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EDITORIALS

# Upper extremity deep vein thrombosis – *current trends*

Ecaterina BONTAS[a], Delia TIMOFTE[b], Mario Parreno CAPARROS[c], Dorin IONESCU[d], Daniela BARTOS[e], Dan OLTEANU[f], Maria DOROBANTU[g]

[a]Registrar of Internal Medicine, Department of Internal Medicine & Cardiology, Clinical Emergency Hospital, Bucharest, Romania
[b]Specialist Registrar of Internal Medicine, Department of Nephrology & Dialysis, Universitary Emergency Hospital, Bucharest, Romania
[c]Specialist Registrar, Department of Internal Medicine, Universitary Hospital Virgen de la Arrixaca, SN Carretera del Palmar, Murcia, Spain
[d]Senior Lecturer of Internal Medicine, Department of Nephrology & Dialysis, Universitary Emergency Hospital, Bucharest, Romania
[e]Associate Professor, Department of Internal Medicine & Cardiology, Clinical Emergency Hospital, Bucharest, Romania
[f]Professor of Internal Medicine, Department of Internal Medicine I-II & Gastroenterology, Universitary Emergency Hospital, Bucharest, Romania
[g]Professor of Internal Medicine and Cardiology, Internal Medicine & Cardiology Department, Clinical Emergency Hospital, Bucharest, Romania

***ABSTRACT***

*Upper extremity deep vein thrombosis (UEDVT) refers to thrombosis of the axillary and/or of the subclavian veins of the thoracic aperture. Based on pathogenesis UEDVT is classified as primary and secondary. Primary UEDVT is a rare disorder represented by Paget-Schroetter syndrome (or effort-related thrombosis) and idiopathic UEDVT. Secondary UEDVT accounts for most cases and usually develops in patients with the presence of a central venous catheter, pacemakers, or cancer. Symptoms are usually present within the first 24 hours after the trigger episode, however partial venous occlusions may cause a slow down in diagnosis. Less than 50% of symptomatic patients have imaging evidence of an UEDVT. It has a significant morbidity because of pulmonary embolism and a high incidence of posthrombotic syndrome. Both conservative and surgery therapy (thrombectomy, systemic or catheter-directed thrombolytic therapy, balloon angioplasty followed by stenting) have value as options therapies.*

**Key words:** upper extremity, effort-related thrombosis, venous thrombosis, hypercoagulability

*Address for correspondence:*
Ecaterina Bontas, MD, 4 Mamulari Street, Bl. C2, Sc. 2, Ap. 52, District 3, Bucharest, Romania
email address: ebanir@yahoo.com

## BACKGROUND

Upper extremity deep vein thrombosis (UEDVT) describes the thrombosis of the axillary and/or subclavian veins from the level of the thoracic aperture. Although deep venous thrombosis is common in the lower limbs, it rarely occurs in the upper limbs (1). Prior to 1967, thrombosis of the UEDVT was reported in about 2% of deep venous thrombosis cases (2). Alternatively, since 1970s the number of published data about detection of UEDVT has been increased (3,4). It should be emphasized that UEDVT is regarded as the most familiar vascular condition among athletes (5,6). As already noted, Kroger et al. (4) reported that around 0.2% of hospitalized patients may develop UEDVT. Over the last few decades the published reports found in 4% of cases with deep venous thrombosis the association with the thrombosis of the upper extremities (7). However even if now nearly 10% of all episodes of venous thrombosis are due to UEDVT (8), there is no published information regarding the rate of recurrence of UEDVT.

Based on pathogenesis, UEDVT is classified as primary and secondary **(Table 1)**. Primary UEDVT is a rare disorder with 2 cases per 100,000 persons per year (5), and is represented by (1) Paget-Schroetter syndrome (effort-related thrombosis) or (2) idiopathic UEDVT. Secondary UEDVT represents the most common diagnosis, with an obviously dominance of cases due to the presence of a central venous catheter (7). ❑

## PRIMARY UEDVT

Primary UEDVT occurs in the absence of the risk factors, and is recognized in about 30% of cases (9). It has two forms:

1. Paget-Schroetter syndrome (effort thrombosis),
2. idiopathic UEDVT.

| Primary UEDVT (5): | Secondary UEDVT (1,7,8) |
|---|---|
| • Paget-Schroetter syndrome (effort thrombosis)<br>• Idiopathic UEDVT | • central venous catheters<br>• pacemakers<br>• cancer<br>• chemotherapy<br>• collagen disease<br>• growth colony stimulating factors<br>• inherited thrombotic risk factors |

**TABLE 1.** The aetiology of upper extremity deep venous thrombosis (UEDVT)

Primary axillary-subclavian vein thrombosis or Paget-Schroetter syndrome classically involves younger patients, and accounts around 4 to 12% of thoracic outlet syndrome (10). Paget-von Schröetter disease is also known as „Paget-Schröetter syndrome", „Schröetter's syndrome", „von Schröetter syndrome", axillary vein traumatic thrombosis, effort thrombosis, intermittent venous claudication, primary thrombosis of the upper extremity, thrombosis venae axillaries, or traumatic thrombosis of the axillary vein. Regardless of the mechanisms, primary UEDVT should always be differentiated by thoracic outlet syndrome (10).

Paget-Schroetter syndrome of upper extremity was described independently by Sir Paget in 1875 (11) and von Schroetter in 1884 (12). After that, Hughes coined in 1948 the term Paget-Schroetter syndrome based on 320 cases (13). In keeping with the aforementioned data, the Paget-Schroetter syndrome frequently arise in the dominant arm of healthy males between the ages 18 and 50 years, after intense activities (rowing, wrestling, weight lifting, and baseball pitching) or with no clear cause (14). The most used explicatory mechanism for developing of primary UEDVT is repetitive strong exercise that causes microtrauma to the vascular intima (15). Furthermore, temporary elevation of the levels of factor VIII and von Willebrand factor during the intense physical effort triggers the activation of the coagulation cascade.

In contrast to patients with Paget-Schroetter syndrome, patients with idiopathic UEDVT develop thrombosis with unknown trigger factor in 20% of episodes (8). It was a matter of debate but not confirmed that UEDVT is commonly associated with occult cancer. Looking back to one study, one fourth of patients presenting with idiopathic UEDVT were diagnosed with cancer, most commonly being lung cancer or lymphoma within 1 year of follow-up (16). With respect to these findings, cancer is not a cause of idiopathic UEDVT. ❑

## SECONDARY UEDVT

UEDVT should no longer be regarded as a rare and benign disease (8). Patients with secondary UEDVT have generally precipitating factors such as the indwelling central venous catheters, transvenous pacemakers, local tumour, cancer, chemotherapy, collagen disease, administration of growth colony stimulating

factors, or inherited thrombotic risk factors (8). Up to now published data sustains the occurring of the clinical evidence of venous obstruction in 3% to 40% of patients with central venous catheters (17). The most common risk factors associated with thrombosis formation due to central venous catheters include size of the catheter, and the site of catheter insertion (19). Other studies nearly 10% of the patients who received chemotherapy through peripherally inserted central catheters developed thrombosis (19). The association of malignancy with UEDVT is also well-established, and it was reported in 45% (20) to 64% of patients (21). Recent information offered by the RIETE registry sustain that UEDVT is a serious complication in patients with cancer, with a high incidence of recurrences and bleeding complications (22). Not surprisingly, Park J et al. reported a case of extensive venous thrombosis of the upper extremity in a patient with a hyperosmolar hyperglycemic state (7). Curiously, the incidence of UEDVT is estimated to be 0.08-0.11% of treatment cycles in women undergoing assisted reproductive techniques (23). Finally, it is important to bear in mind that the event of thrombosis to an unusual anatomic site may be the first sign of the hypercoagulable state (24). The published studies support antiphospholipid antibodies (lupus anticoagulant and anticardiolipin antibodies) as the most common acquired thrombophilic factors (24,25). Up to now the most prevalent genetic risk factors for the hypercoagulable state are factor V Leiden and prothrombin G20210A mutation, and lesser for deficit of protein C, or protein S (25, 26). Meanwhile, Ruggeri et al. reported a low prevalence of anticoagulant protein deficiency in patients with UEDVT (27). In the same time, Martinelli et al., found a hypercoagulable state and hyperhomocysteinemia nearly in 15% of patients with UEDVT (24), and Prandoni et al. (20) reported a prevalence of 10-26% of inherited thrombophilic alterations in patients bearing UEDVT. It seems that the prevalence of antiphospholipid antibodies in patients with UEDVT varies from 3.7% to 26.8% (28,29), but more studies should be considered. Also, a higher rate of thrombosis recurrence is observed in adult patients diagnosed with primary UEDVT and thrombophilic factors (26) but more studies are necessary on this area. ❑

## DIAGNOSIS CRITERIA

The management guidelines of the deep vein thrombosis of the arm are well established (30). Symptoms such as pain, cramps, pruritus and paresthesia are non-specific, and on the other side patients may be full asymptomatic (6). On the other hand, the situations of vigorous subjects who develop a Paget-Schroetter syndrome with pulmonary hypertension as a result of pulmonary embolism are also common (31).

There is now clear evidence that sudden onset of arm swelling, pain, and/or venous engorgement is highly suggestive for UEDVT. Symptoms are usually present within the first 24 hours of the triggering episode, although not proven conclusively the partial venous occlusions may cause a slow down in diagnosis. Most patients' complaint is the pain described as a 'feeling of tightness' that getting worse with exertion; often associated with localized swelling to the arm and face, with visual or vestibular symptoms, or with tingling sensation on arm's hyperabduction. It is important to point out that the typically feature of UEDVT is swelling of the involved limb. The oedema characteristically involves the entire arm and hand, and is often no pitting. Mild cyanosis with or without a palpable cord can also be found at presentation. The low-grade fever is generally ascribed to thrombosis, but high-grade fever is more suggestive of septic thrombophlebitis. Other reported signs may be ecchymosis and non-oedematous swelling of the shoulder, arm, and hand; functional impairment; discoloration and mottled skin; and distension of the cutaneous veins of the involved upper extremity (6, 32). Abduction of the upper limbs, cervical extension, and dropping of the shoulders promotes rising of clinical manifestations. In the case of axillary vein thrombosis, collaterals will usually develop from the shoulder to the chest wall, whereas in thrombosis of the subclavian vein, collaterals will develop to the ipsilateral posterior neck or from the shoulder to the contralateral neck (33). Alternatively, localized erythema, palpable tenderness, and paraesthesias are non-specific and can occur in cellulites, lymphedema, and neoplastic compression of blood vessels, muscle injury, or superficial vein thrombosis, among other diagnoses.

Less than 50% of symptomatic patients have imaging evidence of an UEDVT (30). The

presence of thrombus may be established by duplex ultrasonography examination, venography, magnetic resonance angiography or computerized tomography (CT). Colour duplex ultrasonography is the best initial evaluation because it is non-invasive and has a high sensitivity and specificity (30). In turn, venography is still the 'gold standard' in evaluating subclavian-axillary vein thrombosis. This test is limited by the fact that a substantial percentage of the normal population may present with an abnormal finding during extreme arm abduction (33). Upper extremity venography is a cost-effective imaging examination, and a normal image for upper extremity venography should reveal bilateral, symmetric, rapid, and smooth radiolabeled radiotracer flow from the upper extremities to the central venous system. It should be emphasized that colour Doppler duplex sonography is the modality of choice for the diagnosis of central venous catheters – related UEDVT in symptomatic cancer patients and for screening for asymptomatic thrombosis in this specific population (34). Magnetic resonance imaging of the vessels and soft tissue is a non-invasive method for detecting thrombus and describing the local anatomy. In the presence of thrombosis, magnetic resonance angiography has good correlation with contrast venogram when the latter is contraindicated (35). The main advantage of contrast-enhanced multislice chest computer tomography (CT) for the diagnosing venous thromboembolism is that it may allow the detection of both pulmonary embolia and UEDVT (36). In contrast to ultrasonography, venous plethysmography can provide quantitative information about venous outflow function (37). Impendance plethysmography detects increased venous outflow resistance in the deep veins of the proximal lower extremities. The main limitation of impendance plethysmography is it may not distinguish between venous obstruction due to deep venous thrombosis, and also among obstructions from non-thrombotic lesions, such as haematoma or cancer. ❑

## DIFFERENTIAL DIAGNOSIS

The differential diagnosis is largely difficult because patients with UEDVT typically display compressive signs usually associated with thoracic outlet syndrome (32,38). Shortly, thoracic outlet syndrome refers to compression of the neurovascular bundle (the brachial plexus, subclavian artery, and subclavian vein) at the level of the thoracic aperture bordered by the scalene muscles, the clavicle, and the first rib **(Table 2)**. The syndrome has been attributed to cervical ribs, long transverse processes, first thoracic ribs, compression by the scalene muscles, broken clavicles, and tumours at the thoracic outlet. ❑

## PROGNOSIS AND COMPLICATIONS

Up to this time UEDVT was considered a benign and self-limited condition. Over the last years ongoing studies have demonstrated that UEDVT may have significant complications, including pulmonary embolism (PE), superior vena cava syndrome, loss of vascular access, and postthrombotic venous insufficiency (30,39).

UEDVT has a significant morbidity because of pulmonary embolism (30) and a high incidence of posthrombotic syndrome. Therefore

| UEDVT | Thoracic outlet syndrome |
|---|---|
| – symptoms: shoulder or neck heaviness;<br>– signs: arm or hand oedema, supraclavicular fullness, dilated cutaneous veins, palpable cord, upper extremity cyanosis, jugular venous distension; | – symptoms: pain radiating to arm/forearm, hand weakness;<br>– signs: arm or hand atrophy, brachial plexus tenderness; positive Adson or Wright manoeuvre;<br>– Positive Adson manoeuvre: the examiner extends the patient's arm on the affected side while the patient extends the neck and rotates the head toward the same side. The test is positive if there is weakening of the radial pulse with deep inspiration, and suggests compression of the subclavian artery.<br>– Positive Wright manoeuvre: the patient's shoulder is abducted and the humerus is externally rotated. The test is positive if symptoms are reproduced with the failing of the radial pulse; and suggests compression of neurovascular structures in the subcoracoid region by the coracobrachialis and short head of the biceps. |

**TABLE 2.** Differential diagnosis between UEDVT and thoracic outlet syndrome (6)

7%-9% of patients with UEDVT have been reported to develop acute pulmonary embolism (39). Concomitantly, the pulmonary embolism was reported in 2.5% of patients with subclavian vein thrombosis (40). Apart from these data, up to one third of the patients develop pulmonary embolism with possible fatal course (8). Postthrombotic syndrome and recurrent thromboembolism are also frequent complications (8). Based on the available data, it seems that about 30% of patients diagnosed with UEDVT develop postthrombotic syndrome (41). On the other side, recurrent disabling symptoms may occur in up to 75% of patients. The occurrence of postthrombotic syndrome correlates to the ipsilateral venous thromboembolism recurrence and high body mass index (1). Finally, UEDVT is very unusual characterized by complications as stasis dermatitis and ulceration, venous gangrene, and upper-extremity phlegmasia cerulea dolens. ❑

## MANAGEMENT OF UEDVT

Prompt diagnosis of deep venous thrombosis allows right treatment and improves the clinical outcome of the patient with UEDVT. The initial measures based on rest and elevations of the affected limb followed by anticoagulation are usually used. Both conservative and surgery therapy (thrombectomy, systemic or catheter-directed thrombolytic therapy, balloon angioplasty followed by stenting) are common alternative treatments for UEDVT. From the physician's standpoint, the optimal management of subclavian vein effort thrombosis is still a problem because of missing approved treatment guidelines.

Anticoagulation is the basis of the management of UEDVT with the mainly objective to prevent further propagation of thrombus (5). The most physicians advised for using in deep vein thrombosis therapy of unfractionated heparin or low molecular weight heparin as initial step, followed by the acenocoumarol therapy. The current standard is 6 months of oral anticoagulation (6,30). The anticoagulation is from 12 months to lifelong in the case of recurrent idiopathic events, or in the case of the first event associated with any of the following – cancer, homozygous form of thrombophilic defect, heterozygous for two thrombophilic defects, antiphospholipid antibodies, or deficiency of antithrombin, protein C or S. In case of central venous catheter carriers, unfractionated or low molecular weight heparins followed by oral anticoagulants should be regarded as the treatment of choice, whereas thrombolysis and surgery may be indicated only in selected cases (8).

It is interesting that recent studies have supported the safety and efficacy of catheter-directed thrombolysis in patients with no contraindication to thrombolytic therapy, and have recommended early catheter-directed thrombolysis (7). Unfortunately, patients receiving chemotherapy through peripherally inserted central catheters are at increased risk of thrombosis. Therefore we should not ignore the role for prophylactic low-dose anticoagulation in these high-risk patients (19). An intense anticoagulation and surgery interventions are indicated in younger and active patients with Paget-Schroetter syndrome which have a significant risk for developing long-term complications.

Thrombolysis may restore venous flow early, reducing damage to the vessel endothelium with decreasing the risk of long-term complication. Contraindications include active bleeding, neurosurgery within the preceding 2 months, a history of hemorrhagic stroke, hypersensitivity to the thrombolytic agent, and surgery within the preceding 10 days. The risks for systemic side effects due to thrombolysis are reduced by the method of catheter-directed thrombolysis. Catheter-directed thrombolysis should be considered in healthy patients, for patients with symptomatic superior vena cava syndrome or those who need to maintain a central venous catheter. The surgical procedures include thrombectomy or reconstruction by autologous vein grafting. Thrombectomy should be done within 48 hours from the onset of obstruction. Alternative procedures utilized in the UEDVT are resection of the first rib, intravenous placing of a metallic stent, and balloon venoplasty (39).

Women with inherited thrombophilia have a greater risk of UEDVT in case of concomitantly using of oral contraceptives **(Figures 1,2,3)** (26). Therefore, discontinuation of oral contraceptives after a first episode of UEDVT should be recommended in women with inherited thrombophilia (26). Meta-analyses have shown LMWH (eg enoxaparin 1.5mg/kg/24h SC) to be superior to unfractioned heparin. At the present, conservative measures are the most common approach. Once UEDVT develops in

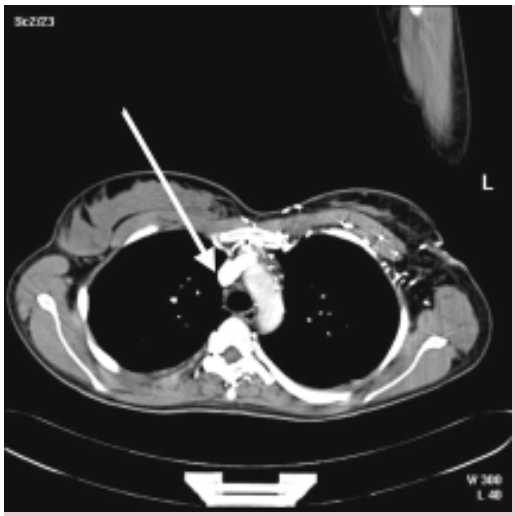

**FIGURE 1.** CT scan of 23-years-old woman with thrombosis of left brahiocephalic trunk (increased confluence of left and right brahiocephalic veins – see white arrow)

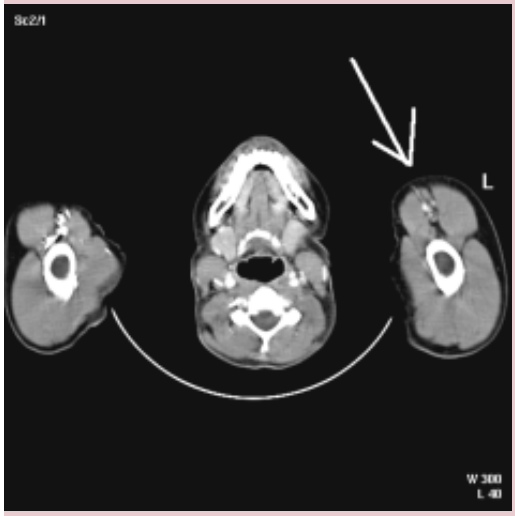

**FIGURE 2.** CT scan of 23-years-old woman with thrombosis of left brahiocephalic trunk (oedema of left upper extremity – see white arrow)

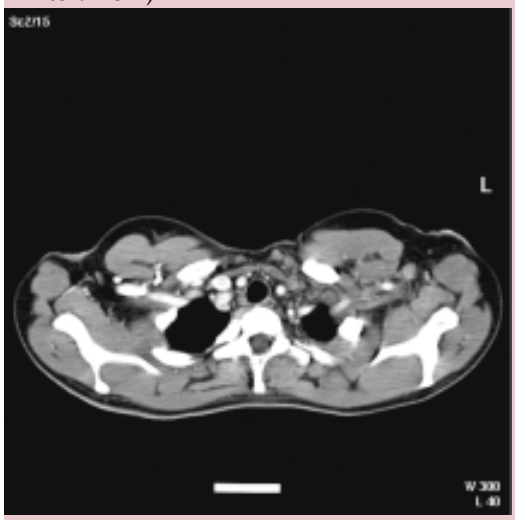

**FIGURE 3.** CT scan of 23-years-old woman with thrombosis of left brahiocephalic trunk (see white arrow)

cases of pregnant women due to assisted reproductive techniques, anticoagulation treatment should be rapidly set up (23). Based on the available data, long term treatment with low molecular weight heparin (LMWH) is ideal for pregnant women. The preferred LMWH for pregnant women are dalteparin (therapeutic dose = 100U/kg twice daily, or prophylactic dose = 5000U daily) and enoxaparin (therapeutic dose = 1 mg/kg twice daily or 1.5mg/kg daily, and prophylactic dose= 40mg daily). It is generally recommended that therapeutic doses of unfractioned heparin or LMWH be continued throughout pregnancy. In case of pregnant woman, anticoagulant therapy starts with unfractioned heparin, and after 12 weeks change to a prophylactic dose of LMWH and continue with this dose until labour. Later than 4-6 hours after delivery, prophylactic doses of unfractioned heparin or LMWH should be started about 4-6 hours after delivery if significant bleeding has stopped. Common practice in many medical settings is to use LMWH during pregnancy, with either LMWH or oral anticoagulant for six to 12 weeks after the birth. Anticoagulant treatment should be continued at least until the patient is outpatient. For patients in the puerperium period but with history of thromboembolism, full dose oral anticoagulant therapy is necessary. Moreover, compared with hospitalization for intravenous unfractioned heparin, outpatient use of LMWH is uniformly efficient, safe, and less costly. ❑

## SUMMARY

- Venous thromboembolism is a multifactorial disease in which inherited and acquired risk factors are involved.
- UEDVT are less common than lower extremity deep venous thrombosis.
- UEDVT is considered as the most familiar vascular condition among athletes.
- Venography is still the gold standard in evaluating subclavian-axillary vein thrombosis.
- Less than 50% of symptomatic patients have imaging evidence of an UEDVT.
- At the present, conservative measures are the most common approach.
- The initial measures based on rest and elevations of the affected limb followed by anticoagulation are usually used.
- Once UEDVT develops in cases of pregnant women due to assisted reproductive techniques, anticoagulation treatment should be rapidly set up. ❑

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