

Upper Extremity Deep Vein Thrombosis

Mubina Gaffar, MD, FACP

Although once thought to be an uncommon and benign disorder, upper extremity deep vein thrombosis (UEDVT) has been recognized as more common than previously reported.^{1,2} Studies have demonstrated an increased incidence of UEDVT,^{3,4} partly attributable to more frequent use of central venous catheters (CVCs). UEDVT has the potential for considerable morbidity, including pulmonary embolism (PE) and persistent upper extremity pain and swelling. In addition, the therapy for UEDVT is not standardized. This article presents an overview of the etiology, pathogenesis, and clinical features of UEDVT. Potential complications are reviewed and management options are discussed.

INCIDENCE

UEDVT was previously thought to account for about 1% to 2% of all cases of deep vein thrombosis (DVT).⁵ The increased incidence of UEDVT appears to be related to the more frequent use of CVCs in patients who receive chemotherapy, parenteral nutrition, and hemodialysis and in bone marrow transplant patients.⁶ In addition, liberal use of Doppler scans and heightened physician awareness has led to an increase in diagnosis of UEDVT. Lindblad summarized the results of 10 series, and thrombosis was identified in 18.9% of patients with CVCs.⁷ UEDVT has major clinical consequences, including PE and disabling chronic venous insufficiency of the upper extremity. According to a study reported by Prandoni et al,⁸ the prevalence of both symptomatic and asymptomatic PE in patients with UEDVT was 36%; this result was close to that observed in patients with lower extremity venous thrombosis in previous studies.⁹⁻¹¹

ETIOLOGY AND PATHOGENESIS

UEDVT refers most commonly to thrombosis of the axillary and/or subclavian vein and is classically divided into primary and secondary forms. Primary UEDVT is either truly idiopathic or is related to physical activity or arm positioning with or without anatomic compression at the thoracic outlet (also called *effort thrombosis* or *Paget-Schroetter syndrome*). The typical patient is young and healthy and develops rapid onset of DVT in the

dominant arm after strenuous activity (eg, rowing, weightlifting, or wrestling). Exertion causes intimal damage to the vessel wall, which activates the coagulation system. This effect is magnified if mechanical vessel compression is also present,¹² including compression by an abnormal first rib or clavicle, congenital webs or bands, and muscle structures (abnormal anterior scalene or pectoral minor muscle). A subgroup of patients with primary UEDVT has idiopathic thromboses with no known underlying cause; however, some of these patients may have an occult malignancy, which typically remains elusive until some time after the thrombotic manifestation. The most commonly associated malignancies are lymphoma and lung cancer.¹²

Secondary UEDVT occurs in patients with CVCs or other venous instrumentation, intravenous drug use, malignancy (attributable to hypercoagulability of malignancy and external compression by tumor mass), or radiation therapy. Reported rates of catheter-related DVT vary from 2% to 42%.¹³⁻¹⁶ Catheters placed incorrectly are more likely to result in thrombosis. It is recommended that the tip of the catheter be positioned in the lower third of the superior vena cava (SVC) or at the junction of the SVC and right atrium.¹⁷

The role of hypercoagulable states in causing both primary and secondary UEDVT remains controversial, mainly due to lack of data. In contrast, hypercoagulability has been shown to be an important risk factor for lower extremity DVT in large epidemiologic studies.¹⁸ Small observational studies on patients with UEDVT provide conflicting data. A recent review by Leebeek et al¹⁹ concluded that hypercoagulable states are frequently found in UEDVT, while Martinelli et al²⁰ concluded that hypercoagulable states do not occur often in patients with UEDVT. However, both studies concluded that further studies are needed to clarify this issue. Furthermore, screening for coagulation disorders is

At the time this manuscript was written, Dr. Gaffar was an attending physician, Department of Ambulatory Care Medicine, Veterans Affairs Medical Center, and clinical assistant professor, University of Oklahoma Health Sciences Center, Oklahoma City, OK. Dr. Gaffar is now a fellow in pulmonary and critical care medicine, Emory University, Atlanta, GA.

Table 1. Presenting Signs and Symptoms of Upper Extremity Deep Vein Thrombosis

Symptoms	
	Asymptomatic
	Pain (ie, shoulder, neck, or arm)
	Swelling (ie, arm or facial)
	Paresthesias
	Pruritus
	Vein tenderness
Signs	
	Low-grade fever
	Edema
	Palpable cord
	Extremity cyanosis
	Dilated cutaneous veins on chest or arms

controversial. A recent review by Joffe and Goldhaber¹⁷ suggests screening patients who present with idiopathic UEDVT, recurrent UEDVT, a family history of UEDVT, or recurrent pregnancy loss. Various disorders that have been implicated include deficiency of protein C, protein S, and antithrombin III, factor V Leiden, prothrombin gene mutation, hyperhomocysteinemia, and antiphospholipid antibodies.

CLINICAL FEATURES

Common signs and symptoms of UEDVT are presented in **Table 1**. Patients with UEDVT typically present with pain and swelling of the affected arm or vague shoulder or neck pain with arm swelling.⁸ Other symptoms include mild cyanosis of the extremity, paresthesias, pruritus, and tender veins.²¹ Occasionally, patients may be completely asymptomatic.¹⁷ Physical examination may reveal low-grade fever (due to thromboses), mild cyanosis of the involved arm, edema, a palpable cord,²¹ dilated cutaneous collaterals over the chest or upper arm,⁸ supraclavicular fullness, or elevated jugular venous distention. If thromboses are severe enough to cause SVC syndrome, patients may present with edema of the arm and face, facial flushing, blurred vision, vertigo, or dyspnea.

DIAGNOSIS

Differential Diagnosis

Several problems may result in upper extremity pain and swelling and masquerade as UEDVT. These conditions need to be reliably excluded in order to avoid morbidity related to empiric anticoagulation. Examples include hematomas, muscle contusions or

tears in the upper extremity, cellulitis, lymphedema, and gangrene. Superficial thrombophlebitis and neoplastic compression of the subclavian vein should also be identified and appropriately treated.

Making a diagnosis of UEDVT can be difficult. After a thorough history and physical examination, diagnostic imaging is necessary to confirm the diagnosis. The most commonly used tests are compression ultrasound with color flow Doppler and venography. Recently, magnetic resonance angiography (MRA) has been used more effectively to diagnose UEDVT.²²

Doppler Ultrasound

With the advantages of being noninvasive, safe, and reliable and having a high sensitivity for diagnosing UEDVT,⁸ Doppler ultrasound should be the initial test of choice because DVT is diagnosed by the inability to compress a segment of the vein, absence of increased blood flow with respiration and augmentation maneuvers, and the absence of a color signal in the lumen or by visualization of an intraluminal filling defect (**Figure 1** and **Figure 2**). However, Doppler ultrasound is limited in that acoustic shadowing from the clavicle hinders visualization of a short segment of the subclavian vein, resulting in a false-negative study.²³ If there is a strong clinical suspicion of UEDVT and results of a Doppler study are negative, venography is mandatory.

Venography

Venography is considered the gold standard for diagnosing UEDVT.²¹ With this test, contrast material is introduced into the basilic vein; an intraluminal filling defect confirms the presence of a thrombus. Venography provides excellent characterization of vessel anatomy and can further define the location and extent of the thrombus. It can also delineate collateral circulation and identify extrinsic compression when the patient's arm is in the neutral or military position. However, its invasive nature and complications associated with iodinated contrast agents limit its use. Venography can also induce thromboses, especially with repeated use. However, this has become an unusual complication with modern contrast media.

Magnetic Resonance Angiography

MRA is a noninvasive and accurate technique used in the diagnosis of UEDVT. It provides for better and higher resolution imaging compared with Doppler studies of the central thoracic veins (eg, SVC, brachiocephalic vein).²² MRA findings correlate well with those of venography.¹⁷ In addition, a more complete visualization of central collateral vessels and better

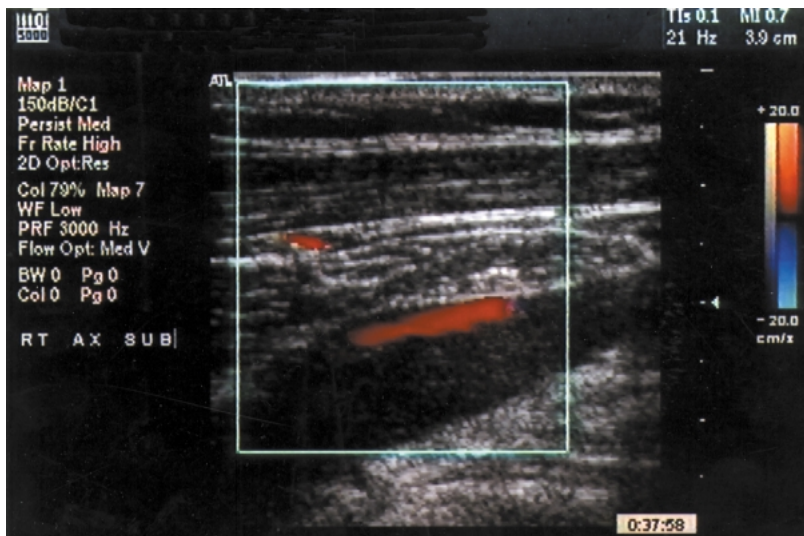


Figure 1. The absence of a color signal in the lumen on Doppler ultrasound is shown.

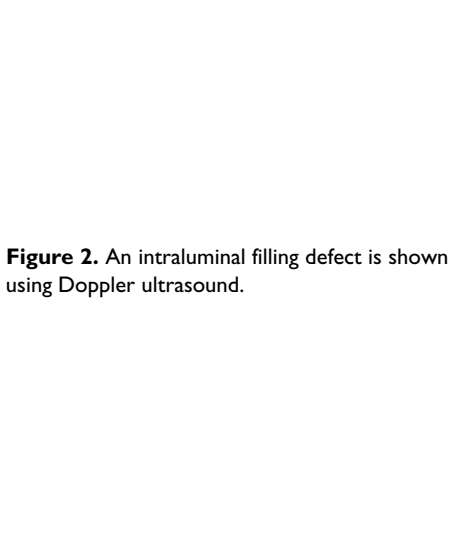


Figure 2. An intraluminal filling defect is shown using Doppler ultrasound.

information regarding blood flow is possible with this modality. Because MRA is noninvasive, it is especially useful when contrast venography is contraindicated.²²

TREATMENT

Effective treatment of UEDVT remains controversial due to the lack of large randomized controlled trials and because etiology and prognosis of primary and secondary UEDVT vary widely. Treatment strategies for UEDVT are listed in **Table 2**.

Anticoagulation

Previously, UEDVT was managed conservatively with bedrest, local heat, and limb elevation. However, given its long-term morbidity due to chronic venous insufficiency and a high incidence of PE,⁸ there is con-

sensus that anticoagulation is the minimum appropriate intervention required. Anticoagulation has been shown to prevent clot propagation, facilitate the maintenance of venous collaterals,²⁴ and prevent PE.²⁵ There is also evidence that anticoagulation is effective in preventing long-term sequelae of chronic venous insufficiency.^{1,26}

Conventionally, unfractionated heparin is initiated at the time of diagnosis to maintain activated partial thromboplastin time 2 to 3 times control values for 5 to 7 days, followed by oral anticoagulation with warfarin for 3 to 6 months, with a goal international normalized ratio of 2.0 to 3.0.²¹ Recent studies have demonstrated that low-molecular-weight heparin (LMWH) is safe and effective in treating UEDVT²⁷ and has the potential to simplify treatment. A prospective study by Savage

Table 2. Treatment Options for Upper Extremity Deep Vein Thrombosis

Conservative management
Bed rest
Local heat
Limb elevation
Compression arm sleeve
Anticoagulation
Thrombolytics
Surgical management
Adhesion lysis
Resection of first rib, clavicle, or scalene muscles
Subclavian vein patching or bypass procedure
Subclavian balloon angiopathy with or without stents
Superior vena cava filter

et al²⁷ on the use of dalteparin in the outpatient setting for UEDVT management established the safety and efficacy of LMWH in the treatment of UEDVT. Because these patients were treated as outpatients, the authors reported a potential for huge cost savings.²⁷

Thrombolytics

Chronic venous insufficiency due to venous thrombosis can cause valvular damage and considerable morbidity from post-thrombotic syndrome.^{1,21} Venous insufficiency can be very disabling in patients with Paget-Schroetter syndrome, who are usually young and healthy. Catheter-directed thrombolysis has been shown to restore venous patency early and have excellent outcomes with minor complications in several small series of carefully selected patients.^{28–30} Many experts recommend thrombolysis for UEDVT in young, healthy, active patients. Contraindications to thrombolysis include history of hemorrhagic stroke, recent neurosurgery (within 2 months), any surgery (within 10 days), or any active bleeding.

Agents that have been used with reasonable results include streptokinase, urokinase, and tissue plasminogen activator. Heparin is given concurrently to prevent clot formation at the site of catheter insertion.²¹ The withdrawal of urokinase from the market in 1999 led physicians to explore alternative regimens. Experience with alternative agents such as alteplase and reteplase is accumulating. Alteplase is currently one of the most commonly used thrombolytic agents, with several reports published on its local use in UEDVT.^{31–33} Preliminary experience supports the safety profile of several dosing regimens in candidates for thrombolytics.^{32,33}

Table 3. Recommended Dosing Regimens for Management of Upper Extremity Deep Vein Thrombosis Using Thrombolytic Agents

Weight-based high-dose regimen
Continuous infusion at a rate of 0.025 to 0.05 mg/kg per hour
No subtherapeutic heparin dosing
Non-weight-based high-dose regimen
Continuous infusion at a rate of 3 to 4 mg/h
No subtherapeutic heparin dosing
High-volume low-dose regimen
Continuous infusion at a rate of 0.5 mg/h (5 mg alteplase in 500 mL normal saline solution [0.01 mg/mL] to be infused at a rate of 50 mL/h); concomitant therapeutic heparin dosing is recommended.

Data from Sharafuddin MJ, Sun S, Hoballah JJ. Endovascular management of venous thrombotic diseases of the upper torso and extremities. *J Vasc Interv Radiol* 2002;13:975–90.

Treatment durations vary from 24 to 48 hours depending on the extent of disease and clot burden. Due to recent reports of a higher risk of bleeding complications when heparin is used with high-dose alteplase,^{32,33} a subtherapeutic dosing regimen with heparin has been recommended (2000–3000 IU bolus with 400–500 IU/h infusion). Some recommended dosing regimens are outlined in **Table 3**.

Complications associated with thrombolytic therapy include hemorrhage (eg, intracranial, retroperitoneal, gastrointestinal, genitourinary, and at the sites of invasive procedures), fever, headaches, and anaphylaxis.^{21,28} Furthermore, the longer the history of thrombosis, the less likely that thrombolytic therapy will be successful.²¹

Surgical Management

Patients with venographically demonstrated external compression or intrinsic venous abnormalities have been treated with several different surgical procedures with varying success. Correction involves lysis of adhesions around the subclavian vein,³⁴ resection of part of the first rib or clavicle¹ and/or scalene muscle resection,³⁵ subclavian vein patching, or bypass procedures. Endovascular therapy, including subclavian balloon angioplasty with or without intraluminal stent deployment, has been attempted in a small number of patients.³⁶ However, controlled studies with larger groups of patients are needed to compare invasive treatments with standard anticoagulation with or without thrombolysis. Until then, these methods should be approached with caution.

SVC Filters

For patients who have contraindications to anticoagulation or those who have PE or clot progression despite adequate anticoagulation, SVC filters have been proposed in several small series to provide benefit.^{33,36} However, placement of SVC filters cannot be accepted as standardized therapy based on these studies alone, and randomized trials are needed to investigate this question. Filters have also raised concerns about filter migration, fractures, dislodgement, and precipitation of SVC syndrome.¹⁷

PREVENTION

In view of the high incidence of UEDVT in patients with CVCs, several trials have investigated the efficacy of prophylaxis with low-dose warfarin^{37,38} or LMWH³⁹ for patients with cancer who need CVCs for chemotherapy or parenteral nutrition. These trials have shown a low risk of bleeding and a decreased incidence of thrombus formation. Based on these studies, some physicians prescribe low-dose warfarin (1 mg) or once-daily subcutaneous deltaparin to such patients. However, more studies are needed to better define standards of care.

COMPLICATIONS

Earlier reports indicated that UEDVT was an innocuous, self-limiting disease. Now that physicians are more aware of UEDVT and it is diagnosed more often, complications are also recognized more frequently. The majority of patients improve over time; however, a significant proportion of patients with either primary or secondary UEDVT suffer long-term morbidity (ie, post-thrombotic syndrome) due to chronic venous insufficiency. Potential complications of UEDVT are provided in **Table 4**.

PE is an important and potentially lethal complication of UEDVT; it has been reported in the literature to occur in more than one third of UEDVT patients when symptomatic and asymptomatic emboli are considered.⁸ Venous gangrene is a rare but possible complication of UEDVT.² Other complications reported include brachial plexopathy, SVC syndrome, thoracic duct obstruction, and septic thrombophlebitis. Loss of vascular access in some groups of patients, especially those receiving life-saving chemotherapy, can be devastating.

CONCLUSION

The incidence of UEDVT is increasing as a result of the more frequent use of invasive cannulation. UEDVT is now recognized as a major cause of morbidity and mortality due to chronic venous insufficiency and the

Table 4. Complications of Upper Extremity Deep Vein Thrombosis

Brachial plexopathy
Chronic venous insufficiency
Loss of vascular function
Pulmonary embolism
Septic thrombophlebitis
Superior vena cava syndrome
Thoracic duct obstruction
Venous gangrene

risk for PE. Therefore, prompt recognition with appropriate diagnosis and treatment is essential. The management of these patients remains controversial. Options available include anticoagulation using warfarin or LMWH, thrombolysis, and surgical intervention. Further research in the form of controlled randomized trials is needed to address the many questions surrounding the treatment options available for UEDVT. **HP**

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