The Arm is Not the Leg: Pathophysiology, Diagnosis, and Management of Upper Extremity Deep Vein Thrombosis

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ABSTRACT

Upper extremity deep venous thrombosis (UEDVT) involves thrombosis of the deep veins of the arm as they enter the thorax. They are increasing in frequency, largely due to the rising use of central venous catheters and implantable cardiac devices, and represent more than 10% of all DVT cases, Upper extremity deep venous thrombosis has been historically misunderstood when compared to lower extremity deep vein thrombosis (LEDVT). Their associated disease states may carry devastating complications, with mortality rates often higher than that of LEDVT. Thus, education on recognition, classification and management is critical to avoid long-term sequelae and mortality from UEDVT.

KEYWORDS: Upper extremity deep vein thrombosis, catheter associated deep vein thrombosis, pacemaker associated deep vein thrombosis, thoracic outlet syndrome, Paget-von Schröetter syndrome

INTRODUCTION

Upper extremity deep venous thrombosis (UEDVT) accounts for more than 10% of all cases of deep venous thrombosis (DVT).[1-3] UEDVT is about 1/5 as common as lower-extremity deep vein thrombosis (LEDVT) (0.19 vs 0.96 per 100,000 hospitalizations).[4] The subclavian vein is most often affected,[5,6] with the internal jugular, brachial, and basilic veins involved in approximately 4–30% of patients.[5,6] Complications, such as pulmonary embolism (PE) as well as mortality are more frequent and more severe when UEDVT involves the axillary or more proximal veins than if thrombosis is confined to the brachial vein.[11] As such, the term "UEDVT" is typically used only when referring to thrombosis involving axillary and more proximal veins. In addition, UEDVT has associated under-recognized and distinct disease states,[13] which are often misunderstood when compared to LEDVTs.[12] Prompt recognition and appropriate management of UEDVT is vital due to the significant risk of PE,[4,16,17] mortality,[4,11,14,15] and observable long-term sequelae.

In this article, we review the pathogenesis, diagnosis, classification, and clinical characteristics of the different forms of UEDVT as well as treatment and management.

ANATOMY OF THE VEINS OF THE UPPER EXTREMITY

The superficial veins of the arm include the cephalic, basilic, and median cubital veins. These veins drain into the deep veins, which are the radial and ulnar veins in the forearm and the brachial, axillary, and subclavian veins in the upper arm and shoulder. The subclavian vein continues, joining with the internal jugular vein and eventually emptying into the superior vena cava (SVC).

CLASSIFICATION AND PATHOGENESIS

The mechanism of DVTs was first described by Rudolf Virchow as a triad of factors thought to contribute to thrombosis: hypercoagulability, hemodynamic stasis or turbulence, and endothelial dysfunction.[18] From this, the mechanism of UEDVT can be further characterized as primary, or "spontaneous," and secondary.

Primary Upper Extremity Deep Venous Thrombosis

A DVT of the arm veins without apparent predisposing factors in the patient's history is classified as primary UEDVT and accounts for up to 33% of all thromboses involving the upper extremities.[6,14,15] Classifying an UEDVT as primary requires thorough evaluation for predisposing anatomic and hematologic abnormalities. Primary UEDVT can be further classified into effort thrombosis, otherwise referred to by the eponym Paget-von Schröetter Syndrome (PSS), and idiopathic thrombosis.

Paget-von Schröetter Syndrome is the most common form of primary UEDVT and typically occurs in young and otherwise healthy individuals with a male to female ratio of approximately 2:1.[20] UEDVT occurs in the dominant arm after strenuous, repetitive or unusual physical activity, such as lifting weights, playing tennis, pitching a baseball, or performing repetitive overhead activities such as painting.[20] Patients with PSS have an underlying anatomic abnormality involving the thoracic outlet. The repetitive physical activity leads to damage to the subclavian vein intima with subsequent fibrosis and activation of the coagulation cascade. This elicits effort-related thrombosis due to compression of the subclavian vein from anatomic abnormalities within the anterior portion of the thoracic outlet triangle leading to the formation of the venous thoracic outlet syndrome (VTOS).[1,20]

The subset of primary UEDVT where there are no evident predisposing factors or underlying VTOS is identified as

idiopathic. However, occult malignancies in this subgroup of patients have been reported in up to 25% of cases,[22] and the prevalence of coagulation abnormalities appears to be even higher in patients with idiopathic thrombosis than in those with PSS thrombosis or other forms of secondary thrombosis. [14,24] Patients with PSS generally have good functional status with longer life expectancies than that of idiopathic UEDVT.[21]

Secondary UEDVT

Secondary UEDVT accounts for up to 80% of UEDVT and is defined as any UEDVT related to a predisposing factor, such as central venous catheters (CVC), implantable cardiac rhythm devices, malignancy, or insertion of other prosthetic or foreign material.[14] Compared to primary UEDVT, there is increased mortality in patients with secondary UEDVT, usually related to the underlying disease state.[25] The incidence of secondary UEDVT is increasing due to growing use of medical devices,[2,21,26] particularly use of central venous catheters, which have been reported in 25–50% of UEDVT.[4,21,26] The internal jugular, subclavian or axillary veins can be involved, and the risk of thrombosis is equal, regardless of vascular access site.[28] The risk of developing catheter-related thrombosis depends on an individual patient's profile, and is as high as 66% in cancer patients with CVCs.[30]

UEDVTs occurred in 23% of patients following implantation of a permanent pacemaker,[32] while peripherally inserted central catheters were associated with UEDVT in 9% of patients.[35] Other related risk factors include personal or family history of thrombosis and thrombophilia (11–60%);[21] surgery, trauma or immobilization of the arm;[33] pregnancy and oral contraceptive use.[26] Malignancy is an independent risk factor for secondary UEDVT and is present in approximately 33% of cases,[3] particularly ovarian and lung adenocarcinoma.[1] Catheter-related risk factors such as technically difficult or left-sided catheter placement, location of the catheter tip not at the atriocaval junction, prior CVC, and large-lumen catheters also pose increased risk.[35]

CLINICAL PRESENTATION AND DIAGNOSIS

The most common clinical features of UEDVT are unilateral arm erythema, edema and discomfort, and dilated superficial veins, dyspnea, low-grade fever and failure to withdraw blood from a catheter may also be present.[33] In cases where there is central vein obstruction or occlusion, SVC syndrome may be seen.[21] When PSS is present, venous distention was reported in all cases, with edema of the arm (93%), cyanosis (77%) and pain with exercise (66%) also occurring.[21,36] Compression of the brachial plexus can lead to paresthesias and arm pain, which worsens with hyperabduction of the shoulder when VTOS is associated with PSS.[20] The incidence of symptomatic and asymptomatic UEDVT following CVC placement is 2–6% and 11–19%, respectively.[21]

Clinical probability scores have a sensitivity of 78% and specificity of 64% for diagnosing UEDVT.[38] Furthermore, 13% of patients with low probability scores were later diagnosed with UEDVT;[38] thus, scores alone should not be used to rule out the likelihood of UEDVT. In contrast to LEDVT, D-dimer testing has not been prospectively tested and cannot be used to exclude UEDVT with one study showing a specificity of 14%.[39]

The mainstay in diagnosis of UEDVT is imaging. Duplex ultrasonography (US) is commonly used as the initial study and should be considered the first-line diagnostic imaging procedure for UEDVT (**Figure 1 and 2**).[33] It is readily available, portable, non-invasive, inexpensive, and without radiation exposure. Ultrasound has 97% sensitivity and 96%

Figure 1. Greyscale image (A) of subclavian vein (arrows) with intraluminal PICC line (arrowhead) surrounded by heterogeneous echodensity filling the vessel consistent with thrombus. Color Doppler (B) shows flow (blue) between the vessel wall and thrombus demonstrating near-occlusive thrombus.

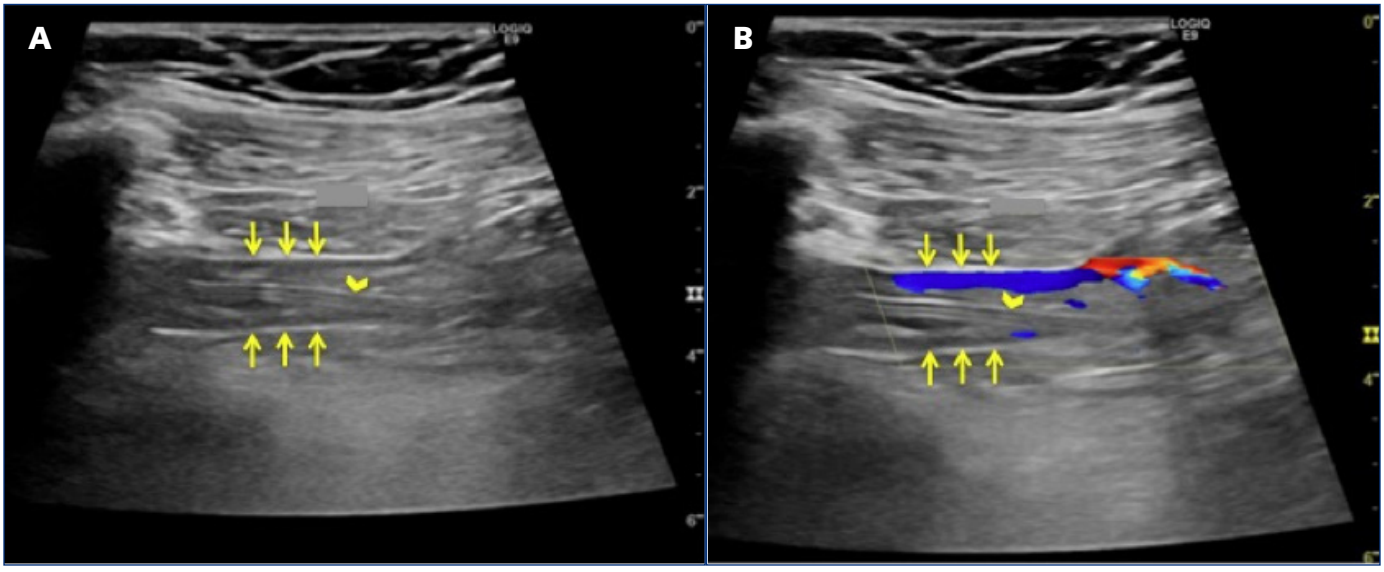
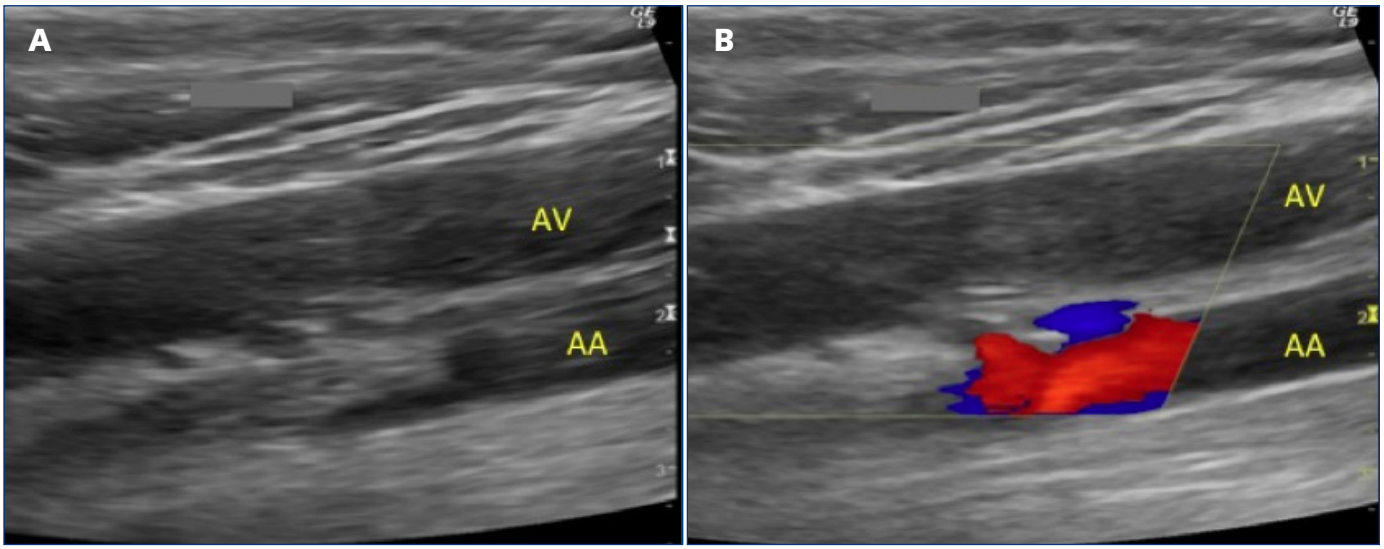


Figure 2. Greyscale image (A) showing axillary vein (AV) and artery (AA). The vein is dilated and filled with heterogenous echogenic material consistent with spontaneous thrombosis. Color Doppler (B) showing no flow within the vein demonstrating complete occlusion of the vessel. Red color in the axillary artery consistent with normal arterial flow.



specificity for the diagnosis of UEDVT.[40] Applying pressure to compress the visualized vein should easily collapse the vessel under normal conditions, with lack of expected venous collapse indicating presence of a thrombus. This technique cannot be used for centrally located veins, such as the SVC, where manual compression is not possible. Echogenicities visualized within the vessel lumen may represent acute or age indeterminate thrombus. Pulsed wave- and color-flow Doppler US can further assess dynamics of venous blood flow. Absence of flow, or conversion of the normal biphasic flow pattern into a non-pulsatile, continuous flow signal suggests venous obstruction and the presence of a DVT.[14]

Contrast venography has the ability to visualize the entire deep venous system and can define complex and difficult anatomy not otherwise visualized with US. It is utilized infrequently and is typically reserved for these situations or if there is a disparity between US and clinical findings. Contrast venography is invasive and exposes the patient to iodinated contrast and radiation. When contrast is injected into the venous system, a non-filling venous segment suggests thrombosis.[14]

Additionally, contrast-enhanced computed tomography and magnetic resonance venography are potential diagnostic tests for UEDVT, though limited evidence exists to guide their use.[40] Sensitivity of magnetic resonance venography has been reported at 71%,[41] and the value of computed tomography venography has not been systematically evaluated.[14] However, both computed tomography and magnetic resonance imaging are useful not only to confirm UEDVT but also to diagnose concomitant pathologies, including cancer, adenopathy, or anatomic abnormalities suggestive of VTOS and have largely supplanted contrast venography.[1]

TREATMENT AND PREVENTION

Goals of therapy can be divided into the acute treatment phase, defined as the first three months following diagnosis, and the secondary prevention phase, which refers to therapy beyond three months.[11, 42] In the acute treatment phase, the optimal treatment duration and intensity has not been determined in randomized controlled trials. However, a small prospective cohort study has shown low rates of recurrent DVT, PE, and episodes of major bleeding when acute UEDVT is treated similarly to LEDVT.[43] The 2012 consensus guidelines of the American College of Chest Physicians[11] recommend anticoagulation therapy with low molecular weight heparin (LMWH), unfractionated heparin, or fondaparinux followed by 3 months of vitamin K antagonists for idiopathic UEDVT involving the axillary and more proximal veins.[11] Anticoagulation for isolated brachial vein thrombosis is not well studied, but is recommended if the thrombus is symptomatic or involves a CVC. In contrast to idiopathic LEDVT, anticoagulation therapy beyond 3 months is generally not recommended after a first episode of idiopathic UEDVT.[11]

In UEDVT associated with malignancy, treatment with LMWH monotherapy for 3-6 months is preferred over the administration of vitamin K antagonists and should continue as long as the cancer remains active and the event was not related to a CVC.[11] In patients with catheter-associated UEDVT (with or without cancer), anticoagulation therapy can be discontinued after at least 3 months if the CVC is removed. If the catheter is not removed, anticoagulation therapy should be continued as long as the catheter remains.[11] In most patients with CVC-associated UEDVT, it is recommended that the catheter not be removed if it is functional and there is an ongoing need for central access.[11]

The use of direct thrombin inhibitors and Xa inhibitors over vitamin K antagonists or LMWH for the long-term treatment of UEDVT is not recommended as their use has not been studied.[11]

Criteria for placement of SVC filters are similar to those in LEDVT, and should only be considered in patients with contraindications to anticoagulant treatment and PE.[11]

In patients with UEDVT due to PSS, physical therapy may reduce symptoms. If symptoms persist with evidence of residual subclavian vein stenosis by positional venography, surgical decompression should be considered.[1]

PROGNOSIS AND FOLLOW-UP

Mortality rates are significantly higher with UEDVT compared to LEDVT (7.6% vs. 4.2%; p<0.001),[4] and two- and 12-month mortality rates following diagnosis of UEDVT have been reported at 30 and 40%, respectively.[44, 45] Pulmonary embolism is a dire complication and drives mortality in both UEDVT and LEDVT, although rates in one large retrospective study showed a lower incidence of PE in UEDVT compared to LEDVT (5.4% vs. 27.9% p<0.001). Nonetheless, the prevalence of hemodynamically unstable PE was higher among patients with UEDVT than LEDVT (5.2% vs. 3.6%; p<0.001). [4] Another analysis reported the rate of PE to be 6% in primary UEDVT, 13% in secondary UEDVT and 17% in catheter-related UEDVT.[17]

Post-thrombotic syndrome (PTS) of the arm, a condition characterized by persistent pain, edema, and functional limitation due to persistent obstruction and valvular insufficiency, has been reported in up to 20% of patients after treatment for UEDVT.[11] In contrast to LEDVT, use of compression therapy to prevent PTS of the arms is not recommended due to lack of evidence of efficacy in this population and a difference in the suspected pathophysiology of PTS in the upper extremity.[11] Additionally, there is no evidence or recommendations to support the practice of serial US imaging in UEDVT.[11]

CONCLUSION

The clinician's understanding and recognition of UEDVT is essential in avoiding PE. Mortality is elevated in patients with UEDVT, and prompt identification of thrombosis and initiation of anticoagulation is essential. Specific differences exist between the various types of UEDVT and can alter approaches to treatment. Further research should focus on use of novel anticoagulants given the anticipated increase in UEDVT incidence due to increasing use of CVC.

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