When deep vein thrombosis occurs in the upper limb

Upper extremity deep vein thrombosis is a relatively rare condition which has thus far not attracted much interest in the literature. The differences in its aetiopathology, different diagnostic modalities and the current standard of care are discussed in this article.

Upper extremity deep vein thrombosis has historically been considered relatively rare, perhaps because of the focus on the more frequently occurring lower limb counterpart. Upper extremity deep vein thrombosis may be less common than lower limb deep vein thrombosis, probably because of the relatively increased blood flow in the upper limbs, lesser likelihood of blood stasis and a reduced gravitational effect (Sajid et al, 2007). Deep vein thromboses overall have an incidence of 1 in 1000 in the UK, out of which approximately 4–10% are located in the upper extremities (Kucher, 2011; Bleker et al, 2016). There has been an increase in the number of cases being reported as a result of increased use of central venous catheters, cardiac pacemaker devices and defibrillators (Kucher, 2011).

Upper extremity deep vein thrombosis is classified into two major categories – primary and secondary. Primary upper extremity deep vein thrombosis has no identifiable trigger factor, while secondary upper extremity deep vein thrombosis is any thrombosis to which one or more trigger factors can be attributed such as cancer, central venous catheters or pacemakers (Bleker et al, 2016). Both primary and secondary upper extremity deep vein thrombosis are generally treated using the same principles with the obvious exception of attempting to remove the trigger factor in secondary upper extremity deep vein thrombosis.

Aetiopathogenesis

Primary upper extremity deep vein thrombosis

This category can be defined as any upper extremity venous thrombus formation 'which is without evident predisposing factors in the patient's history' and accounts for between 20–33% of patients presenting with upper extremity deep vein thrombosis (Kommareddy et al, 2002; Mai and Hunt, 2011). The two main subsections are unprovoked or idiopathic and effort-related.

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By definition, in idiopathic upper extremity deep vein thrombosis, there is no underlying anatomical cause or identifiable trigger factor. However, one study found that a quarter of patients presenting with idiopathic upper extremity deep vein thrombosis had a diagnosis of cancer within 1 year (Girolami et al, 1999). On the other hand, effort-related thrombosis is a more certain diagnosis and refers to a 'primary thrombosis of the subclavian vein at the costoclavicular junction' (Illig and Doyle, 2010). Another term used to describe this condition is 'Paget–Schroetter syndrome', first coined by an English surgeon Hughes in 1948.

Primary effort-related thrombosis has an incidence of around 1–2 in 100 000 (Illig and Doyle, 2010) and current knowledge about the condition is limited and is based on single case series, retrospective studies and expert opinion. Effort-related thrombosis occurs more frequently in the right arm (probably as a result of right hand dominance) and typically occurs in young healthy individuals with an average age of onset around 30 years. It has been postulated that around 60–80% of patients have a history of strenuous exercise involving the upper limbs (Van Stralen et al, 2005; Illig and Doyle, 2010; Lutter et al, 2015). An interesting case was described in a 40-year-old cameraman who developed an upper extremity deep vein thrombosis after a prolonged and strenuous episode of TV camera work, emphasizing the importance of considering occupational causes of effort-related thrombosis (Beasley et al, 2015) (*Table 1*).

The main risk factor for developing an effort-related thrombosis is thoracic outlet syndrome. This is a disorder in which there is compression of the neurovascular contents of the thoracic outlet which includes the brachial plexus, subclavian artery and subclavian vein. In most cases this compression is a result of congenital narrowing of the thoracic outlet which is made up of the first rib, the clavicle, the subclavian muscle tendon and the costoclavicular ligament (Czihal and Hoffmann, 2011). A combination of this narrowing and repeated strenuous use of upper limb muscles can result in venous compression. This compression results in damage to the vessel intima, activation of the coagulation cascade and the potential for scarring to occur on the vessel lining (Czihal and Hoffmann, 2011).

Table 1. Occupational or leisure activities which may cause upper limb deep vein thrombosis

Painters
Gym users who frequently lift weights
Surfing
Playing tennis
Rock climbing
Nursing staff who frequently put up drips
Swimming
Rowing
Sleeping with hands bent under the pillow

Secondary upper extremity deep vein thrombosis

This category accounts for between 66 and 80% of all upper extremity deep vein thromboses (Sajid et al, 2007). By definition this category includes any case of upper extremity deep vein thrombosis for which a substantial risk factor or cause can be found that is not an effort thrombosis. The predominant risk factors which increase the likelihood of secondary upper extremity deep vein thrombosis are central venous catheter placement and malignancy. One study found that 93% of patients with upper extremity deep vein thrombosis had central venous catheters in situ and 49% of patients with upper extremity deep vein thrombosis had some form of malignancy (Lee et al, 2012). Other significant risk factors include prolonged bed rest, history of upper extremity deep vein thrombosis, recent surgery (within 30 days) and a history of cardiac disease (Lee et al, 2012).

The incidence of upper extremity deep vein thrombosis in patients with central venous access varies in the literature from 1–66% (Bérubé and Zehnder, 2016). Although the internal jugular vein is most commonly affected, the other major vessels including the brachial, subclavian and axillary can be involved (Major et al, 2008). In relation to catheters being risk factors for thrombosis, peripherally inserted catheters have higher risk of thrombus formation than catheters inserted centrally. The explanation for this may be the increased diameter of the catheter in relation to the size of the blood vessel into which it is inserted, as this can be an important factor in determining the free flow of blood and therefore the likelihood of clot formation (Bérubé and Zehnder, 2016). In addition to interrupted flow, infections at the catheter site, catheter malposition and the effects of certain medications (e.g. highly viscous drugs) administered through the catheter can contribute to the increased risk of thrombus formation. Although many patients with a malignancy also have an indwelling venous catheter in place, malignancy itself can account for an 18-fold increase in risk of upper extremity deep vein thrombosis (Czihal and Hoffmann, 2011).

Table 2. Rates of occurrence for symptoms of upper limb deep vein thrombosis

Symptom	Occurrence rate
Oedema or welling	80%
Extremity pain	30–50%
Erythema	15%
No symptoms	5%

From Mai and Hunt (2011)

Clinical features

The clinical presentation of upper extremity deep vein thrombosis can be variable. Around 80% of patients have oedema of the arm, 30–50% have some form of extremity pain and 15% have erythema (*Table 2*). Other less frequently found symptoms include cyanosis and jugular distention (Czihal and Hoffmann, 2011). Around 5% of patients with a positive diagnosis of upper extremity deep vein thrombosis were noted to have no symptoms (Mai and Hunt, 2011). Cases of upper extremity deep vein thrombosis related to central venous catheter placement often remain subclinical and may only be discovered after complications have occurred or failure of the catheter function is noted (Czihal and Hoffmann, 2011). Clinicians should therefore suspect an upper extremity deep vein thrombosis in any patient with arm swelling who has additional risk factors for thrombosis (Sajid et al, 2007).

Upper extremity deep vein thrombosis may also present with the symptoms of its complication, pulmonary embolism. Thoracic outlet syndrome usually remains asymptomatic before the venous compression leads to effort thrombosis. If symptoms are present before the thrombosis, they are most commonly of neurovascular origin caused by compression of the brachial plexus (Czihal and Hoffmann, 2011).

Complications

There are two main complications of upper extremity deep vein thrombosis: pulmonary embolism and post-thrombotic syndrome.

Pulmonary embolism

The rates of occurrence of pulmonary embolism in relation to ongoing upper extremity deep vein thrombosis are between 3 and 12% (16–29% in lower limb deep vein thrombosis) (Czihal and Hoffmann, 2011). Although it would seem that pulmonary embolism is less likely to occur with upper extremity deep vein thrombosis, there was no difference in mortality rate in both categories. In addition, although at presentation rates of pulmonary embolism were lower in upper extremity deep vein thrombosis, during follow up the incidence of new pulmonary emboli remained similar (Muñoz et al, 2008).

Post-thrombotic syndrome

Post-thrombotic syndrome is an important and chronic complication of upper extremity deep vein thrombosis. Its clinical manifestations include oedema, erythema, pain, hyperpigmentation, sensation of heaviness, fatigue and thickening of the skin (Kahn et al, 2016). If post-thrombotic syndrome occurs it can cause significant disability and has the potential to decrease a patient's quality of life, especially if it occurs in the dominant arm (Czihal and Hoffmann, 2011). Czihal et al (2012) found that 32% of patients suffering from primary upper extremity deep vein thrombosis also suffered from mild to moderate post-thrombotic syndrome. Very little guidance is available for the treatment of post-thrombotic syndrome but one recent study suggests benefits of compression sleeves to reduce symptoms and exercise training programmes to regain function (Kahn et al, 2016).

Diagnosis of upper extremity deep vein thrombosis

The diagnosis of upper extremity deep vein thrombosis begins with clinical inspection which has a relatively low specificity between 30 and 64% (Grant et al, 2012). Unlike the well-established clinical prediction scores like the Well's score for the diagnosis for lower limb deep vein thrombosis, similar prediction scores are not yet available for upper extremity deep vein thrombosis. Constans et al (2008) attempted to create a pre-test probability score for upper extremity deep vein thrombosis but its efficacy has not been measured. Benefits of D-dimer testing in the diagnosis of upper extremity deep vein thrombosis are also unknown in this setting. Although it has been suggested that D-dimer testing may have a high negative predictive value in diagnosis of upper extremity deep vein thrombosis, there is not enough evidence for it to be used clinically as a method of excluding upper extremity deep vein thrombosis (Di Nisio et al, 2010). Radiological imaging is the best diagnostic technique for upper extremity deep vein thrombosis.

Non-contrast imaging for upper extremity deep vein thrombosis

Imaging is an essential part of upper extremity deep vein thrombosis diagnosis and currently ultrasonography is the most commonly used technique. It is relatively cost effective, non-invasive and does not result in exposure to radiation (Grant et al, 2012). A deep vein thrombosis is defined as a non-compressible portion of blood vessel on ultrasound imaging. Veins should compress relatively easily under manual pressure from the probe so any lack of expected venous collapse can indicate a thrombus. However, as this technique requires manual compression, it can be limited by the anatomical location of vessels in relation to the bony structures of the shoulder (Grant et al, 2012). A complete examination should involve visualization of the basilic, cephalic, axillary and brachial veins as well as the internal jugular vein and the subclavian vein distal to the clavicle (Czihal and Hoffmann, 2011).

In addition to compression ultrasonography, Doppler and colour flow Doppler ultrasonography can be used to assess the flow of blood. Reduction in flow or alterations of the normal biphasic pattern of flow can suggest deep vein thrombosis (Grant et al, 2012). A systematic review demonstrated an overall 97% sensitivity and 96% specificity for compression ultrasonography in the diagnosis of upper extremity deep vein thrombosis while also reporting no increase in diagnostic accuracy when Doppler testing was used. This would seem to suggest that Doppler imaging does not add any diagnostic benefit, although the evidence in the literature was considered neither strong nor convincing (Di Nisio et al, 2010). Overall, ultrasound imaging is widely considered to be first line in upper extremity deep vein thrombosis management, but the safety of withholding treatment in cases where a symptomatic patient has an unremarkable ultrasound scan remains unclear (Czihal and Hoffmann, 2011).

Contrast imaging

Contrast venography is said to be the 'accepted reference standard' for diagnosing deep vein thrombosis but has been superseded by compression and/or Doppler because of its ease of use (Grant et al, 2012). However, it may be used in exceptional cases when there is diagnostic uncertainty after ultrasonography. There are two main categories of contrast venography: magnetic resonance venography and computed tomography venography. Systematic review and meta-analysis reported a sensitivity of 91.5% and specificity of 94.8% for diagnosis of lower limb deep vein thrombosis by magnetic resonance venography and a sensitivity of 95.9% and specificity of 95.2% by computed tomography venography (Sampson et al, 2007; Thomas et al, 2008). *Figure 1* shows a flowchart of the diagnostic pathway for upper extremity deep vein thrombosis.

Management

The management of upper extremity deep vein thrombosis is multifaceted and there are very few good-quality trials in this area which means there is a distinct lack of guidance available to clinicians. Both the Scottish Intercollegiate Guidelines Network and the American College of Chest Physicians suggest that upper extremity deep vein thrombosis should be largely treated in the same way as lower limb deep vein thrombosis (Scottish Intercollegiate Guidelines Network, 2010; Kearon et al, 2012). Major aspects of management which will be covered include anticoagulation, thrombolysis, superior vena cava filter placement and surgical resection in cases of primary upper extremity deep vein thrombosis. *Figure 2* shows a flowchart with a pathway for management.

Anticoagulation

Current guidelines recommend that upper extremity deep vein thromboses are managed in a similar fashion to lower limb deep vein thromboses but there is uncertainty about optimal length of treatment (Scottish Intercollegiate

Guidelines Network, 2010; Kearon et al, 2012). The 2012 American College of Chest Physicians guidance (Kearon et al, 2012) recommends acute treatment with parenteral anticoagulation, namely low molecular weight heparin or fondaparinux, followed by vitamin K anticoagulation for a minimum of 3 months. Despite the lack of randomized trials, the benefits of anticoagulation for upper extremity deep vein thrombosis include improved vessel patency, prevention of clot propagation and reduced incidence of pulmonary embolism (Hingorani et al, 1997).

Although the duration of anticoagulation for upper extremity deep vein thrombosis is uncertain, the Scottish Intercollegiate Guidelines Network (2010) guidance recommends that patients with upper extremity deep vein thrombosis, without underlying risk factors, do not require anticoagulation for longer than 3–6 months. Although newer oral anticoagulants have not been studied typically in this setting, they are often prescribed for a similar duration in patients with upper extremity deep vein thrombosis.

In addition to anticoagulation, removing the causative factors for thrombosis formation is important, particularly in cases of secondary upper extremity deep vein thrombosis. One instance in which this is not the case is when a central venous catheter is the causative factor but intravenous access is still required clinically. It is reported that it is safe to leave the catheter in situ as long as symptomatic relief is achieved with anticoagulation and the site does not become infected (van den Houten et al, 2016).

Thrombolysis

Two types of thrombolytic treatments are used in the management of deep vein thrombosis: systemic and catheter-directed thrombolysis, of which the latter has superior efficacy and fewer complications (Grant et al, 2012). Streptokinase is the most commonly studied agent while tissue plasminogen activator has also been used effectively (Watson et al, 2014). Catheter-directed thrombolysis can significantly increase vessel patency and reduce rates of post-thrombotic syndrome by up to a third (Watson et al, 2014). Grant et al (2012) report thrombus clearance rates of 72–91%. Clots older than 2 weeks are generally less susceptible to thrombolysis (Grant et al, 2012). The most common complication of thrombolysis is bleeding in 8–17% of cases (Wicky, 2009; Koury and Burke, 2011). Carefully selecting patients with a low risk of bleeding may maximize the potential benefits. It has been suggested that catheter-directed thrombolysis should be used in every case of primary upper extremity deep vein thrombosis with recent onset of symptoms and a low bleeding risk (van den Houten et al, 2016).

Surgical resection

In cases of primary upper extremity deep vein thrombosis where other causes of venous stasis have been ruled out, the thrombus is often at the level of the costoclavicular space. The reasons for clot formation here are likely to be anatomical, as a result of mechanical compression and repeated trauma to the subclavian vein. In these cases, decompression can be achieved by removal of the first rib, part of the scalene muscle and the costoclavicular ligament (van den Houten et al, 2016). van den Houten et al (2016) state that 'with acute primary upper extremity deep vein thrombosis full recovery is best achieved by a combination of anticoagulation, thrombolysis and surgical decompression within the first 14 days after onset of upper extremity deep vein thrombosis symptoms.'

Figure 1. Flowchart showing the diagnostic pathway of upper extremity deep vein thrombosis.

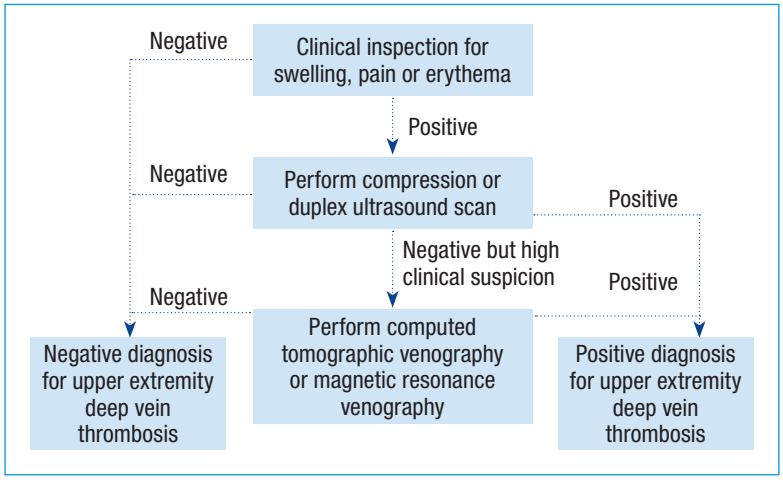
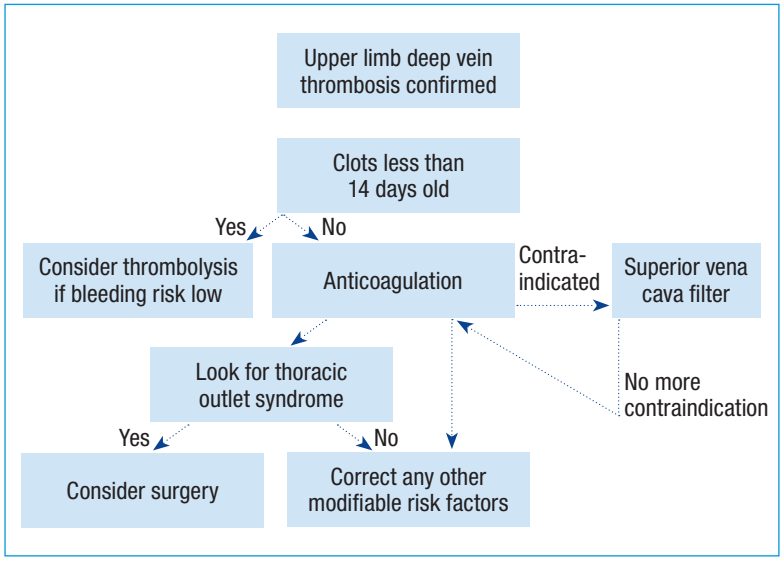


Figure 2. Flowchart showing suggested management pathway.



Superior vena cava filter placement

Superior vena cava filter placement is another technique that can be used in patients with a failure of or with a contraindication to conventional anticoagulation (Grant et al, 2012). The technique involves passing the filter into the venous system by the common femoral vein and placing the filter in the superior vena cava with the filter hooks positioned above the level of the azygous vein (Koury and

KEY POINTS

- Upper extremity deep vein thrombosis is a rare condition; key symptoms include swelling, erythema and pain.
- Diagnosis is usually made using ultrasound imaging.
- Management is usually anticoagulation with other options including thrombolysis, surgical resection and superior vena cava filter placement.

Burke, 2011). The main aim of filter placement is to reduce the risk of thrombus migration; Owens et al (2010) reported no recurrence of pulmonary embolisms after placement of superior vena cava filters in 209 patients. They also found a major complication rate of 3.8% (comprising mostly of superior vena cava perforation) and suggested that the risk of a pulmonary embolism occurring as a direct result of a upper extremity deep vein thrombosis must outweigh the risks of filter insertion before it can be justified.

Prognosis

Recurrence

Recurrence after a primary event of upper extremity deep vein thrombosis is dependent on a number of factors including circumstances of the primary event, the presence of risk factors and the treatment provided for the first event. Retrospective and prospective studies quote recurrence rates varying from 3.1–9.8% during follow-up periods of between 3 months to 5 years. A recent systematic review also found that the incidence of recurrence increased with longer follow-up periods and the most common site of recurrence was in the ipsilateral arm (Bleker et al, 2016). The same review found that there was a 3–4-fold increase in risk of recurrent venous thromboembolism in patients with malignancy and that there was a 'substantial risk of recurrence' in patients with upper extremity deep vein thrombosis related to central venous catheters. It is thought that rates of recurrence are lower in cases of idiopathic primary upper extremity deep vein thrombosis possibly as a result of the lack of underlying risk factors and that the rates of recurrence are similar in upper extremity deep vein thrombosis and lower extremity deep vein thrombosis (Czihal and Hoffmann, 2011).

Mortality

In a similar fashion to rates of recurrence, mortality rates in cases of upper extremity deep vein thrombosis can be variable. Mortality rate at 3 months and 12 months after the primary event ranged from 11–35% and 19–32% respectively. Interestingly the same systematic review reported higher mortality rates when looking at data from prospective studies when compared to retrospective studies (Bleker et al, 2016). Mortality increased significantly in cases of malignancy with Muñoz et al (2008) noting an eightfold increase. Mortality rates are higher in secondary upper extremity deep vein thrombosis, possibly because patients are more likely to be elderly or have other comorbidities (Czihal and Hoffmann, 2011).

Conclusions

With the increasing use of central venous catheters in patients with complex conditions, and better treatment of malignancies, the incidence of upper extremity deep vein thrombosis is on the rise. Currently the most commonly used diagnostic method is compression ultrasonography while the cornerstone of treatment is anticoagulation, with thrombolysis and surgical techniques considered in select cases. The sparsity of guidance available to clinicians reflects a distinct lack of good quality trials in this setting. **BJHM**

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