for proximal deep-vein thrombosis. *N Engl J Med* 1996; 334:677–81.
52. Koopman MM, Prandoni P, Piovella F, et al. Treatment of venous thrombosis with intravenous unfractionated heparin administered in the hospital as compared with subcutaneous low-molecular-weight heparin administered at home. The Tasman Study Group. *N Engl J Med* 1996;334:682–7.
53. Levine M. Treatment of thrombotic disorders in cancer patients. *Haemostasis* 1997;27(Suppl 1):38–43.
54. Haire WD, Atkinson JB, Stephens LC, Kotulak GD. Urokinase versus recombinant tissue plasminogen activator in thrombosed central venous catheters: a double-blinded, randomized trial *Thromb Haemost* 1994;72:543–7.
55. Atkinson JB, Bagnall HA, Gomperts E. Investigational use of tissue plasminogen activator (t-PA) for occluded central venous catheters. *JPEN J Parenter Enteral Nutr* 1990; 14:310–1.
56. Chesler L, Feusner JH. Use of tissue plasminogen activator (rt-PA) in young children with cancer and dysfunctional central venous catheters. *J Pediatr Hematol Oncol* 2002;24:653–6.
57. Kleta R, Schleef J, Jurgens H. Tissue plasminogen activator and obstructed central venous catheters. *Med Pediatr Oncol* 1998;30:376.
58. Food and Drug Administration. *FDA Talk Paper: Serious Manufacturing Deficiencies with Abbokinase Prompt FDA Letter to Abbott Labs.* Rockville FL, MD: FDA. Available at: http://www.fda.gov/bbs/topics/ANSWERS/ANS00964.html (Date accessed: July 16, 1999)
59. Neil G. *Important Safety Information.* VP Clinical Research, AstraZeneca, 1999. Available at: http://www.fda.gov/medwatch/safety/1999/strept.htm
60. Roberts S, Johnson M, Davies S. Near-fatal air embolism: fibrin sheath as the portal of air entry. *South Med J* 2003;96:1036–8.