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Janine Dörffler-Melly

Clinic of Angiology,
University Hospital of Zurich, Switzerland

Diagnostic strategies in deep venous thrombosis

Summary

The modalities to diagnose deep venous thrombosis (DVT) have improved substantially over the past decade. The contemporary diagnostic approach has shifted to an algorithm that includes the combination of clinical pre-test probability, non-invasive imaging, and D-dimer testing. Such algorithms are not only focused on accurate diagnosis of DVT but on identification of low-risk patients who do not need antithrombotic therapy. This article reviews the various diagnostic tests and their incorporation into a useful diagnostic algorithm.

Key words: deep venous thrombosis; diagnosis; D-dimer

Zusammenfassung

Die diagnostischen Möglichkeiten der venösen Thromboembolie haben sich innerhalb der letzten zehn Jahre deutlich gewandelt. Aktuelle Abklärungsalgorithmen basieren auf der Einschätzung der klinischen Vortest-Wahrscheinlichkeit kombiniert mit einer nichtinvasiven Bildgebungsmethode und dem D-Dimer-Test. Solche Algorithmen erlauben nicht nur eine treffsichere Diagnostik der tiefen Beinvenenthrombose, sondern auch die Identifizierung von Patienten mit niedrigem Risiko, welche keiner antithrombotischen Therapie bedürfen. Der vorliegende Artikel gibt einen Überblick der verschiedenen diagnostischen Methoden und deren Integrierung in einen nützlichen diagnostischen Algorithmus.

Key words: tiefe Venenthrombose; Diagnose; D-Dimer

Introduction

Deep venous thrombosis (DVT) is a common condition affecting 2 to 3 per 1000 individuals in Europe per year. DVT increases with age, and 1/100 among the population aged more than 70 years are affected each year [1, 2]. Consequences of untreated DVT at the acute stage are thrombus propagation and pulmonary embolism; chronic complications include recurrent thrombosis, post-thrombotic syndrome (PTS) and chronic pulmonary hypertension [3–6]. Fast and accurate diagnosis of DVT allows immediate treatment and improves the clinical outcome. Conversely, it is important to identify low-risk patients in whom anticoagulation can safely be withheld.

DVT does not cause unique clinical symptoms, and clinical findings are both insensitive and non-specific [7–9]. Additional information on the presence or absence of individual risk factors for VTE can improve clinical prediction considerably [10]. However, the clinical presentation combined with the presence of individual risk factors allows to stratify patients into high, moderate, and low pre-test probability categories [11]. Additionally, when pre-test probability is combined with objective diagnostic imaging and D-dimer testing, accuracy of thrombosis detection or exclusion can be further improved. This article provides an overview on assessment of pre-test probability for acute symptomatic DVT, imaging tests, and D-dimer. Asymptomatic DVT, recurrent events, and other specific clinical scenarios are also discussed.

Clinical probability and risk factor assessment for the diagnosis of DVT

Acute symptomatic proximal DVT

Difficulty in diagnosing DVT is based on the presence of non-specific symptoms in many

Correspondence:
Janine Dörffler-Melly, MD, PhD
Clinic of Angiology
University Hospital of Zurich
Rämistrasse 100
CH-8091 Zurich
Switzerland
E-Mail: janine.doerffler@usz.ch

patients. Symptoms are sometimes misleading due to the possibility of non-thrombotic extravascular disease mimicing signs of DVT. The differential diagnosis of pelvic and lower extremity DVT includes haematoma, ruptured Baker's cyst, lymphedema, cancer, and postthrombotic syndrome. Common non-thrombotic differential conditions are listed in table 1. Typical clinical signs of DVT include spontaneous leg pain, swelling of the leg, pitting edema, livid skin colour, formation of superficial venous collaterals, and tenderness along the deep venous system during overextension of the foot (Homan's sign) (table 2).

Table 1
List of the most frequent diagnoses causing leg edema.

Differential diagnosis of DVT
Haematoma
Baker's cyst
Pulled muscles or tendons
Postthrombotic syndrome
Lymphedema
Compartment syndrome
Cardial, renal, hypoproteinaemic edema
Lymphangitis
Erysipela
Superficial thrombophlebitis
Lumbar and ischiatic pain

Table 2
List of clinical signs that are associated with deep venous thrombosis.

Clinical signs suggestive for DVT
Spontaneous pain within 5 to 7 days of DVT onset
Swelling of the extremity
Pitting edema
Livid skin colour
Formation of superficial venous collaterals
Homans' signs

Based on the presence of clinical signs and adding further known individual risk factors for VTE, categories of estimated pre-test probability have been prospectively evaluated by Wells et al. using a clinical score (table 3) [11]. Risk factors such as cancer, immobility, and postoperative states have been included in the score, whereas age, cardiac, pulmonary and renal disease, or thrombophilic disorders, such as Factor V Leiden mutation or antiphospholipid antibodies were not integrated in the score.

A further step in improving accuracy of acute symptomatic proximal DVT diagnosis on an evidence-based level was the adoption of an algorithm that combines objective testing with the estimation of clinical pre-test probability. Wells et al. suggested an algorithm based on the determination of pre-test probability and compression ultrasound (CUS) screening. A negative D-dimer test is highly sensitive for the exclusion of VTE [12] and was integrated into the algorithm as shown in figure 1. For patients with atypical signs of DVT and a negative D-dimer test result, post-test probability is low, allowing the exclusion of DVT. When D-dimer testing is positive, CUS or colour coded duplex sonography (CCDS) should initially be performed to accurately exclude or confirm DVT (fig. 1). In patients with suspected DVT, serial CUS can be avoided if the D-dimer test is negative [13]. For high and medium pre-test probability, however, first-line sonographic assessment already allows DVT detection in the majority of patients, whereas in cases of negative sonographic findings, an additional negative D-dimer test allows exclusion of acute proximal DVT. In a patient with a high pre-test probability in combination with a positve D-dimer test and a negative CUS, magnetic resonance (MR) imaging or multislice computed tomography (CT) may be used to diagnose pelvic DVT (fig. 1).

Table 3
The Wells Score for the prediction of clinical probability of DVT [11].

Clinical feature	**score**
Active cancer	1
Paralysis, recent plaster cast of lower extremity	1
Recent immobilisation or surgery (≥7 days or surgery within <4 weeks)	1
Tenderness along entire deep vein system	1
Swelling of entire leg or Calf swelling (>3 cm difference compared with other leg, 10 cm below the tibial tuberosity)	1
Collateral superficial veins	1
Pitting edema	1
Alternative diagnosis more likely	–2
High probability	**≥3**
Moderate probability	**1–2**
Low probability	**≤0**

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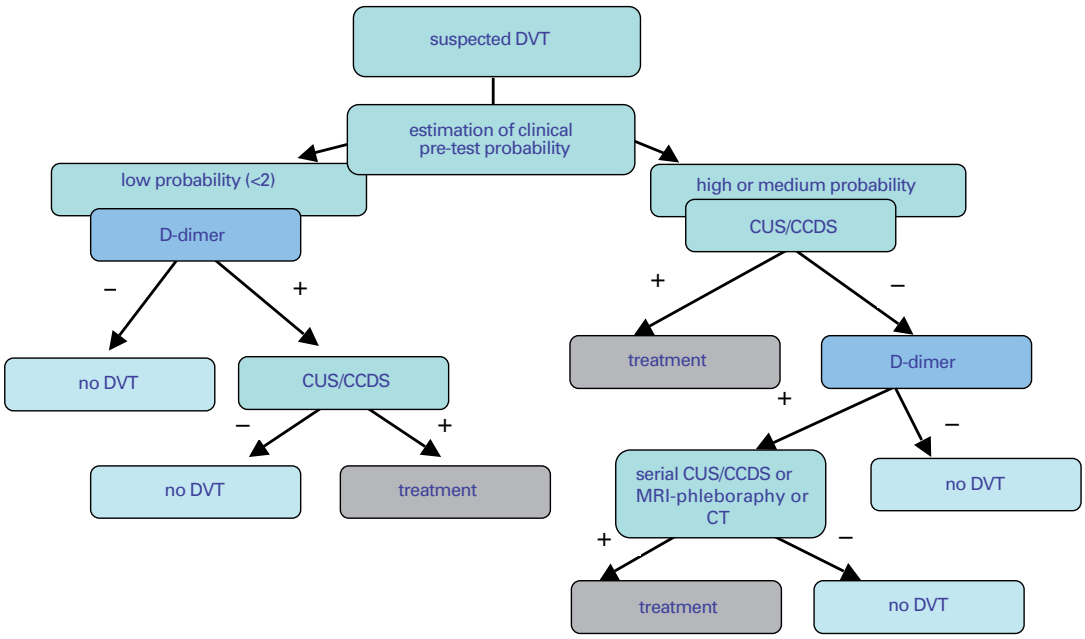

Figure 1
Diagnostic algorithm for DVT screening.

Lower leg thrombosis

The strategy by Wells et al. focuses on the exclusion of *symptomatic proximal* DVT, ie the proximal venous segments of the pelvic region, groin and thigh, including the popliteal vein. *Until recently, symptomatic distal* DVT was considered less important because of its low risk of pulmonary embolisation. The need to diagnose and treat isolated calf vein thrombosis was controversial for many years [14]. Serial CUS testing approximately one week after presentation was considered sufficient for detecting thrombus propagation to the popliteal vein. The authors of the Seventh American College of Chest Physician (ACCP) Conference on Antithrombotic and Thrombolytic Therapy recommended antithrombotic treatment for *all* patients with DVT, including symptomatic distal DVT [14, 15].

Asymptomatic DVT

Asymptomatic DVT is often diagnosed when DVT is found accidentally on ultrasound, CT, or MR ordered for other reasons than suspected DVT. The need for accurate diagnosis of suspected *asymptomatic DVT* also occurs in a clinical scenario when a patient suffers acute pulmonary embolism (PE) and concomitant DVT that was diagnosed during the same CT study that was performed to confirm PE. Justification for DVT screening in patients with acute PE is, that the treatment of lower extremity DVT includes compression therapy to diminish the risk for PTS even in asymptomatic patients. Detection of asymptomatic DVT, however, is associated with considerably lower sensitivity for both ultrasound and D-dimer testing. Orthopedic patients should be classified as a jeopardised group because postoperative asymptomatic DVT after hip or knee arthroplasty often remains undetected. CUS or CCDS have poor sensitivity to detect DVT due to wound-related leg swelling or haematoma, and assessment by contrast phlebography or non-invasively by MRI or CT phlebography is superior.

Recurrent DVT

Recurrent DVT is a frequent clinical problem as reflected by the 5-year-recurrence-rate of idiopathic DVT of approximately 25% [16]. Clinical differentiation between acute and chronic DVT is difficult. Moreover, diagnostic algorithms are not always helpful, because D-dimer testing is confounded by the presence of comorbidities. The precise thrombus extension during the primary event is important for identifying new thrombus formation. MRI can be a useful alternative for detecting recurrent DVT [17].

Upper extremity DVT

Upper extremity DVT is often seen in patients with central venous catheters (75%), it occurs spontaneously in patients with an effort-induced thrombosis (Paget von Schrötter syndrome). Patients with cancer may present with upper extremity swelling from cancer-associated venous compression of the superior vena cava or subclavian vein. CUS or CCDS might be useful as a first screening method in acute symptomatic thrombosis with sensitivities of

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75 to 100% [18, 19], but a low sensitivity of only approximately 30% for the central subclavian region in asymptomatic patients [20]. For both methods, the superior vena cava and the central part of the brachiocephalic vein are inaccessible. MR- or CT-phlebography are the most sensitive non-invasive diagnostic tools in this situation.

Objective testing methods

Imaging

Contrast venography

Among the imaging modalities, none has a 100% accuracy, including the "gold standard" contrast venography with 98.8% sensitivity (CI 95.6–99.8%). This procedure is invasive, technically sophisticated, requires the injection of a contrast medium and often is painful. Therefore, non-invasive diagnostic tools have replaced conventional phlebography for diagnosing symptomatic patients.

Real-time compression ultrasound and colour coded duplex sonography

Real-time compression ultrasound (CUS) and colour coded duplex sonography (CCDS) are non-invasive, cheap, easily available screening tools for acute symptomatic proximal DVT with high sensitivity and specifity for proximal symptomatic DVT, ranging from 89 to 100% for both CUS and CCDS, but only 73 to 87% for calf vein thrombosis [21]. One major disadvantage of CUS is that it does not provide acceptable accuracy for iliac or caval thrombosis. CCDS uses full compression of the target vein as principal criterion for the detection of DVT like CUS. CCDS is used at regions with restricted visibility, including the pelvic region or in the calf veins. Its main advantage over CUS is that partial thrombosis with remaining marginal flow can be detected more accurately. Both methods are operator and patient dependent. Figure 2 shows an acute thrombosis with a marginal flow in the femoral vein as visualised by CCDS.

MRI phlebography

MRI phlebography is the preferred imaging tool when the diagnosis is uncertain after a non-conclusive CUS or CCDS. The visualisation of thrombi by MRI in the pelvic region appears to be more reliable. Moreover, MRI allows detection of PE and of DVT of the lower extremities simultaneously. It is also suitable to diagnose venous compression by extravascular entities. Contraindications to MR imaging include certain metallic devices, obesity, and claustrophobia [17, 22].

Contrast-enhanced multislice chest computer tomography (CT)

The main advantage of CT for diagnosing venous thromboembolism (VTE) is that it allows the detection of both PE and proximal DVT [23–25]. In postoperative or intensive care patients, CT may be preferred over CUS or CCDS.

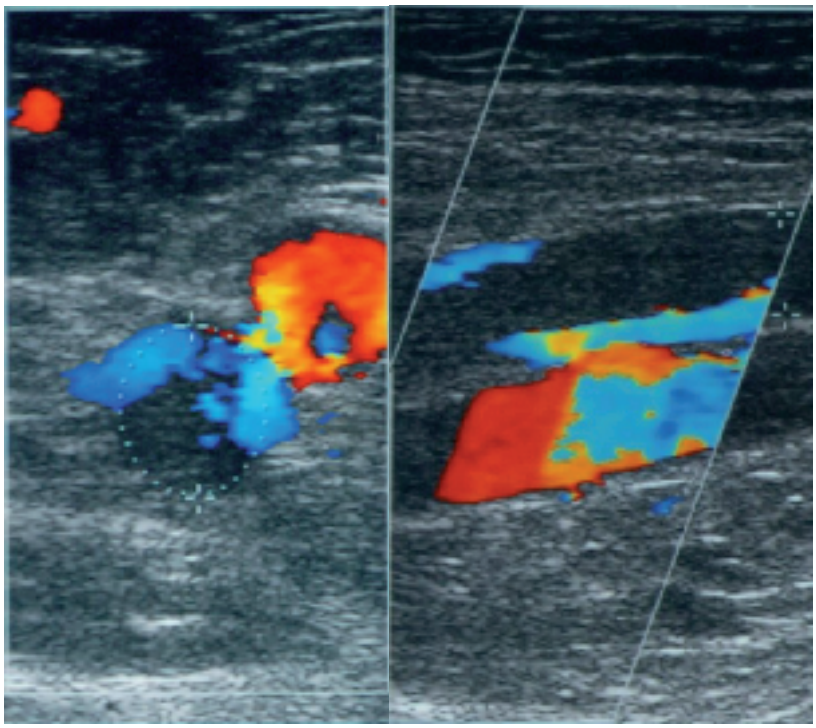

Figure 2
Superficial vein thrombosis with marginal flow (blue) as presented by colour coded duplexsonography. The neighbouring artery is contrasted in red.

Impendance plethysmography (IPG)

IPG detects increased venous outflow resistance in the deep veins of the proximal lower extremities. The main limitation of IPG is its unspecificity; it does not distinguish between venous obstruction due to DVT and obstructions from non-thrombotic lesions, such as haematoma or cancer. The method has limited sensitivity, as its application is bound to validated equipment and specific protocols. If accurately used, sensitivity reaches 90% for proximal symptomatic DVT, but only 30% for asymptomatic DVT [21]. The method is not widely used as a primary diagnostic screening tool for suspected acute DVT in Switzerland, but is considered as more suitable for the quantification of chronic venous obstruction as in PTS.

D-dimer assessment

D-dimer is a sensitive fibrin degradation protein that is released into the circulation during fibrinolysis and is used as a thrombosis marker. Other markers of activated coagulation or fibrinolysis have insufficient sensitivity to be used as screening tool for DVT. Among the various D-dimer assays, the quantitative VIDAS ELISA assay (Biomerieux, France) is the best documented and most sensitive assay. It is a fluorescence-based immunoassay that can be performed within less than one hour. The reported sensitivity ranges from 98 to 100% at a cutoff of 550 ng/ml in venographically proven DVT [12]. As an acute phase protein, it is, however, unspecific and only useful to exclude DVT by a negative result in combination with high or medium pre-test probability.

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