Clotting Around Catheters and Devices

13

Natalie S. Evans, Manoj K. Dhariwal, and Lee Joseph

Clinical Vignette 1

A 54-year-old man presents to the emergency department with a 3-day history of right upper extremity tenderness and swelling. Seven days ago, a peripherally inserted central catheter (PICC) was placed for 3 weeks of intravenous antibiotic therapy to treat methicillin-resistant *Staphylococcus aureus* osteomyelitis that developed after open reduction and internal fixation of a left femur fracture. He denies shortness of breath, chest pain, and fever. Physical examination is remarkable for right upper extremity edema, tenderness, warmth, and erythema around the PICC site.

The first-year emergency department resident suspected upper extremity deep vein thrombosis and performed a bedside ultrasound, which showed absence of color flow and compressibility in the right axillary and subclavian veins adjacent to the PICC. What is the best next step?

1. Remove the PICC.
2. Admit the patient, start anticoagulation, continue antibiotics, and continue to use the PICC.
3. Send the patient home on current antibiotics, and recommend arm elevation with warm compresses and anti-inflammatory/analgesic gel topically.
4. Admit the patient, start anticoagulation, continue antibiotics, and remove the PICC.

N.S. Evans, M.D. (✉)
Section of Vascular Medicine, Department of Cardiology, Cleveland Clinic Foundation, Cleveland, OH, USA
e-mail: evansn2@ccf.org

M.K. Dhariwal, M.D.
Department of Family Medicine, Indiana University, Indianapolis, Indiana
e-mail: dhariwalmanoj@aol.com

L. Joseph, M.D.
Division of Cardiology, Department of Internal Medicine, University of Iowa, Iowa City, Iowa
e-mail: leeaims@gmail.com

Catheter-Related Thrombosis

Introduction

Venous thromboembolism (VTE) related to central venous catheters (CVCs) and devices is a common complication encountered in clinical practice that can lead to significant morbidity and mortality (Joffe et al. 2004; van Rooden, Molhoek 2004). Catheter-related thrombosis (CRT) is associated with increased risk of pulmonary embolism (PE), catheter-related infection, post-thrombotic

A. Lichtin and J. Bartholomew (eds.), *The Coagulation Consult: A Case-Based Guide*,
DOI 10.1007/978-1-4614-9560-4_13,

syndrome, and difficulty obtaining later vascular access (van Rooden, Molhoek et al. 2004; Baskin et al. 2009; Elman and Kahn 2006; Owens et al. 2010).

Epidemiology

The incidence of CRT varies depending on the type of catheter and its site of insertion, technical issues at insertion, diagnostic test used, and patient population (Acedo Sanchez et al. 2007). Up to a third of patients with indwelling catheters develop symptomatic CRT (Agnelli and Verso 2006; Camara 2001; van Rooden, Rosendaal et al. 2004; Verso and Agnelli 2003). Approximately 15 % of patients in medical intensive care units diagnosed with any DVT have catheter-related UEDVT (Hirsch et al. 1995). Of patients with cancer and CVC followed prospectively for up to a year, 4.3 % developed symptomatic CRT, with thrombosis diagnosed on average within 30 days after catheter insertion (Lee et al. 2006).

Inherited defects of coagulation factors may play a role in the development of CRT. In one study of more than 250 hospitalized patients with CVCs who were followed prospectively with Doppler ultrasound examinations, 30 % developed CRT. The presence of the factor V Leiden or prothrombin gene mutations was a risk factor for CRT, with a relative risk of 2.7 (95 % confidence interval 1.9–3.8) (van Rooden, Rosendaal et al.2004).

Pathophysiology

The pathophysiology of CRT is best explained by Virchow's triad, which describes the three key components of thrombus formation: endothelial injury, circulatory stasis, and hypercoagulable states (Fig. 13.1). First, intimal damage from CVC insertion or malpositioning exposes tissue factor, leading to platelet aggregation and thrombus formation by means of activation of the coagulation cascade. Irritation from drugs infused via the catheter may also lead to intimal damage. Second, venous stasis occurs as a result of immobilization, reduced cardiac output, and turbulent flow secondary to displacement of the faster

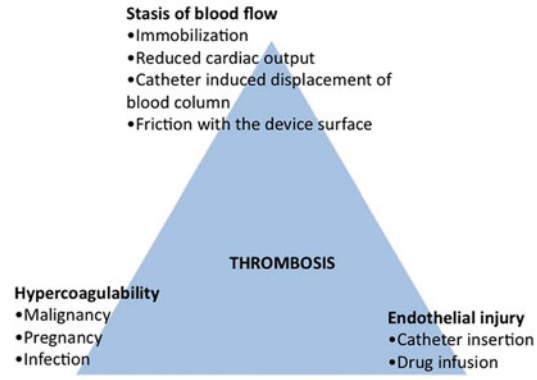

Fig. 13.1 Virchow's triad

moving central blood column by an indwelling venous catheter. Third, hypercoagulability is an important contributor to thrombus formation. Commonly encountered hypercoagulable states in CRT include malignancy, pregnancy, and infections (Verso and Agnelli 2003; Holmgren et al. 2008; Schmidt et al. 2012).

Though fibrin sheath formation around the catheter, with an incidence as high as 87 %, and thrombus formation within the catheter lumen are common, these events do not predict subsequent development of venous thrombosis (De Cicco et al. 1997; Kuter 2004).

Risk Factors

Patient-Related Risk Factors

Hypercoagulable states such as malignancy, in particular lung adenocarcinomas and ovarian tumors, and especially cancer chemotherapy, including such drugs as thalidomide, lenalidomide, tamoxifen, fluorouracil, anthracycline, cisplatin, hematopoietic growth factors, and antiangiogenic agents, are strongly associated with CRT (Agnelli and Verso 2006; Lee et al. 2006; Kuter 2004; Andtbacka et al. 2006; King et al. 2006; Prandoni and Bernardi 1999). Other patient-related risk factors include extremes of age; body mass index greater than 28; female sex; chronic illnesses such as lupus, inflammatory bowel disease, stroke, and end-stage renal disease; hip and knee replacement surgery; trauma and spinal injuries; and prior history of venous thromboembolic disease (Joffe et al. 2004; van Rooden, Rosendaal

et al.2004; King et al. 2006; Davidson 1999; Ong et al. 2006; Otten et al. 2003).

As mentioned previously, the factor V Leiden and prothrombin gene mutations are known to predispose to UEDVT, but data are sparse for their contribution to CRT. Nevertheless, a meta-analysis involving 1,000 patients and examining the association between factor V Leiden and prothrombin gene mutations and CRT showed a pooled odds ratio of 4.6 (95 % confidence interval 2.6–8.1) (Dentali et al. 2008).

Catheter-Related Risk Factors

Suboptimal placement of the catheter tip, difficult or traumatic catheter insertion, prior catheter placements, PICCs, multi-lumen devices, larger diameter of catheter, and presence of additional vascular devices such as pacemakers may increase the risk for CRT (Lee et al. 2006; Kuter 2004; Ascher et al. 2005; Cortelezzi et al. 2005; Cortelezzia et al. 2003; Grove and Pevec 2000; Male et al. 2003; Penney-Timmons and Sevedge 2004). PICCs may be particularly problematic. In a study examining intensive care unit patients using Doppler ultrasound and comparing CVCs with PICCs, nearly 30 % of PICC patients developed thrombosis, while less than 10 % of CVC patients developed thrombosis (Bonizzoli et al. 2011). In a recent systematic review of more than 5,000 cancer patients, those individuals with PICCs were more likely to develop CRT than those with implanted ports (Saber et al. 2011). Although PICCs typically are smaller in diameter than CVCs, they are longer, and they may completely fill the vein at the insertion site, leading to stagnation of blood and potential for thrombus formation. Underscoring this point, in more than 2,000 PICC insertions at a tertiary hospital, double-lumen and triple-lumen PICCs were associated with higher thrombosis rates than single-lumen PICCs (Evans et al. 2010). In another study examining catheters by diameter, catheters smaller than 3 French had no thrombosis, while 6 French catheters thrombosed in 10 % of cases (Grove and Pevec 2000).

There is an up to eightfold increase in the risk for CRT, phlebitis, or catheter mechanical dysfunction if the catheter tip is malpositioned (Verso and Agnelli 2003; Bona 2003; Racadio et al. 2001). In a study of 145 patients with indwelling catheters, those with optimally positioned catheter tip, either in the superior vena cava or at the junction of the superior vena cava and right atrium, had a CRT rate of just 9 %, compared with 45 % in patients with malpositioned catheter tips (Luciani et al. 2001). Subclavian insertion has the lowest incidence of thrombosis compared with other access sites (McGee and Gould 2003). Internal jugular venous access is the most common site of CRT, associated with a fourfold increased risk of thrombosis compared with subclavian insertion (Biffi et al. 2009; Major et al. 2008). CRT complicates 21.5 % of cases of femoral venous access compared with 1.9 % with subclavian venous access (Merrer et al. 2001).

Diagnosis

Clinical Manifestations

CRT is often asymptomatic (van Rooden, Rosendaal et al. 2004), but common clinical manifestations may include pain and swelling in the affected arm and palpable venous cords. Patients who develop chronic venous occlusion may have superficial venous collaterals on the chest wall and anterior shoulder. Patients who develop pulmonary embolism may complain of chest pain and be short of breath and tachycardic, and those with obstruction of the superior vena cava may have swelling or plethora of the face, neck, trunk, and arms, along with shortness of breath that may be positional.

Up to 30 % of otherwise asymptomatic patients may present with catheter malfunction, with inability to aspirate blood from the catheter (Baskin et al. 2009).

Diagnostic Studies

Though chest X-ray and D-dimer are quick, relatively inexpensive tests, they are not specific for diagnosing CRT. Duplex ultrasound, combining grayscale compression and Doppler waveform analysis, is the diagnostic test of choice. Thrombus may appear occlusive or non-occlusive

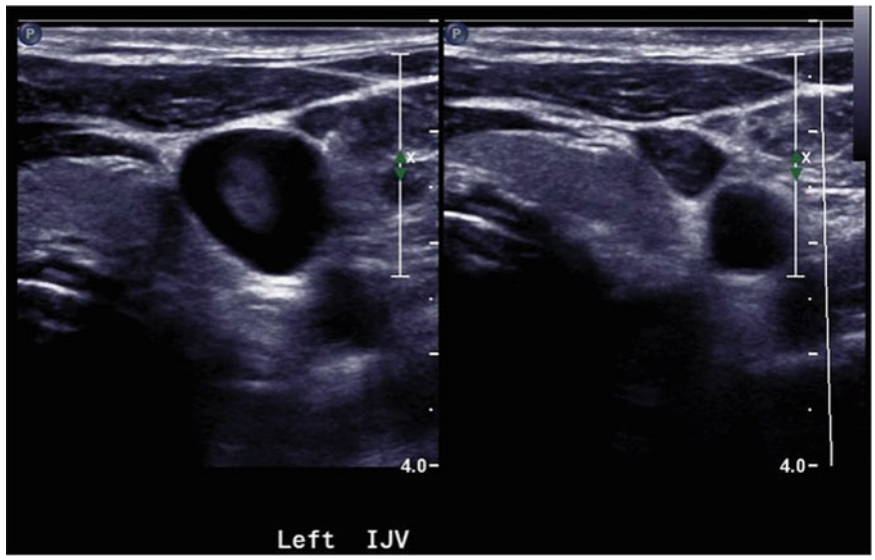

Fig. 13.2 In the *left panel*, ultrasonography shows the internal jugular vein filled with echogenic thrombus. In the *right panel*, the vein walls do not coapt with compression

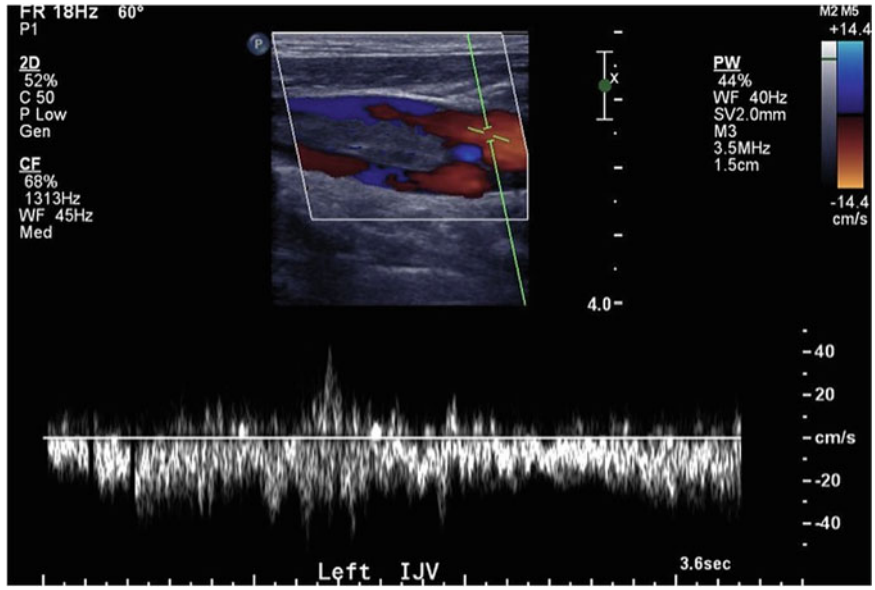

Fig. 13.3 Color Doppler shows partially occlusive thrombus in the internal jugular vein

on duplex ultrasound (Figs. 13.2 and 13.3). Though venography historically has been the gold standard for diagnosing acute venous thrombosis, it is an invasive procedure and thus less preferred (Bettmann 1988; Lensing et al. 1992).

Ultrasound is sensitive and specific for the diagnosis of UEDVT, but false-negative studies may occur due to shadowing from the clavicle that obscures thrombus in the subclavian vein or presence of non-occlusive thrombus that is adherent to the vein wall (Prandoni et al. 1997).

To aid in diagnosis, a clinical prediction score has been developed among patients hospitalized with suspicion of UEDVT. The score incorporates

the presence of indwelling venous device, localized pain, unilateral pitting edema, and presence or absence of an equally likely alternative diagnosis, assigning one point to each item. UEDVT was objectively confirmed with ultrasound, and the prediction score was validated among another group of patients. A score of 2 or 3 identified high-probability patients, with 60–74 % prevalence of UEDVT (Constans et al. 2008).

Prevention

There are no standard guidelines for prevention of CRT. Various non-pharmacologic measures have been studied for the prevention of CRT. Indwelling venous catheters should be placed in appropriate position by experienced clinicians with adequate technological support. Measures to decrease intimal damage include selection of appropriate devices (smallest diameter of catheter with fewest number of lumens), ideal sites of access (right preferred over left, subclavian preferred over other sites), and adequate catheter care (Biffi et al. 2009). Intermittent pneumatic compression devices of the arms theoretically could be beneficial but have not been adequately studied (Berlin et al. 1999; Knight and Dawson 1976). Though earlier studies focusing primarily on oncologic patients demonstrated that various antithrombotic agents are effective in preventing CRT, recent studies have shown no significant benefit (Lee et al. 2006; Abdelkefi et al. 2004; Bern et al. 1990; Eastman et al. 2001; Heaton et al. 2002; Karthaus et al. 2006; Klerk et al. 2003; Magagnoli et al. 2005; Monreal and Davant 2001; Tesselaar et al. 2004). Low-dose warfarin was shown to be effective in the prevention of CRT primarily in oncologic patients with central venous catheters. One mg per day of warfarin compared with no warfarin for 90 days resulted in lower rates of asymptomatic (9.5 % vs. 37.5 %) and symptomatic (9.5 % vs. 32.5 %; $p=0.001$) thrombosis (Bern et al. 1990). In a study on cancer patients undergoing chemotherapy, patients who received anticoagulation with nadroparin or coumarins had significantly lower rates of CRT in chest ports (1 % vs. 33 %; OR, 34.8; 95 % CI, 7.3–165) but not in arm ports (32 % vs. 28 %) (Tesselaar et al. 2004). However, there was no significant difference in patients who received coumarins versus those who did not receive coumarins in a non-randomized study of patients with melanoma or renal cell cancer (Eastman et al. 2001). Patients with hematologic malignancies and Hickman catheter had no significantly different occurrence of CRT when they received 1 mg warfarin per day compared to the control arm (Heaton et al. 2002).

Data for heparins are similarly mixed. In a double-blind placebo-controlled phase III trial in 439 patients undergoing cancer chemotherapy, Karthaus et al. reported no significant difference between dalteparin 5,000 IU and placebo in frequency of CRT (3.7 % vs. 3.4 %; $p=0.88$; RR, 1.0883; 95 % CI, 0.37–3.19) (Karthaus et al. 2006). In a prospective randomized controlled trial in 128 hematology–oncology patients, those who had continuous infusion of unfractionated heparin of 100 U/kg daily had lower risk of CRT than patients receiving 50 mL daily of normal saline (1.5 % vs. 12.6 %; $p=0.03$) (Abdelkefi et al. 2004). Currently available evidence is inconclusive regarding the use of anticoagulation for the prevention of CRT, while the role of antithrombotic prophylaxis in the prevention of CRT in non-oncologic patient populations has not been studied to date. In the face of conflicting data, the American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (Guyatt et al. 2012) suggest against routine prophylaxis with heparin, low-molecular-weight heparin, and vitamin K antagonists.

Though the mechanism is unclear, urokinase instillation into CVCs is effective in reducing CRT in pediatric populations, but it has not been adequately studied in adults (Dillon et al. 2004; Kalmanti et al. 2002).

Treatment of CRT usually consists of anticoagulation with or without instillation of fibrinolytic agent in the catheter lumen. Parenteral anticoagulation with full-dose unfractionated heparin, LMWH, or fondaparinux should be initiated as soon as the CRT is suspected or confirmed. Catheter removal is warranted only if there is catheter malfunction and certain catheter-related

infections (such as *S. aureus*, gram-negative bacilli, and Candida species) or when the catheter is no longer needed. Anticoagulation after removal is suggested for a minimum duration of 3 months if the DVT involves the axillary or more proximal veins (Guyatt et al. 2012). If the catheter is not removed, anticoagulation should be continued as long as the CVC is in place. Once removed, anticoagulation is often continued another 6 weeks to prevent new thrombosis.

Catheter malfunction due to intraluminal thrombus can be treated by a thrombolytic instillation into the catheter lumen (Dillon et al. 2004; Kalmanti et al. 2002). Pharmacological thrombolysis or mechanical thrombectomy may be considered in patients who remain symptomatic despite adequate anticoagulation (Kim et al. 2006; Vik et al. 2009). Although SVC filter is a management option for UEDVT in those with contraindications to anticoagulation, failed anticoagulation with PE despite therapeutic anticoagulation, and complications of anticoagulation, data are sparse on the safety and efficacy of SVC filter and it is not recommended by standard guidelines (Usoh et al. 2009).

Complications

Complications associated with CRT include the post-thrombotic syndrome, PE, catheter-related infection, progression to SVC syndrome, and loss of viable vascular access sites (van Rooden, Rosendaal et al.2004; Verso and Agnelli 2003; Monreal and Davant 2001). 15 to 30 % of patients with UEDVT develop the post-thrombotic syndrome, including such signs and symptoms as chronic limb edema, cyanosis, and pain, but it is unclear how many patients with CRT go on to develop this syndrome, as studies generally have been too small (Kahn et al. 2005; Maki and Ringer 1991; Prandoni et al. 2004). Several studies have shown that persistent catheter-related bloodstream infection may be associated with CRT or development of a fibrin sheath (van Rooden, Molhoek et al.2004; Kuter 2004; Chemaly et al. 2002; Da Costa et al. 2002; Mehall et al. 2002; Ngo and Murphy 2005).

Pulmonary embolism is less common in UEDVT than lower extremity DVT, but the risk is not negligible, ranging from 6 to 36 % after UEDVT (King et al. 2006; Monreal and Davant 2001; Sticherling et al. 2001). In the prospective RIETE registry of patients with symptomatic venous thromboembolism, of patients presenting with pulmonary embolism, just 9 % had UEDVT compared with 29 % who had lower extremity DVT (Munoz et al. 2008).

Clinical Vignette 2

A 79-year-old woman presents to the emergency room with complaints of dyspnea and bilateral arm swelling that have been progressive over the last 6 months. Vital signs are normal. The left arm is more swollen than the right. Electrocardiogram reveals paced rhythm. Chest X-ray shows an implanted pacemaker with leads in the right atrium and ventricle but no abnormalities. Two-dimensional echocardiography shows left ventricular ejection fraction of 30 % and right ventricular dilation and dysfunction. Doppler ultrasound of the upper extremities shows no thrombosis in the axillary veins and more distal veins; the subclavian veins are not visualized. What is the next best step?

1. Right arm cooling.
2. Start therapeutic anticoagulation.
3. Apply compression wraps and extremity elevation.
4. Removal of pacemaker.
5. Venography.

Clotting Related to Implantable Cardiac Devices

Pathophysiology, Epidemiology, and Risk Factors

Venous complications related to implantable cardiac devices include thrombosis, stenosis, and occlusion of the central veins. In patients with

implanted pacemakers, the incidence of device-related venous abnormalities is high, ranging from 20 to 60 % depending on the population studied, though in most cases patients are asymptomatic and the clinical relevance remains uncertain (Antonelli et al. 1989; Crook et al. 1977; Goto et al. 1998; Lickfett et al. 2004; Oginosawa et al. 2002; Stoney et al. 1976).

The pathophysiology is similar to that of CRT. A history of prior transvenous pacing leads and left ventricular ejection fraction less than 40 % are associated with development of venous abnormalities such as thrombosis and stenosis in patients with permanent pacemaker (Da Costa et al. 2002). Dual-coil leads, prior DVT, prior central venous catheter, use of temporary wires, infection, and oral contraceptive agents also increase the risk for cardiac device-related thrombosis in patients with pacemaker or implanted defibrillator (Antonelli et al. 1989; Goto et al. 1998; Lickfett et al. 2004). The number of leads is not a consistent risk factor for device-related thrombosis (Goto et al. 1998). Access site, type of lead (unipolar vs. bipolar), lead material, and lead caliber are not associated with device-related thrombosis (Lickfett et al. 2004; Oginosawa et al. 2002; Stoney et al. 1976).

Clinical Manifestations and Complications

Cardiac device-related thrombosis is usually asymptomatic. In a study looking at 105 patients with implantable defibrillators in place for more than 3 years, a quarter of them had some degree of venous occlusion, but no one was symptomatic (Lickfett et al. 2004). In a smaller study following patients with permanent pacemaker for a year after implantation, 23, more than a third, developed some degree of venous occlusion, but less than 20 % of those patients were symptomatic (Antonelli et al. 1989). When symptomatic, patients with cardiac device-related thrombosis may complain of nonspecific shoulder or neck discomfort or have ipsilateral arm swelling with cyanosis, dilated collateral cutaneous veins at the shoulder or anterior chest wall, and jugular vein distention.

As with CRT, pulmonary embolism, post-thrombotic syndrome, and SVC syndrome may complicate device-related thrombosis (Nishino et al. 1997). A history of prior device-related thrombosis may make lead revision more challenging (Spittell and Hayes 1992).

Diagnosis

Compressive ultrasonography and/or two-dimensional echo combined with pulsed Doppler and color flow evaluation are commonly used to diagnose device-related venous thrombosis (Nishino et al. 1997). Compressive ultrasonography has limitations in diagnosing SVC and innominate venous thrombosis due to shadowing from the clavicle. However, combined color flow and pulse wave Doppler had 94 % sensitivity and 100 % specificity for detecting SVC or innominate vein thrombosis compared with digital subtraction angiography in detecting 19 cases of thrombosis or stenosis in a group of 53 patients (Conte and Orzel 1986).

Spiral computed tomography venography (CTV) and magnetic resonance venography (MRV) are noninvasive and accurate diagnostic tools for detecting deep venous thrombosis; however, the presence of a pacemaker or an implanted defibrillator is a relative contraindication for MR imaging (Spittell and Hayes 1992; Hartnell et al. 1995; Kommareddy et al. 2002; Tello et al. 1993). Conventional venography remains the gold standard and may often be used prior to vascular interventional treatment for thrombosis and to assess the response to the treatment (Bettmann 1988).

Management

There are no universal guidelines for the primary prevention of implantable cardiac device-related thrombosis because of insufficient data. One small study found that warfarin in high-risk patients may be beneficial in preventing device-related venous

complications, but further study is required (Costa et al. 2009).

Device-related venous thrombosis may be treated with a multimodal approach, involving anticoagulation and catheter-directed thrombolytic therapy (depending on the extent of the thrombosis and the severity of the symptoms), followed by a minimum of 3 months of anticoagulation, venous decompression as needed, and balloon angioplasty with stenting for treatment of residual stricture (Chan et al. 2002; Montgomery et al. 1985; Spittell et al. 1990).

Anticoagulation is the cornerstone of therapy in patients with symptomatic device-related thrombosis. Thrombolytic therapy used in cases of lower extremity venous thrombosis may improve early patency or recanalization, but this has not been studied for symptomatic cardiac device-related thrombosis. Furthermore, many patients may not be candidates for thrombolysis due to bleeding risk and other clinical factors.

At times, percutaneous venoplasty may be performed to treat venous stenosis or occlusion and/or to facilitate pacemaker revision (Chan et al. 2002; Montgomery et al. 1985; Spittell et al. 1990). Surgical treatment options, though associated with significant morbidity, exist for the management of the lead-related thrombosis that is not amenable to anticoagulation and endovascular interventional treatment options (Barakat et al. 2000).

Clinical Vignettes

Clinical Vignette 1 answer: 2. The patient has catheter-related right UEDVT. He was treated with anticoagulation for a total of 3 months, and the PICC was initially left in place. Antibiotics were continued, and the catheter was removed at the completion of the antibiotic treatment.

Clinical Vignette 2 answer: 5. Venography showed visible thrombus or obstruction in the left subclavian vein and formation of collaterals. The pacemaker was left in place, and the patient was treated with anticoagulation for 3 months.

References

Abdelkefi A, Ben Othman T, Kammoun L, Chelli M, Romdhane NB, Kriaa A, et al. Prevention of central venous line-related thrombosis by continuous infusion of low-dose unfractionated heparin, in patients with haemato-oncological disease. A randomized controlled trial. Thromb Haemost. 2004;92(3):654–61. Epub 2004/09/08.

Acedo Sanchez JD, Batlle JF, Feijoo JB. Catheter-related thrombosis: a critical review. Support Cancer Ther. 2007;4(3):145–51. Epub 2008/07/18.

Agnelli G, Verso M. Therapy insight: venous-catheter-related thrombosis in cancer patients. Nat Clin Pract Oncol. 2006;3(4):214–22. Epub 2006/04/06.

Andtbacka RH, Babiera G, Singletary SE, Hunt KK, Meric-Bernstam F, Feig BW, et al. Incidence and prevention of venous thromboembolism in patients undergoing breast cancer surgery and treated according to clinical pathways. Ann Surg. 2006;243(1):96–101. Epub 2005/12/24.

Antonelli D, Turgeman Y, Kaveh Z, Artoul S, Rosenfeld T. Short-term thrombosis after transvenous permanent pacemaker insertion. Pacing Clin Electrophysiol. 1989;12(2):280–2. Epub 1989/02/01.

Ascher E, Salles-Cunha S, Hingorani A. Morbidity and mortality associated with internal jugular vein thromboses. Vasc Endovascular Surg. 2005;39(4):335–9. Epub 2005/08/05.

Barakat K, Robinson NM, Spurrell RA. Transvenous pacing lead-induced thrombosis: a series of cases with a review of the literature. Cardiology. 2000;93(3):142–8. Epub 2000/08/31.

Baskin JL, Pui CH, Reiss U, Wilimas JA, Metzger ML, Ribeiro RC, et al. Management of occlusion and thrombosis associated with long-term indwelling central venous catheters. Lancet. 2009;374(9684):159–69. Epub 2009/07/15.

Berlin E, Gjores JE, Ivarsson C, Palmqvist I, Thagg G, Thulesius O. Postmastectomy lymphoedema. Treatment and a five-year follow-up study. Int Angiol. 1999;18(4):294–8. Epub 2000/05/16.

Bern MM, Lokich JJ, Wallach SR, Bothe Jr A, Benotti PN, Arkin CF, et al. Very low doses of warfarin can prevent thrombosis in central venous catheters. A randomized prospective trial. Ann Intern Med. 1990;112(6):423–8. Epub 1990/03/15.

Bettmann MA. Noninvasive and venographic diagnosis of deep vein thrombosis. Cardiovasc Intervent Radiol. 1988;11(Suppl):S15–20. Epub 1988/01/01.

Biffi R, Orsi F, Pozzi S, Pace U, Bonomo G, Monfardini L, et al. Best choice of central venous insertion site for the prevention of catheter-related complications in adult patients who need cancer therapy: a randomized trial. Ann Oncol. 2009;20(5):935–40. Epub 2009/01/31.

Bona RD. Central line thrombosis in patients with cancer. Curr Opin Pulm Med. 2003;9(5):362–6. Epub 2003/08/09.

Bonizzoli M, Batacchi S, Cianchi G, Zagli G, Lapi F, Tucci V, et al. Peripherally inserted central venous catheters and central venous catheters related thrombosis in post-critical patients. Intensive Care Med. 2011;37(2):284–9. Epub 2010/09/22.

Camara D. Minimizing risks associated with peripherally inserted central catheters in the NICU. MCN Am J Matern Child Nurs. 2001;26(1):17–21. quiz 2. Epub 2001/02/24.

Chan AW, Bhatt DL, Wilkoff BL, Roffi M, Mukherjee D, Gray BH, et al. Percutaneous treatment for pacemaker-associated superior vena cava syndrome. Pacing Clin Electrophysiol. 2002;25(11):1628–33. Epub 2002/12/24.

Chemaly RF, de Parres JB, Rehm SJ, Adal KA, Lisgaris MV, Katz-Scott DS, et al. Venous thrombosis associated with peripherally inserted central catheters: a retrospective analysis of the Cleveland Clinic experience. Clin Infect Dis. 2002;34(9):1179–83. Epub 2002/04/10.

Constans J, Salmi LR, Sevestre-Pietri MA, Perusat S, Nguon M, Degeilh M, et al. A clinical prediction score for upper extremity deep venous thrombosis. Thromb Haemost. 2008;99(1):202–7. Epub 2008/01/25.

Conte FA, Orzel JA. Superior vena cava syndrome and bilateral subclavian vein thrombosis. CT and radionuclide venography correlation. Clin Nucl Med. 1986;11(10):698–700. Epub 1986/10/01.

Cortelezzia A, Fracchiolla NS, Maisonneuve P, Moia M, Luchesini C, Ranzi ML, et al. Central venous catheter-related complications in patients with hematological malignancies: a retrospective analysis of risk factors and prophylactic measures. Leuk Lymphoma. 2003;44(9):1495–501. Epub 2003/10/21.

Cortelezzi A, Moia M, Falanga A, Pogliani EM, Agnelli G, Bonizzoni E, et al. Incidence of thrombotic complications in patients with haematological malignancies with central venous catheters: a prospective multicentre study. Br J Haematol. 2005;129(6):811–7. Epub 2005/06/15.

Costa R, Da Silva KR, Rached R, Martinelli Filho M, Carnevale FC, Moreira LF, et al. Prevention of venous thrombosis by warfarin after permanent transvenous leads implantation in high-risk patients. Pacing Clin Electrophysiol. 2009;32 Suppl 1:S247–51. Epub 2009/03/11.

Crook BR, Gishen P, Robinson CR, Oram S. Occlusion of the subclavian vein associated with cephalic vein pacemaker electrodes. Br J Surg. 1977;64(5):329–31. Epub 1977/05/01.

Da Costa SS, Scalabrini Neto A, Costa R, Caldas JG, Martinelli FM. Incidence and risk factors of upper extremity deep vein lesions after permanent transvenous pacemaker implant: a 6-month follow-up prospective study. Pacing Clin Electrophysiol. 2002;25(9):1301–6. Epub 2002/10/17.

Davidson BL. Controversies in pulmonary embolism and deep venous thrombosis. Am Fam Physician. 1999;60(7):1969–80. Epub 1999/11/24.

De Cicco M, Matovic M, Balestreri L, Panarello G, Fantin D, Morassut S, et al. Central venous thrombosis: an early and frequent complication in cancer patients bearing long-term silastic catheter. A prospective study. Thromb Res. 1997;86(2):101–13. Epub 1997/04/15.

Dentali F, Gianni M, Agnelli G, Ageno W. Association between inherited thrombophilic abnormalities and central venous catheter thrombosis in patients with cancer: a meta-analysis. J Thromb Haemost. 2008;6(1):70–5. Epub 2007/11/09.

Dillon PW, Jones GR, Bagnall-Reeb HA, Buckley JD, Wiener ES, Haase GM. Prophylactic urokinase in the management of long-term venous access devices in children: a Children's Oncology Group study. J Clin Oncol. 2004;22(13):2718–23. Epub 2004/07/01.

Eastman ME, Khorsand M, Maki DG, Williams EC, Kim K, Sondel PM, et al. Central venous device-related infection and thrombosis in patients treated with moderate dose continuous-infusion interleukin-2. Cancer. 2001;91(4):806–14. Epub 2001/03/10.

Elman EE, Kahn SR. The post-thrombotic syndrome after upper extremity deep venous thrombosis in adults: a systematic review. Thromb Res. 2006;117(6):609–14. Epub 2005/07/09.

Evans RS, Sharp JH, Linford LH, Lloyd JF, Tripp JS, Jones JP, et al. Risk of symptomatic DVT associated with peripherally inserted central catheters. Chest. 2010;138(4):803–10. Epub 2010/10/07.

Goto Y, Abe T, Sekine S, Sakurada T. Long-term thrombosis after transvenous permanent pacemaker implantation. Pacing Clin Electrophysiol. 1998;21(6):1192–5. Epub 1998/06/20.

Grove JR, Pevec WC. Venous thrombosis related to peripherally inserted central catheters. J Vasc Interv Radiol. 2000;11(7):837–40. Epub 2000/08/06.

Guyatt GH, Akl EA, Crowther M, Gutterman DD, Schuunemann HJ. Executive summary: antithrombotic therapy and prevention of thrombosis, 9th ed: American college of chest physicians evidence-based clinical practice guidelines. Chest. 2012;141(2 Suppl):7S–47. Epub 2012/03/15.

Hartnell GG, Hughes LA, Finn JP, Longmaid 3rd HE. Magnetic resonance angiography of the central chest veins. A new gold standard? Chest. 1995;107(4):1053–7.

Heaton DC, Han DY, Inder A. Minidose (1 mg) warfarin as prophylaxis for central vein catheter thrombosis. Int Med J. 2002;32(3):84–8. Epub 2002/03/12.

Hirsch DR, Ingenito EP, Goldhaber SZ. Prevalence of deep venous thrombosis among patients in medical intensive care. JAMA. 1995;274(4):335–7. Epub 1995/07/26.

Holmgren C, Aagaard-Tillery KM, Silver RM, Porter TF, Varner M. Hyperemesis in pregnancy: an evaluation of treatment strategies with maternal and neonatal outcomes. Am J Obstet Gynecol. 2008;198(1):56 e1–4. Epub 2008/01/02.

Joffe HV, Kucher N, Tapson VF, Goldhaber SZ. Upper-extremity deep vein thrombosis: a prospective registry

of 592 patients. Circulation. 2004;110(12):1605–11. Epub 2004/09/09.

Kahn SR, Elman EA, Bornais C, Blostein M, Wells PS. Post-thrombotic syndrome, functional disability and quality of life after upper extremity deep venous thrombosis in adults. Thromb Haemost. 2005;93(3):499–502. Epub 2005/03/01.

Kalmanti M, Germanakis J, Stiakaki E, Syfridaki C, Christidou A, Tsetis D, et al. Prophylaxis with urokinase in pediatric oncology patients with central venous catheters. Pediatr Hematol Oncol. 2002;19(3):173–9. Epub 2002/04/09.

Karthaus M, Kretzschmar A, Kroning H, Biakhov M, Irwin D, Marschner N, et al. Dalteparin for prevention of catheter-related complications in cancer patients with central venous catheters: final results of a double-blind, placebo-controlled phase III trial. Ann Oncol. 2006;17(2):289–96. Epub 2005/12/01.

Kim HS, Patra A, Paxton BE, Khan J, Streiff MB. Catheter-directed thrombolysis with percutaneous rheolytic thrombectomy versus thrombolysis alone in upper and lower extremity deep vein thrombosis. Cardiovasc Intervent Radiol. 2006;29(6):1003–7. Epub 2006/09/13.

King MM, Rasnake MS, Rodriguez RG, Riley NJ, Stamm JA. Peripherally inserted central venous catheter-associated thrombosis: retrospective analysis of clinical risk factors in adult patients. South Med J. 2006;99(10):1073–7. Epub 2006/11/15.

Klerk CP, Smorenburg SM, Buller HR. Thrombosis prophylaxis in patient populations with a central venous catheter: a systematic review. Arch Intern Med. 2003;163(16):1913–21. Epub 2003/09/10.

Knight MT, Dawson R. Effect of intermittent compression of the arms on deep venous thrombosis in the legs. Lancet. 1976;2(7998):1265–8. Epub 1976/12/11.

Kommareddy A, Zaroukian MH, Hassouna HI. Upper extremity deep venous thrombosis. Semin Thromb Hemost. 2002;28(1):89–99. Epub 2002/03/09.

Kuter DJ. Thrombotic complications of central venous catheters in cancer patients. Oncologist. 2004;9(2):207–16. Epub 2004/03/30.

Lee AY, Levine MN, Butler G, Webb C, Costantini L, Gu C, et al. Incidence, risk factors, and outcomes of catheter-related thrombosis in adult patients with cancer. J Clin Oncol. 2006;24(9):1404–8. Epub 2006/03/22.

Lensing AW, Buller HR, Prandoni P, Batchelor D, Molenaar AH, Cogo A, et al. Contrast venography, the gold standard for the diagnosis of deep-vein thrombosis: improvement in observer agreement. Thromb Haemost. 1992;67(1):8–12. Epub 1992/01/23.

Lickfett L, Bitzen A, Arepally A, Nasir K, Wolpert C, Jeong KM, et al. Incidence of venous obstruction following insertion of an implantable cardioverter defibrillator. A study of systematic contrast venography on patients presenting for their first elective ICD generator replacement. Europace : European pacing, arrhythmias, and cardiac electrophysiology : journal of the working groups on cardiac pacing, arrhythmias, and cardiac cellular electrophysiology of the European Society of. Cardiology. 2004;6(1):25–31.

Luciani A, Clement O, Halimi P, Goudot D, Portier F, Bassot V, et al. Catheter-related upper extremity deep venous thrombosis in cancer patients: a prospective study based on Doppler US. Radiology. 2001;220(3):655–60. Epub 2001/08/30.

Magagnoli M, Masci G, Castagna L, Zucali PA, Morenghi E, Pedicini V, et al. Prophylaxis of central venous catheter-related thrombosis with minidose warfarin: analysis of its use in 427 cancer patients. Anticancer Res. 2005;25(4):3143–7. Epub 2005/08/06.

Major KM, Bulic S, Rowe VL, Patel K, Weaver FA. Internal jugular, subclavian, and axillary deep venous thrombosis and the risk of pulmonary embolism. Vascular. 2008;16(2):73–9. Epub 2008/04/02.

Maki DG, Ringer M. Risk factors for infusion-related phlebitis with small peripheral venous catheters. A randomized controlled trial. Ann Intern Med. 1991;114(10):845–54. Epub 1991/05/15.

Male C, Chait P, Andrew M, Hanna K, Julian J, Mitchell L. Central venous line-related thrombosis in children: association with central venous line location and insertion technique. Blood. 2003;101(11):4273–8. Epub 2003/02/01.

McGee DC, Gould MK. Preventing complications of central venous catheterization. N Engl J Med. 2003;348(12):1123–33. Epub 2003/03/21.

Mehall JR, Saltzman DA, Jackson RJ, Smith SD. Fibrin sheath enhances central venous catheter infection. Crit Care Med. 2002;30(4):908–12. Epub 2002/04/10.

Merrer J, De Jonghe B, Golliot F, Lefrant JY, Raffy B, Barre E, et al. Complications of femoral and subclavian venous catheterization in critically ill patients: a randomized controlled trial. JAMA. 2001;286(6):700–7. Epub 2001/08/10.

Monreal M, Davant E. Thrombotic complications of central venous catheters in cancer patients. Acta Haematol. 2001;106(1–2):69–72. Epub 2001/09/11.

Montgomery JH, D'Souza VJ, Dyer RB, Formanek AG, Prabhu SH. Nonsurgical treatment of the superior vena cava syndrome. Am J Cardiol. 1985;56(12):829–30. Epub 1985/11/01.

Munoz FJ, Mismetti P, Poggio R, Valle R, Barron M, Guil M, et al. Clinical outcome of patients with upper-extremity deep vein thrombosis: results from the RIETE Registry. Chest. 2008;133(1):143–8. Epub 2007/10/11.

Ngo A, Murphy S. A theory-based intervention to improve nurses' knowledge, self-efficacy, and skills to reduce PICC occlusion. J Infus Nurs. 2005;28(3):173–81. Epub 2005/05/25.

Nishino M, Tanouchi J, Ito T, Tanaka K, Aoyama T, Kitamura M, et al. Echographic detection of latent severe thrombotic stenosis of the superior vena cava and innominate vein in patients with a pacemaker: integrated diagnosis using sonography, pulse Doppler, and color flow. Pacing Clin Electrophysiol. 1997;20(4 Pt 1):946–52. Epub 1997/04/01.

Oginosawa Y, Abe H, Nakashima Y. The incidence and risk factors for venous obstruction after implantation of transvenous pacing leads. Pacing Clin Electrophysiol. 2002;25(11):1605–11. Epub 2002/12/24.

Ong B, Gibbs H, Catchpole I, Hetherington R, Harper J. Peripherally inserted central catheters and upper extremity deep vein thrombosis. Australas Radiol. 2006;50(5):451–4. Epub 2006/09/20.

Otten TR, Stein PD, Patel KC, Mustafa S, Silbergleit A. Thromboembolic disease involving the superior vena cava and brachiocephalic veins. Chest. 2003;123(3):809–12. Epub 2003/03/12.

Owens CA, Bui JT, Knuttinen MG, Gaba RC, Carrillo TC. Pulmonary embolism from upper extremity deep vein thrombosis and the role of superior vena cava filters: a review of the literature. J Vasc Interv Radiol. 2010;21(6):779–87. Epub 2010/05/04.

Penney-Timmons E, Sevedge S. Outcome data for peripherally inserted central catheters used in an acute care setting. J Infus Nurs. 2004;27(6):431–6. Epub 2004/12/09.

Prandoni P, Polistena P, Bernardi E, Cogo A, Casara D, Verlato F, et al. Upper-extremity deep vein thrombosis. Risk factors, diagnosis, and complications. Arch Intern Med. 1997;157(1):57–62.

Prandoni P, Bernardi E. Upper extremity deep vein thrombosis. Curr Opin Pulm Med. 1999;5(4):222–6. Epub 1999/07/17.

Prandoni P, Bernardi E, Marchiori A, Lensing AW, Prins MH, Villalta S, et al. The long term clinical course of acute deep vein thrombosis of the arm: prospective cohort study. BMJ. 2004;329(7464):484–5. Epub 2004/07/17.

Racadio JM, Doellman DA, Johnson ND, Bean JA, Jacobs BR. Pediatric peripherally inserted central catheters: complication rates related to catheter tip location. Pediatrics. 2001;107(2):E28. Epub 2001/02/07.

Saber W, Moua T, Williams EC, Verso M, Agnelli G, Couban S, et al. Risk factors for catheter-related thrombosis (CRT) in cancer patients: a patient-level data (IPD) meta-analysis of clinical trials and prospective studies. J Thromb Haemost. 2011;9(2):312–9. Epub 2010/11/03.

Schmidt M, Horvath-Puho E, Thomsen RW, Smeeth L, Sorensen HT. Acute infections and venous thromboembolism. J Intern Med. 2012;271(6):608–18. Epub 2011/10/27.

Spittell PC, Vlietstra RE, Hayes DL, Higano ST. Venous obstruction due to permanent transvenous pacemaker electrodes: treatment with percutaneous transluminal balloon venoplasty. Pacing Clin Electrophysiol. 1990;13(3):271–4. Epub 1990/03/01.

Spittell PC, Hayes DL. Venous complications after insertion of a transvenous pacemaker. Mayo Clin Proc. 1992;67(3):258–65. Epub 1992/03/01.

Sticherling C, Chough SP, Baker RL, Wasmer K, Oral H, Tada H, et al. Prevalence of central venous occlusion in patients with chronic defibrillator leads. Am Heart J. 2001;141(5):813–6. Epub 2001/04/26.

Stoney WS, Addlestone RB, Alford Jr WC, Burrus GR, Frist RA, Thomas Jr CS. The incidence of venous thrombosis following long-term transvenous pacing. Ann Thorac Surg. 1976;22(2):166–70. Epub 1976/08/01.

Tello R, Scholz E, Finn JP, Costello P. Subclavian vein thrombosis detected with spiral CT and three-dimensional reconstruction. AJR Am J Roentgenol. 1993;160(1):33–4. Epub 1993/01/01.

Tesselaar ME, Ouwerkerk J, Nooy MA, Rosendaal FR, Osanto S. Risk factors for catheter-related thrombosis in cancer patients. Eur J Cancer. 2004;40(15):2253–9. Epub 2004/09/30.

Usoh F, Hingorani A, Ascher E, Shiferson A, Tran V, Marks N, et al. Long-term follow-up for superior vena cava filter placement. Ann Vasc Surg. 2009;23(3):350–4. Epub 2008/09/24.

van Rooden CJ, Molhoek SG, Rosendaal FR, Schalij MJ, Meinders AE, Huisman MV. Incidence and risk factors of early venous thrombosis associated with permanent pacemaker leads. J Cardiovasc Electrophysiol. 2004a;15(11):1258–62. Epub 2004/12/03.

van Rooden CJ, Rosendaal FR, Meinders AE, Van Oostayen JA, Van Der Meer FJ, Huisman MV. The contribution of factor V Leiden and prothrombin G20210A mutation to the risk of central venous catheter-related thrombosis. Haematologica. 2004b;89(2):201–6. Epub 2004/03/09.

Verso M, Agnelli G. Venous thromboembolism associated with long-term use of central venous catheters in cancer patients. J Clin Oncol. 2003;21(19):3665–75. Epub 2003/09/27.

Vik A, Holme PA, Singh K, Dorenberg E, Nordhus KC, Kumar S, et al. Catheter-directed thrombolysis for treatment of deep venous thrombosis in the upper extremities. Cardiovasc Intervent Radiol. 2009;32(5):980–7. Epub 2009/07/31.