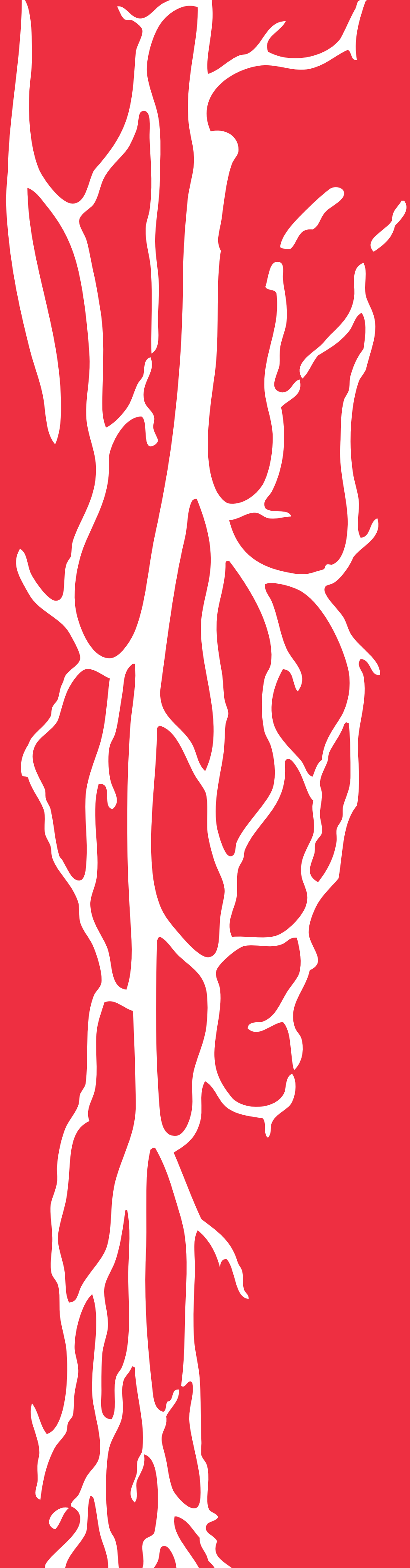
Deep vein thrombosis : diagnostic and prognostic challenges

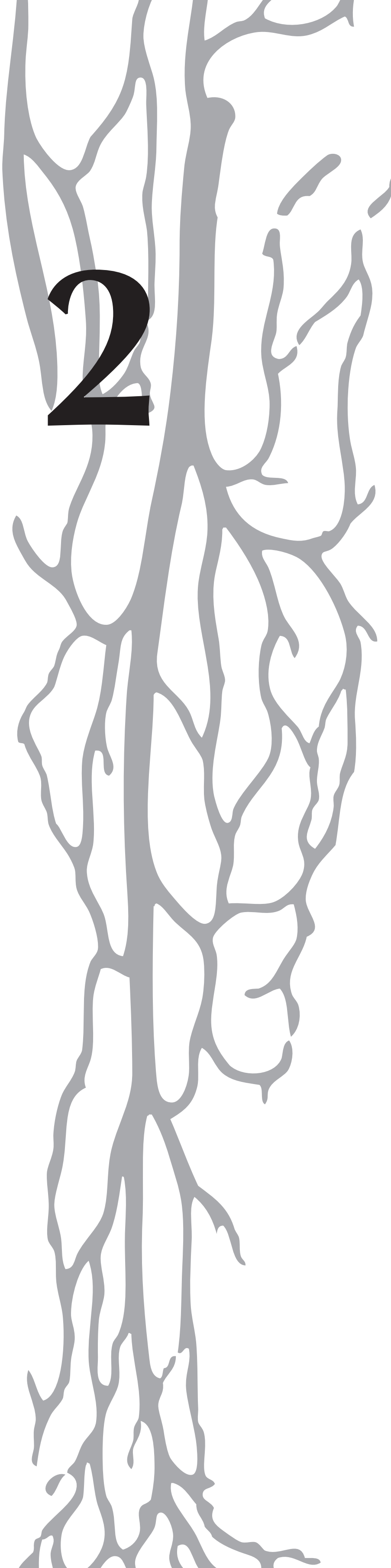
Dronkers, C.E.A.

Author: Dronkers, C.E.A.
Title: Deep vein thrombosis : diagnostic and prognostic challenges
Issue Date: 2019-01-08



Part 1

Challenges in diagnostic management and imaging of deep vein thrombosis



2

Current and future perspectives in imaging of venous thromboembolism

C.E.A. Dronkers, F.A.Klok and M.V. Huisman

Journal of Thrombosis and Haemostasis 2016; 14:1696-710

ABSTRACT

Several thrombus imaging techniques for the diagnosis of venous thromboembolism (VTE) are available. The most prevalent forms of VTE are deep vein thrombosis of the lower extremities and pulmonary embolism. However, VTE may also occur at more unusual sites such as deep veins of the upper extremity and the splanchnic and cerebral veins. Currently, the imaging techniques most widely used in clinical practice are compression ultrasonography and Computed Tomography Pulmonary Angiography (CTPA). Moreover, Single Photon Emission Computed Tomography (SPECT), CT venography (CT-V), Positron Emission Tomography (PET) and different MRI techniques, including Magnetic Resonance Direct Thrombus Imaging (MRDTI), have been evaluated in clinical studies. This review provides an overview of the technique, diagnostic accuracy and potential pitfalls of these established and emerging imaging modalities for the different sites of venous thromboembolism.

INTRODUCTION

Over the past decades, techniques for imaging of venous thromboembolism (VTE) have rapidly evolved. Traditionally, contrast venography was standard of reference for diagnosing deep vein thrombosis (DVT) of the extremities and conventional invasive pulmonary angiography for pulmonary embolism (PE).[1,2] These techniques have been replaced by compression ultrasonography (CUS) and Computed Tomography Pulmonary Angiography (CTPA).[3,4] To standardize the diagnostic process, imaging tests have been implemented in diagnostic algorithms that have been proven safe and efficient in clinical practice.[5]

CUS and CTPA are however not suitable for all patients with suspected VTE. CUS is, for example, not appropriate in patients with plaster casts, for the subclavicular part of the arm veins, or in splanchnic or cerebral veins. Moreover, the difficulty of making a distinction between chronic residual thrombosis and acute recurrent DVT remains challenging.[6,7] To overcome these shortcomings, new imaging techniques have been developed and tested, such as single-photon emission computed tomography (SPECT), CT venography (CT-V), positron emission tomography (PET), and different magnetic resonance imaging (MRI) techniques. In this review, we will provide an overview of the current available and emerging imaging techniques for VTE and briefly discuss the advantages and limitations of these modalities at different thrombus sites (DVT, PE, Upper Extremity Deep Vein Thrombosis [UEDVT], Splanchnic Vein Thrombosis (SVT) and Cerebral Vein Thrombosis [CVT]) (**table 1**). It is beyond the scope of this review to describe diagnostic algorithms, which have been well described elsewhere,[8,9] as well as to consider the relative costs and cost-effectiveness of different diagnostic modalities, either as stand-alone test or within the context of these diagnostic algorithms. However, test availability, costs and safety are important considerations in choosing diagnostic tests.

Ultrasonography

Technique

Ultrasonography (US) is widely accepted as the primary diagnostic procedure for the work up of suspected DVT of the leg. Ultrasound images are created by the turnaround time of sound waves. Using the images to directly diagnose clots has varying success because clot echogenicity is variable and unpredictable, and a fresh clot is often anechoic.[10] With compression US(CUS), veins are compressed with the ultrasound probe. In the absence of a DVT, gentle pressure with the probe causes the venous lumen to collapse. The lack of compressibility of a venous segment under the ultrasound probe is diagnostic for DVT (**Fig. 1**).[11]

Table 1. Overview of available imaging techniques for different locations of venous thrombosis.

Thrombus location	Available Techniques: CUS	CT	SPECT	MRI	PET	Test of choice	Future perspectives
Deep veins of the leg [3,59,76,93]	Se:94%(93-95) Sp:94%(93-94) L: Detection of recurrent DVT	Se:96%(93-98) Sp:95%(94-97) L: radiation dose		Se:92%(88-95) Sp:95%(93-97) L: low availability, long imaging time	Se: 88% Sp:100%[#] L: technique has to be further developed	CUS (2-point or whole-leg)	MRDTI for recurrent ipsilateral DVT
Deep veins of the arm[32,87]	Se:82%(70-93) Sp:82%(72-92) L: compression not possible due to overlying bone	Se: unknown Sp: unknown L: not enough evidence		Se:71%(29-96) Sp:89%(52-100) L: no accuracy		CUS	MRDTI for inaccessible vein segments
Pulmonary artery (acute PE)[37,84,100]	Se:87% (79-92) Sp:82%(71-89) L: small amount of accessible lung area	Se:83%(76-92) Sp:96%(93-97) L: contrast allergy + CI-AKI,radiation dose	Se:83%(61-95) Sp:98%(92-100) L: not validated in a prospective management study	Se:78%(67-86) Sp:99%(96-100) L: high proportion of inconclusive scans	Se: unknown Sp: unknown L: technique has to be further developed	CTPA	MR-PA, Molecular MRI with target specific- contrast agents for reduction of radiation
Pulmonary artery (CTEPH)[52,86]		Se:76%(69-82) Sp:96%(93-98) L: not diagnostic for CTEPH as single test		Se: 83%(77-85) Sp: 99%(89-99)* L: low accuracy from segmental arteries		VQ lung scanning/ DSA	MR techniques for reduction of radiation
Abdominal/ pelvic veins [36,88]	Se:89%(55-99) Sp:92%(88-94)* L: low accuracy due to overlying bowel gas	Se: unknown Sp: unknown L: radiation dose		Se:100%(93-100) Sp:98%(93-98)* L: low evidence		CTV	MRDTI for more accurate diagnosis
Cerebral veins[69]		Se: 75-100% Sp: 82-100% L: low sensitivity		Se: unknown Sp: unknown L: false positives due to artefacts		MRV	MRBTI for direct visualisation of the thrombus

Se, sensitivity; Sp, specificity; L, limitations; CUS, compression ultrasonography; CTV, computed tomography venography; SPECT, single-photon emission tomography; MRI, magnetic resonance imaging; PET, positron emission tomography; MRDTI, magnetic resonance direct thrombus imaging; DSA, digital subtraction angiography; MRV, magnetic resonance venography; MRBTI, magnetic resonance black-blood thrombus imaging; PE, pulmonary embolism; DVT, deep vein thrombosis; CTEPH, chronic thromboembolic pulmonary hypertension *Confidence intervals derived from original article # Confidence interval not derivable from original article

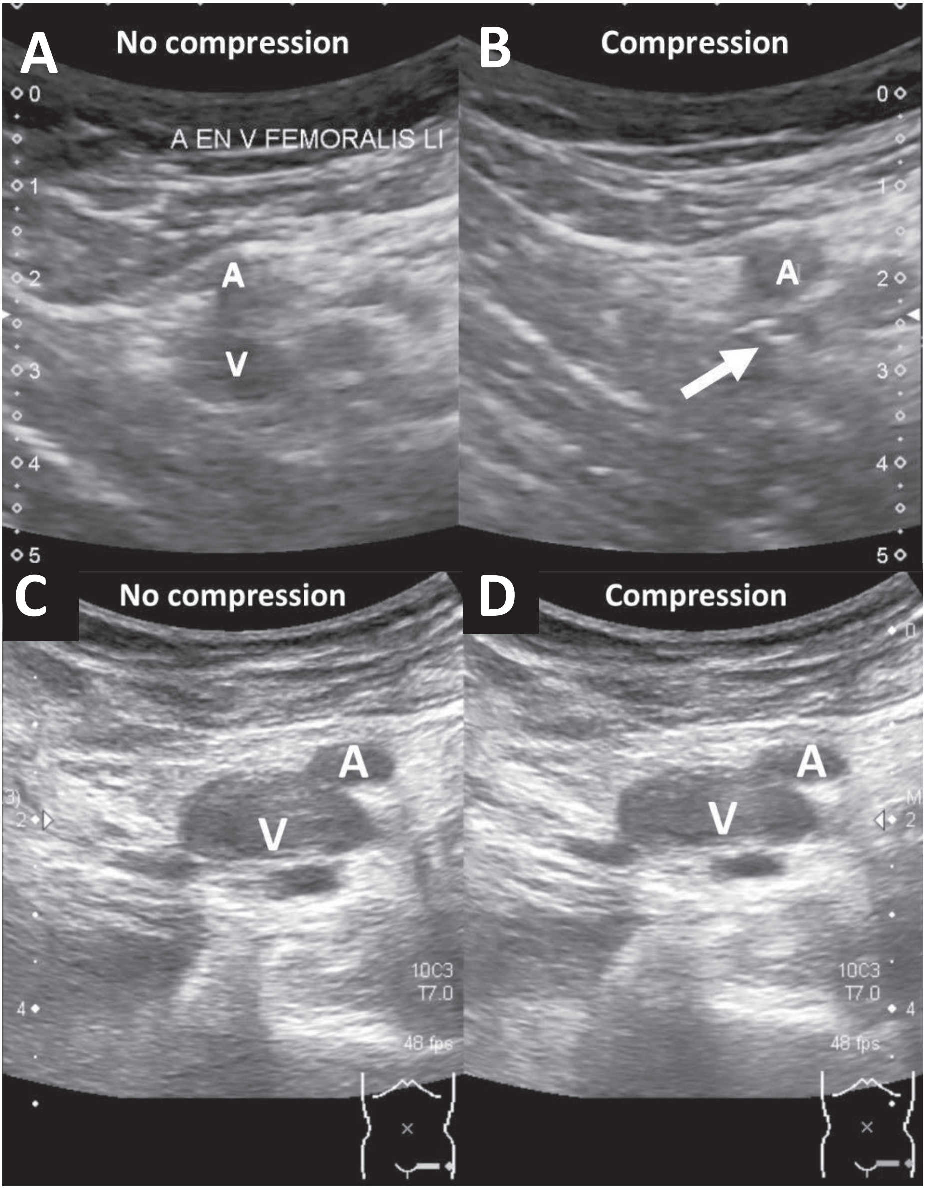


Figure 1. (A,B) A 66-year-old female patient presenting with suspected deep vein thrombosis (DVT). Compression ultrasonography of the left upper leg in axial view at the level of the femoral vein showing good compressible common femoral vein (white arrow), excluding DVT.
(C,D) A 64-year-old female patient with oesophagus carcinoma presenting with suspected DVT. Compression ultrasonography of the left upper leg in axial view at the level of the femoral vein showing incompressible common femoral vein, indicating DVT. A, artery; V, vein.

Color-coded Doppler US may serve as additional technique in the diagnosis of thrombosis. It provides visualization of flow, color-coded for velocity and direction. Absent or partially absent color-coded flow is diagnostic for thrombosis.[3,12] Using Doppler US, proximal vein segments in the pelvis and abdomen that are difficult to assess with CUS may be evaluated.[11]

DVT of the leg

The two most applied US approaches are two-point or whole-leg CUS.[3] With the former, only the proximal veins in the groin and in the popliteal fossa are investigated. Main advantages of this strategy are its simplicity, reproducibility and broad availability. Its major limitation is the need to repeat the test within 1 week in patients with normal findings at presentation, in order to detect extension of non-visualized distal thrombosis to the proximal veins.[3] The advantage of a single whole-leg CUS of the entire deep venous system is the ability to exclude or diagnose DVT in one single examination. The disadvantages of this technique are that it is time consuming and needs experienced operators.[13] Importantly, more patients are subjected to treatment after whole-leg CUS than after two-point CUS because up to 50% of DVTs diagnosed with whole-leg CUS are isolated calf vein thrombi, of which the relevance is uncertain.[1415]

The two strategies were proved to have equal safety in two studies. The first was a trial in 2098 patients with suspected DVT, of whom 1045 patients were randomized to a repeated two-point CUS and 1053 to a single whole-leg CUS. The 3-month incidences of symptomatic VTE in patients with a normal initial test were comparable: 0.9% (95% confidence interval [CI] 0.3-1.8%) vs 1.2% (95% CI 0.5-2.2%).[16] In another study, 1002 patients with suspected DVT were randomized to two-point CUS or whole-leg CUS after application of a clinical decision rule (CDR) and D-dimer test.[17] The 521 patients (52%) with likely probability or abnormal D-dimer were referred for CUS. During 3-month follow-up, the VTE incidence in patients with normal two-point or whole-leg CUS was comparable: 2.0% vs 1.2% ($P=0.69$). The accuracy of use of color-coded Doppler US only for the diagnosis of DVT has been evaluated in a meta-analysis by Goodacre *et al*., showing a sensitivity of 81.7% (95% CI 77.4-85.5%) and a specificity of 92.7% (95% CI 89.7-95.1%).[3]

Recurrent DVT of the leg

Ultrasound for the detection of suspected contralateral recurrent DVT has comparable sensitivity (89-100%) and specificity (87-100%) compared with first suspicion of DVT, because of the very low risk of chronic non-symptomatic thrombus remains in the contralateral leg.[8,18] The diagnostic management in patients with suspected ipsilateral recurrent DVT is more challenging because of the high prevalence of residual thrombi, which has been estimated to be 50% at 1 year after the index diagnosis despite anticoagulation treatment.[19] Accurate distinguishing US features of acute and chronic DVT are lacking. Consequently, CUS is frequently inconclusive in patients with a suspected recurrent ipsilateral DVT.[20] One of the solutions for this diagnostic problem is performing a reference CUS at the end of treatment for the first DVT, to map the location and extent of the thrombotic remains.[21] Ipsilateral recurrent DVT may be diagnosed with some certainty in case of a new non-compressible venous segment, or a pronounced increase in vein diameter (≥2-4 mm) of a previously uncompressible vein compared with the reference CUS.[21,22] In clinical practice, however, this reference CUS is frequently unavailable and interobserver agreement on measurement of residual vein diameter has been reported to be moderate.[23]

Pulmonary embolism

A frequently asked question is whether it is useful to perform CUS among patients presenting with symptoms of PE to eliminate the need for CTPA when DVT can be objectivised. It has been shown that residual DVT is lacking in the majority of PE patients, suggesting that the entire thrombus has already been embolized to the lungs.[24] A prospective management study in 511 patients with suspected PE demonstrated that the sensitivity of CUS of the lower extremities for the presence of PE on CTPA was only 39% (95% CI 32-46%) with a specificity of 99% (95% CI 97-100%).[25] In another study, it has been shown that distal US has an even lower accuracy for predicting PE with a sensitivity of 22% (95% CI 17-29%) and a specificity of 94% (95% CI 91-96%).[26]

It has been suggested that US examination of the lung may also be used in the diagnosis of acute PE. The surface of the lung can be examined on standardized longitudinal sections along the intercostal spaces for the presence of subpleural infarcts, which consist of pleural-based, well-demarcated echo-poor triangular or rounded consolidations.[27] Transthoracic ultrasonography (TUS) has been suggested to have a sensitivity of 74% and a specificity of 95% for PE.[28] Also, TUS may be applied in a diagnostic strategy including lower extremity CUS and echocardiography which may improve its sensitivity.[27,29]

The main drawbacks of TUS are the small amount of accessible lung areas (about 66%), inability to well-visualize aerated lungs, and limited approach because of overlying bony structures. Also, outcome studies are currently lacking, although the results of a prospective study using multi-organ US as part of the diagnostic algorithm of PE are pending(NCT02190110).

Upper extremity deep vein thrombosis

The term Upper Extremity Deep Vein Thrombosis (UEDVT) covers thrombosis in the veins of the upper extremity (brachial, axillary and subclavian), neck (jugular) or central thoracic veins (brachiocephalic and superior caval). UEDVT is relatively uncommon and comprises 4% of all VTE diagnoses.[30] The primary limitation of CUS for UEDVT is that veins may be inaccessible for compression due to overlying anatomical structures. Colour-coded Doppler US may then be used to visualize intraluminal thrombi or abnormal flow patterns. A systematic review summarized 17 studies using US for UEDVT, although the total number of patients was limited and the methodological quality of the studies was low because venography was not used as a reference test in all patients. The summary estimates of sensitivity and specificity of (C)US were 97% (95% CI 90-100%) and 96% (95% CI 87-100%) and for CUS combined with Doppler were 91% (95% CI 85-97%) and 93% (95% CI 80-100%).[31] The most recent study in this systematic review included the largest patient population (126 patients) and compared CUS combined with Doppler to reference standard invasive contrast venography. Compared with the reference standard, the sensitivity and specificity of (C)US were 82% (95% CI 70-93%) and 82% (95% CI 72-92%) respectively. Venous incompressibility correlated well with thrombosis (100%), but only 50% of isolated flow abnormalities were thrombosis related.[32] The use of CUS in a diagnostic algorithm starting with a CDR and D-dimer testing was recently evaluated in a prospective management study, for an overall failure rate of 0.4% (95% CI 0.0-2.2%). Seven of 406 patients (1.7%) had indeterminate US-results. In six of these seven patients, the diagnosis could be completed with repeated US after 3-5 days and one patient required contrast venography. This algorithm can be used in standard clinical practice, although external validation is needed for a higher level of evidence.[33]

Splanchnic vein thrombosis

Splanchic vein thrombosis (SVT) includes portal vein thrombosis (PVT), mesenterial vein thrombosis (MVT), splenic vein thrombosis, and the Budd-Chiari syndrome (BCS). The incidence of SVT varies from 0.5-1/million (BCS) to 0.7-2.7/100.000 (PVT, MVT).[34,35]

For suspected MVT, Doppler US is not accurate due to overlying bowel gas and CTA and CE-MRV should preferably be performed. Although no thorough accuracy studies have been performed in patients with clinically suspected SVT, according to an older study, sensitivity and specificity of Doppler US for suspected PVT was 89% and 92% respectively.[36]

Computed tomography

Technique

Computed tomography involves computer-processed imaging acquired from combinations of consecutive X-ray projections taken from different angles to produce cross-sectional slices of specific areas of the scanned part of the body.

Pulmonary embolism

CTPA is regarded the primary imaging test for diagnosing patients with suspected PE. After the application of iodinated intravenous contrast material, CTPA enables direct visualisation of endovascular abnormalities including luminal clots. Diagnostic criteria for acute PE by CTPA are: (i) failure of contrast material to fill the entire lumen of an artery (central filling defect), (ii) partial filling defect surrounded by contrast material on a cross-sectional image, (iii) contrast material between the central filling defect and the artery wall on an in-plane, longitudinal image, and (iv) a peripheral intraluminal filling defect that forms an acute angle with the artery wall (**Fig 2.**).[37]

Figure 2. A 39-year-old female patient presenting with dyspnoea, chest pain, and tendency to collapse, leading to suspicion of pulmonary embolism. The computed tomography pulmonary angiography in axial orientation shows a 'saddle' pulmonary embolus at the pulmonary artery bifurcation (black arrow) and large central emboli in the left and right main pulmonary arteries (white arrows).

First generation single-detector-row helical CT scanners had a specificity of 90% but a low sensitivity (70%) for acute PE.[38] The introduction of multidetector-row CT scanners has improved the visualization of segmental and subsegmental pulmonary arteries.[39] CTPA studies using multidetector-row CT scanners have showed excellent sensitivity of 96 to 100% and specificity of 97 to 98%.[37,40,41] A normal CTPA result alone can safely exclude PE in all patients in whom CTPA is required to rule out this disease without the need for additional US to rule out DVT.[5,42] The main advantage of multidetector-row CT scanners is that they are widely available. Scan times have been reduced to 4-5 seconds with 64-slice scanners.[43] Another advantage of CTPA is the possibility to detect an alternative diagnosis that may explain the patient's complaints.[44,45] A prospective study in 203 consecutive patients reported an alternative diagnosis in 88 patients (43%); however, only with therapeutic consequences in 10 (4.9%).[46] Limitations of CTPA include the use of iodinated contrast agent, which is a relative contraindication in patients with previous moderate-to-severe allergic reaction to iodinated contrast agents (occurring in 0.7% of patients). Also, the use of iodinated contrast is associated with a risk of (temporary) contrast-induced nephropathy (occurring in 8.9-12% of patients).[6,47] Second, the radiation dose of a single CTPA ranges from 3 to 5 mSv, with an estimated 150 excess cancer deaths/ 1 million.[41] In the last decades, the proportion of detected subsegmental PE with multidetector CTPA increased from 4.7% to 9.4% compared to single- detector CT. This increased incidence of subsegmental PE with CTPA has been associated with a lower severity of illness and lower mortality in the CTPA era.[48,49] These peripheral intraluminal filling defects may not represent true thrombus but could be imaging artefacts with uncertain clinical significance. Indeed, small observational studies have suggested that these subsegmental PEs may not need anticoagulant treatment.[50] An ongoing study in which patients with symptomatic subsegmental PE and no DVT or cancer are left untreated and followed for 3 months will provide more clarity on this matter (NCT01455818).

CTEPH

For reasons still unknown, in some patients acute PE does not resolve completely despite adequate anticoagulation treatment. These unresolved, chronic emboli may ultimately lead to small-vessel arteriopathy, high pulmonary vascular resistance, pulmonary hypertension and right heart failure, a rare condition called chronic thromboembolic pulmonary hypertension (CTEPH). CTEPH is a severe disease with a poor prognosis unless detected in an early stage and anatomic favourable (proximal) location, allowing for successful surgical removal of the chronic clots. Combined with right heart catheterization which is necessary for accurate confirmation of pulmonary hypertension, selective digital subtraction angiography (DSA) has been the traditional method for diagnosing CTEPH and assessing its operability.[51]

Currently, contrast-enhanced CTPA can be used in the diagnostic work-up of CTEPH. Specific findings of CTEPH are dilatation of the central pulmonary arteries, the detection of organized wall-adherent fibrotic material, intraluminal webs and bands, vessel wall irregularities, abrupt vessel cut-offs, complete vessel occlusions and abnormal proximal-to-distal vessel tapering (**Fig. 3**). Compared with DSA, the sensitivity of CTPA for the detection of CTEPH is reported to be 95% (95% CI 92%-97%) at the level of the main and lobar arteries, and 88% (95% CI 87%-90%) at the segmental level, with associated specificities of 96% (95% CI 94%-97%) and 89% (95% CI 87%-91%) respectively.[52] Contemporary CT techniques (i.e. dual-energy and 320-slice CT machines) may even further increase the sensitivity for the segmental arteries.[53,54] Even so and in contrast to planar ventilation/perfusion V/Q lung scan, operable CTEPH may not be excluded by normal CTPA alone. Therefore, the recommended first-line imaging test in the diagnostic work-up of suspected CTEPH is V/Q scintigraphy.[51]

Single photon emission tomography (SPECT)

Pulmonary embolism

Planar V/Q scintigraphy was the first imaging test to replace invasive pulmonary angiography for the diagnosis of acute PE.[55] Perfusion imaging involves an intravenous

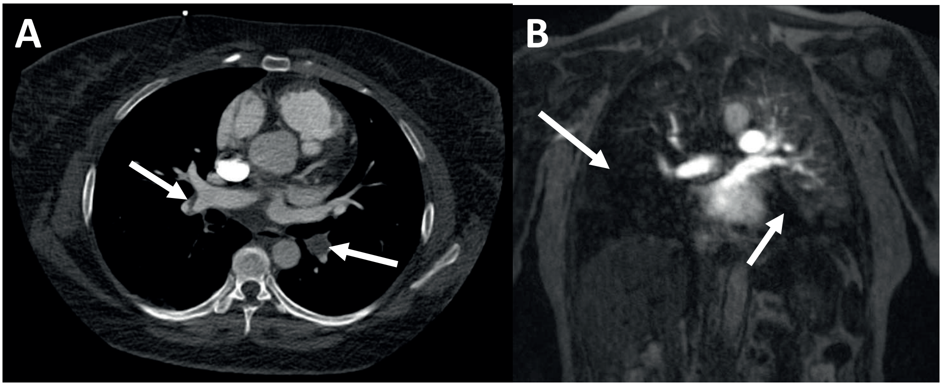


Figure 3. (A) Computed tomography-pulmonary angiography of a patient with chronic thromboembolic pulmonary hypertension (CTEPH). Left white arrow indicates central 'webs' in the lower lobe artery. Right white arrow indicates total occlusion of the left lower lobe artery.
(B) Magnetic resonance pulmonary angiography (twist protocol) of a patient with CTEPH. Left white arrow indicates a total perfusion defect of the right middle and lower lobe, right arrow indicates a perfusion defect of the left lower lobe.

injection of technetium labelled macro-aggregated albumin (^{99m}Tc-MAA). These radioactive particles are small enough to be trapped in the pulmonary capillary bed. The ventilation scan is performed using an inhaled radiopharmaceutical to obtain a pattern of lung ventilation. Acute PE is diagnosed in case of a V/Q mismatch: a thrombus within a pulmonary artery results in reduced perfusion to that lung segment while the alveolar air spaces in the same region remain relatively well aerated. Planar V/Q scintigraphy is a two-dimensional technique: posterior, anterior, oblique and sometimes lateral views are acquired.[56] The main drawback of this technique is the high proportion of non-diagnostic scans in 28-46% of patients.[48] This is because of areas of lung overlap and 'shine through' can occur between segments, which can mask perfusion defects.

SPECT represents a new era in nuclear medicine, which is based on a three-dimensional technique, allowing views in the transverse, coronal and sagittal planes.[56] To date, no large prospective outcome studies evaluating the safety of withholding anticoagulant treatment in patients with normal SPECT have been performed. In a retrospective study the accuracy of SPECT was evaluated in 2328 consecutive patients with suspected PE. SPECT was feasible in 99% of the patients. Based on clinical decision at baseline by expert opinion and 6-month follow-up, sensitivity was quantified as 99% and specificity as 98%. The main drawback of this retrospective study is the lack of reference diagnostic test, which may cause overestimation of the accuracy.[57] A review on 19 studies that comprised 27 data sets including 6393 examinations from 5923 patients concluded that planar V/Q scintigraphy was inferior to both V/Q SPECT and CTPA, with no difference between the latter two. Area under the Curve (AUC) of the Receiver Operating Characteristic (ROC) curves were: 0.85 (95% CI 0.75-0.95), 0.99 (95% CI 0.96-1.0) and 0.98 (95% CI 0.94-1.0) respectively. Advantages of SPECT are the avoidance of iodinated contrast agent injections and the lower overall radiation burden (1.2-2 vs. 3-5 mSv). CTPA, however takes less time to perform, is more cost-effective, and is more widely available. The application of SPECT may be considered in situations where radiation dose is of concern, such as in young female patients, although future outcome studies should be performed before the technique can be recommended for use in day-to-day clinical practice.[58]

CT venography

DVT of the leg

There are a few situations in which CUS is technically impossible to perform, such as in patients with plaster casts. CT venography (CT-V) has the potential to fill this gap. A meta-analysis pooled the sensitivity and specificity of 13 studies comparing CT-V with US for the diagnosis of lower leg DVT, although most of these studies included patients with suspected PE who -in the majority of cases- had no symptoms or clinical signs of DVT. The summary estimate of sensitivity was 95.9% (95% CI 93.0-97.8%) and of specificity 95.2% (95% CI 93.6-96.5%) indicating comparable diagnostic accuracy.[59] One study compared CT-V directly with invasive contrast venography in 52 patients and showed a sensitivity of 100% (95% CI 92-100%) and a specificity of 96% (95% CI 84-98%).[60] Because CUS and CT-V have comparable diagnostic accuracies, CT-V should be reserved for only those situations in which CUS is impossible to perform.[8]

Upper extremity deep vein thrombosis

CT-V can also be used to detect thrombi within the jugular veins, the brachiocephalic veins and the superior vena cava.[61] Importantly, no large studies with CT-V in patients with arm vein thrombosis have been performed. Only one small study in 18 consecutive patients showed a good correlation of CT-V with digital subtraction venography. All the 24 stenotic sites demonstrated with digital subtraction venography were also identified with CT-V.[62]

Splanchnic vein thrombosis

Using CT, incidental cases of SVT are increasingly found. The prevalence of incidental SVT found in a retrospective review was 1.7%.[63] Signs suggestive of intestinal ischemia, such as thinning or thickening of the intestinal wall, lack of mucosal enhancement after contrast injection, or the presence of intramural gas, may be detected (**Fig. 4**).[64] To our knowledge, accuracy studies using CT-V have not been performed in patients with clinically suspected SVT.

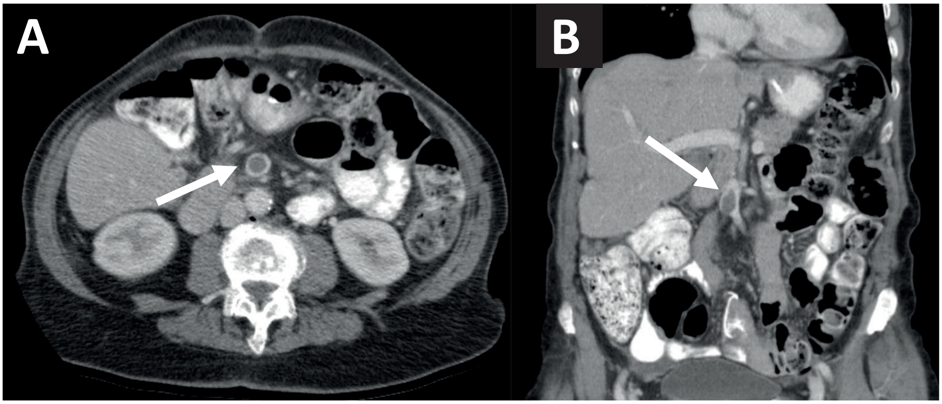


Figure 4. A 79-year-old female patient known with extra-ovarian cancer, presenting with heavy abdominal pain suspected for bowel ischemia. Computed tomography in portal-venous contrast phase showing superior mesenteric vein thrombosis in axial view (arrow in A), and coronal view (arrow in B).

Cerebral vein thrombosis

The cerebral venous system consists of the deep venous system, the dural venous sinuses and the superficial venous system. For the diagnosis of cerebral vein thrombosis (CVT), MRI in combination with contrast enhanced- magnetic resonance venography (CE-MRV) is considered to be the gold standard. CT-V may be a good alternative because of its more widespread availability and shorter imaging time.[65] A further advantage is the possibility to rule out other acute cerebral disorders such as cerebral infarcts or hemorrhages. A non-enhanced CT scan may show the thrombus as a hyperintense signal in one of the cerebral veins ('dense clot sign'). A thrombosed cortical vein can be seen as a linear or cord-like density ('cord sign').[66] The 'empty delta sign' can be detected in 30% of patients with thrombosis of the superior sagittal sinus.[67] This sign consists of a triangular area of enhancement (due to venous collateral circulation surrounding the thrombosed sinus) with a low-attenuating center, which is the thrombosed sinus. More often, in 60-80% of patients with CVT, CT shows only indirect signs of CVT such as brain edema and venous infarction.[68] CT-V has been directly compared to CE-MRV in three small studies. The largest study included 50 patients with suspected CVT and reported a sensitivity of 75-100% and a specificity of 82-100%, depending on thrombus site.[69-71] An example of CVT is shown in **Fig. 5**.

MRI

Technique

With MRI, a magnetic field and pulses of radiowave energy are used to create images of the body.

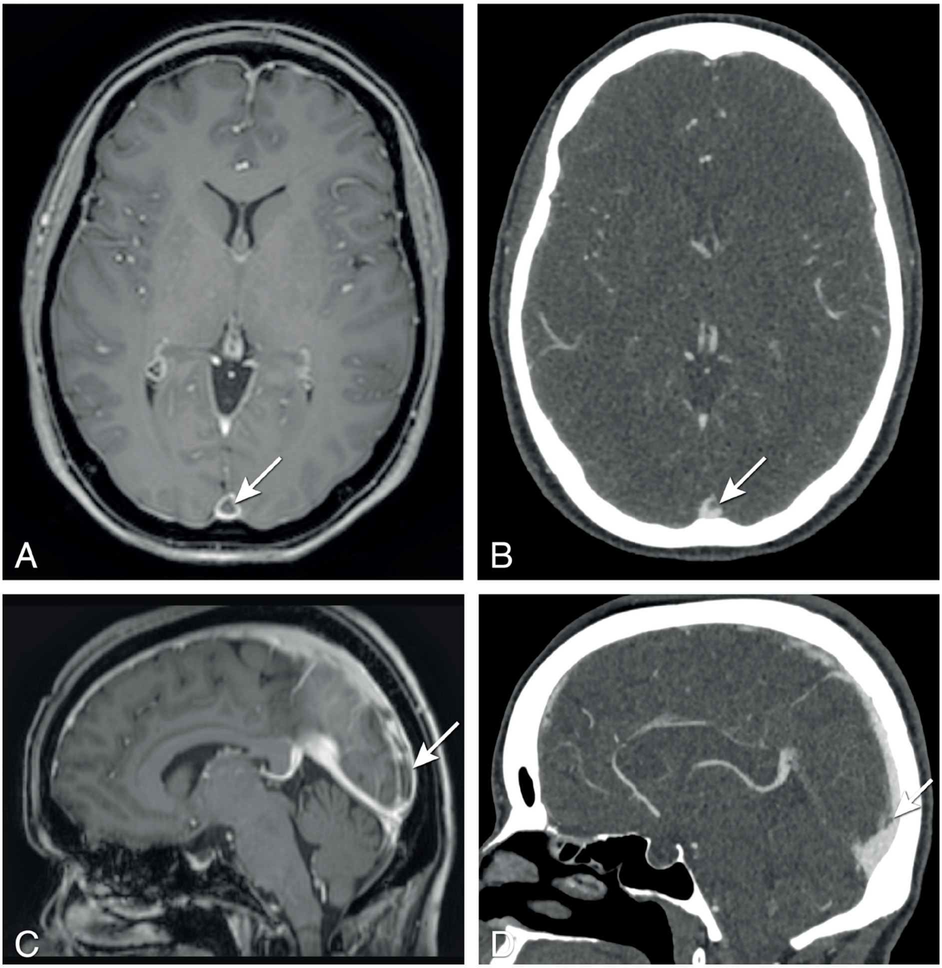


Figure 5. A 32-year-old female with systemic lupus erythematosus and history of pulmonary embolism presenting with 1-week duration of headache. (A,C) Three-dimensional T1-weighted magnetic resonance angiography after gadolinium administration. TE 4.59 ms, TR 9.79 ms, slice thickness 1.2 mm. (B, D) Computed tomography-angiography with iodinated contrast. (B)Axial view. (D) Sagittal view. Filling defect is present in the occipital region of the superior sagittal sinus, representing sagittal sinus thrombosis (arrows) at initial MRI diagnosis (A and C). One week after treatment most of the thrombus has resolved, note residual thrombosis on CT (B and D).

DVT of the leg

Different specific MRI techniques can be used to visualize DVT of the leg. The most described techniques are phase-contrast venography and Time of flight (TOF) venography, which can be used to visualize flow within vessels, without the need of contrast material.[72] Phase-contrast venography is based on using the change in phase shifts of the flowing protons in the region of interest to create an image. Phase-contrast venography was used to study 100 patients with a suspected upper or lower extremity DVT, with contrast venography as reference standard. The sensitivity was 90% and the specificity 100%.[72] With TOF imaging, a high repetition time is used (high rate of radiofrequency pulses) favouring the inflow effect of blood.[73] This technique was tested in 43 patients with clinical suspicion of DVT. Compared with contrast venography, the sensitivity was 100% and the specificity 94%.[74] Both techniques, however, are rarely used because of the long imaging time.

CE-MRV uses a gadolinium based contrast agent. The use of contrast agents increases the vascular signal by shortening the T1 relaxation time. For the so-called indirect approach, gadolinium-based contrast agent is administered via the antecubital vein and imaging is performed when contrast arrives at the tissue level of interest.[75] Direct CE-MRV uses a diluted contrast agent that is injected upstream on the side of the affected extremity. This technique resembles conventional venography and can visualize the full deep and superficial venous system. The most important pitfalls of CE-MRV are, first, the dark intraluminal filling defect that may be masked by the bright signal of blood surrounding the thrombus and, second, insufficient dilution of contrast agent that can induce a T2 shortening effect that can simulate a thrombus.[76] A meta-analysis of 14 MR diagnostic accuracy studies including TOF, phase contrast and CE-MRV techniques reported a summary estimate sensitivity of 91.5% (95% CI 87.5-94.5%) with an interstudy range of 0 to 100%, and a specificity of 94.8% (95% CI 92.6-96.5%) with an inter-study range of 43 to 100%.[76] The large heterogeneity between the studies was caused by major differences in the applied MRI techniques. Of note, management studies using MR(-venography) as first-line test in the diagnostic management of suspected DVT have not been published so far. Hence, recommendations on its use cannot be made.

Another emerging MRI technique is Magnetic Resonance Direct Thrombus Imaging (MRDTI). MRDTI is based on the oxygenation of haemoglobin when blood clots, which results in the formation of methemoglobin. This acts as an endogenous contrast agent and appears as high signal when imaged using a T1-weighted MRI sequence (**Fig. 6**).[77] The MRDTI scan technique has been tested in several studies. A prospective study performed MRDTI scans in 101 patients with suspected DVT in whom the diagnosis was already proven or rejected by venography results. This resulted in an excellent diagnostic accuracy with a sensitivity of 97-100% and a specificity of 100% with good interobserver variability (κ statistic 0.89-0.98).[78] The high signal disappears completely after six months.[79] This characteristic is valuable in the diagnosis of recurrent ipsilateral DVT since it makes the distinction between residual thrombi and an acute recurrent DVT. In a recent study, it has been shown that MRDTI accurately differentiates patients with CUS-confirmed recurrent ipsilateral DVT and asymptomatic residual intravascular clots.[80] Therefore, MRDTI can likely be used as a single and conclusive diagnostic test in case of suspected recurrent ipsilateral DVT. A prospective, multicenter management

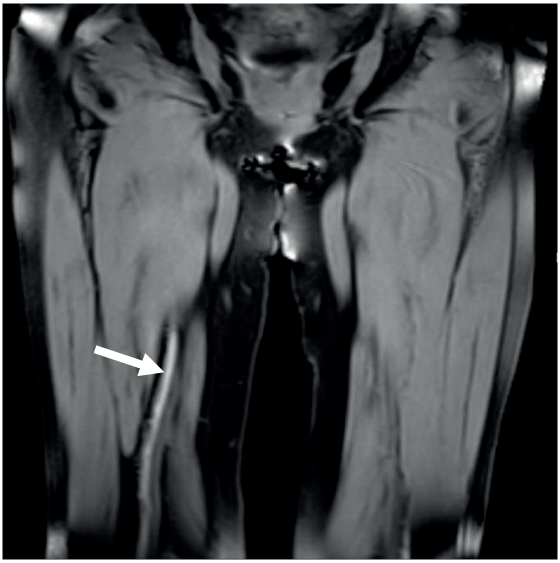


Figure 6. A 76-year-old female patient presenting with suspected ipsilateral recurrent deep vein thrombosis. Magnetic resonance direct thrombus imaging (MRDTI) showing high-signal intensity in the superficial femoral vein and popliteal vein of the right leg, indicating recurrent DVT (arrow).

study aiming to study 305 patients with suspected ipsilateral recurrent DVT managed based on the result of MRDTI only is under way(NCT02262052).

In the last years, new target specific contrast agents have been developed allowing for the use of selective molecular MRI. Targets examined for contrast imaging are fibrin and α2-antiplasmin. Animal models have been developed for fibrin-binding gadolinium-labelled peptides.[81,82] These have been tested in a phase 2 trial and were been shown to be applicable in humans without any adverse effects.[83] Larger prospective studies in humans are however needed.

Pulmonary embolism

Magnetic Resonance Pulmonary Angiography (MR-PA) is an attractive method for the diagnosis of PE because it avoids the use of ionizing radiation. With MR-PA, intravenous gadolinium is used, which can shorten the T1 signal of blood producing bright images of blood. A partially occlusive intraluminal filling defect or complete arterial occlusion with termination of the column of contrast material is diagnostic for PE.

Two large accuracy studies have been performed with MR-PA. The PIOPED III study was a prospective multicentre study that applied MR-PA in 371 patients with suspected PE.[84] The percentage of technically inadequate images was high with a mean of 25%. With CTPA as reference method, the sensitivity and specificity of the remaining technically adequate scans was 78% and 99% respectively. When technically adequate venography was included (52% had technically inadequate results), the sensitivity and specificity increased to 92% and 96%, respectively.[84] The second study was the IRM-EP study, in which 274 patients underwent both CTPA and MR-PA. A total of 30% had inconclusive

MRI results due to artefacts, poor opacification on angiographic sequences or the presence of isolated perfusion abnormalities. Sensitivity and specificity in the remaining patients varied between 79- 85% and 99-100% between the two readers.[85] In an attempt to improve the sensitivity of MR-PA, a study is currently investigating the accuracy of MRI in combination with lower extremity CUS(NCT02059551).

CTEPH

Because of its better safety profile compared with invasive digital subtraction angiography (DSA) and CTPA, the accuracy MR-PA has been investigated in patients with suspected CTEPH. As with acute PE, small studies have shown that MR-PA of the pulmonary vasculature is still inferior to DSA and CTPA from the level of the segmental arteries, with a sensitivity of 83% and a specificity of 99% compared with CTPA.[86] The current role of MR-PA in the work-up of CTEPH patients can be complimentary to DSA and/or CTPA, and used according to local experience in the CTEPH referral centers.[51]

Upper extremity deep vein thrombosis

The different MRI techniques that are used in the diagnosis of DVT can also be used for imaging of the upper extremity veins. In one study including 44 patients with suspected UE-DVT, TOF and CE-MRV were compared to contrast venography. The sensitivity of TOF was 71% (95% CI 29-96%) with a specificity of 89% (95% CI 52-100%). For CE-MRV, the sensitivity was 50% (95% CI 12-88%) with a specificity of 80% (95% CI 44-97%).[87] Both tests, thus, lack the accuracy to be of value in clinical practice.

Splanchnic vein thrombosis

For the diagnosis of SVT, CE-MRV is not the imaging test of choice because motion artefacts limit its accuracy. Even so, in a small case series of 36 patients with portal hypertension, CE-MRV was as accurate as DSA for the diagnosis of thrombosis of the portal, splenic or superior mesenteric veins, with the definite diagnosis confirmed in 22 patients by surgical validation or by means of consensus with the combined reading of the CE-MRV and DSA images in the remaining 14 patients. This resulted in a sensitivity and specificity of 100% and 98% respectively.[88] CE-MRV may, therefore, be a valuable diagnostic alternative in the (near) future in case of suspected abdominal or pelvic vein thrombosis, if these findings are confirmed in external cohorts.

Cerebral vein thrombosis

For thrombosis of the cerebral veins and sinuses, the diagnostic test of first choice is MRI in combination with magnetic resonance venography, although never reliably compared with angiography.[65] The thrombosed veins will appear isointense on T1-weighted images in the first five days, while the T2-weighted images are hypointense. After this period both T1 and T2 weighted images show increased signals at the thrombosis site. The combination with absence flow on flow magnetic resonance venography is diagnostic for thrombosis, although false-positive results due to artefacts may occur.[65,89,90] A recent study investigated the use of Magnetic Resonance Black-Blood Thrombus Imaging (MRBTI). This technique has similarities with the MRDTI technique, because it can assess the thrombus directly instead of visualization of the reduction of venous flow as result of the thrombus. MRBTI uses a T1 variable flip angle turbo spin-echo technique to nullify the intrinsic blood, leading to a hyperintense signal of the thrombus. MRBTI was performed in 23 patients with proven CVT and 24 patients with negative CVT according to conventional imaging techniques (MRI and CT-V). The sensitivity was 97.4% with a specificity of 99.3%.[91]

No studies have evaluated MRDTI in the diagnostic management of unusual vein thrombosis. Only one study reported that when applying total-body MRDTI for detecting the origin of acute PE in 99 patients, thrombi in superficial and abdominal veins were detected in five and three patients respectively.[24]

Positron Emission Tomography

Technique

The principle of PET with F-18 fluoro-2- desoxy-D-glucose (FDG) is based on accumulation of FDG, which occurs among other in activated leukocytes. Inflammation is linked with thrombus formation, due to accumulation of inflammatory cells within the thrombus and surrounding area.[92] This inflammation mechanism with associated FDG accumulation optionally enables imaging of VT with PET.

Deep vein thrombosis

In a study of 12 patients with proximal DVT, FDG PET/CT was accurate in detecting the thrombus, with a sensitivity and specificity of 87.5% and 100% respectively.[93] Although a recent published study including 62 patients with CUS-proved DVT confirmed the detectable higher metabolic activity in DVT, the optimal diagnostic cut-off is unknown and the reported sensitivity and specificity was much lower with values of 31% (95 % CI 24-39%) and 88% (81-92%) respectively.[94] As with MRDTI, the positive signal of FDG PET decreases over time after initiation of anticoagulant treatment. The proposed ability to differentiate acute from chronic clots in the leg veins may suggest a potential role of FDG-PET in the diagnostic workup of patients with suspected recurrent ipsilateral DVT.[95] Of note, its feasibility in clinical practice has to be evaluated, taking into account the necessary fasting period of 6 hours and the >1 hour waiting time after isotope administration before scanning.[96]

Pulmonary embolism

Several case-reports and retrospective studies have described incidental PE on FDG PET/CT images, mostly observed in cancer patients.[97,98] Preliminary results of a prospective observational study indicated disappointing accuracy of FDG/PET: only two of six PE patients showed notable FDG accumulation.[99] The study is recently completed, but results are not published yet (NCT01466426).

CONCLUSIONS

Today's main used thrombus imaging techniques -CUS and CTPA- are highly accurate and widely applied. Disadvantages of these two techniques nonetheless remain, leaving room for development of new imaging techniques for tomorrow's use. Currently, most of the emerging imaging modalities lack full validation and thus cannot (yet) be recommended for standard use in daily practice.

REFERENCES

1. Hull R, Hirsh J, Sackett DL, et al. Clinical validity of a negative venogram in patients with clinically suspected venous thrombosis. Circulation 1981;64:622-5.
2. WILLIAMS JR, WILCOX C, ANDREWS GJ, BURNS RR. Angiography in pulmonary embolism. JAMA 1963;184:473-6.
3. Goodacre S, Sampson F, Thomas S, van BE, Sutton A. Systematic review and meta-analysis of the diagnostic accuracy of ultrasonography for deep vein thrombosis. BMCMed Imaging 2005;5:6.
4. Mos IC, Klok FA, Kroft LJ, DE RA, Dekkers OM, Huisman MV. Safety of ruling out acute pulmonary embolism by normal computed tomography pulmonary angiography in patients with an indication for computed tomography: systematic review and meta-analysis. J ThrombHaemost 2009;7:1491-8.
5. van Belle A, Buller HR, Huisman MV, et al. Effectiveness of managing suspected pulmonary embolism using an algorithm combining clinical probability, D-dimer testing, and computed tomography. JAMA 2006;295:172-9.
6. Kooiman J, Klok FA, Mos IC, et al. Incidence and predictors of contrast-induced nephropathy following CT-angiography for clinically suspected acute pulmonary embolism. J ThrombHaemost 2010;8:409-11.
7. Sarma A, Heilbrun ME, Conner KE, Stevens SM, Woller SC, Elliott CG. Radiation and chest CT scan examinations: what do we know? Chest 2012;142:750-60.
8. Bates SM, Jaeschke R, Stevens SM, et al. Diagnosis of DVT: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest 2012;141:e351S-e418S.
9. Konstantinides SV, Torbicki A, Agnelli G, et al. 2014 ESC guidelines on the diagnosis and management of acute pulmonary embolism. European heart journal 2014;35:3033-69, 69a-69k.
10. Murphy TP, Cronan JJ. Evolution of deep venous thrombosis: a prospective evaluation with US. Radiology 1990;177:543-8.
11. Gornik HL, Sharma AM. Duplex ultrasound in the diagnosis of lower-extremity deep venous thrombosis. Circulation 2014;129:917-21.
12. Cronan JJ, Dorfman GS. Advances in ultrasound imaging of venous thrombosis. SeminNuclMed 1991;21:297-312.
13. Schellong SM. Distal DVT: worth diagnosing? Yes. J ThrombHaemost 2007;5 Suppl 1:51-4.
14. Horner D, Hogg K, Body R, Jones S, Nash MJ, Mackway-Jones K. Single whole-leg compression ultrasound for exclusion of deep vein thrombosis in symptomatic ambulatory patients: a prospective observational cohort study. BrJ Haematol 2014;164:422-30.
15. Righini M. Is it worth diagnosing and treating distal deep vein thrombosis? No. J ThrombHaemost 2007;5 Suppl 1:55-9.
16. Bernardi E, Camporese G, Buller HR, et al. Serial 2-point ultrasonography plus D-dimer vs whole-leg color-coded Doppler ultrasonography for diagnosing suspected symptomatic deep vein thrombosis: a randomized controlled trial. JAMA 2008;300:1653-9.
17. Gibson NS, Schellong SM, Kheir DY, et al. Safety and sensitivity of two ultrasound strategies in patients with clinically suspected deep venous thrombosis: a prospective management study. J ThrombHaemost 2009;7:2035-41.
18. Le Gal G, Robert-Ebadi H, Carrier M, Kearon C, Bounameaux H, Righini M. Is it useful to also image the asymptomatic leg in patients with suspected deep vein thrombosis? J ThrombHaemost 2015;13:563-6.

19. Piovella F, Crippa L, Barone M, et al. Normalization rates of compression ultrasonography in patients with a first episode of deep vein thrombosis of the lower limbs: association with recurrence and new thrombosis. Haematologica 2002;87:515-22.
20. Tan M, Velthuis SI, Westerbeek RE, VAN Rooden CJ, VAN DER Meer FJ, Huisman MV. High percentage of non-diagnostic compression ultrasonography results and the diagnosis of ipsilateral recurrent proximal deep vein thrombosis. J ThrombHaemost 2010;8:848-50.
21. Prandoni P, Lensing AW, Bernardi E, Villalta S, Bagatella P, Girolami A. The diagnostic value of compression ultrasonography in patients with suspected recurrent deep vein thrombosis. ThrombHaemost 2002;88:402-6.
22. Prandoni P, Cogo A, Bernardi E, et al. A simple ultrasound approach for detection of recurrent proximal-vein thrombosis. Circulation 1993;88:1730-5.
23. Linkins LA, Stretton R, Probyn L, Kearon C. Interobserver agreement on ultrasound measurements of residual vein diameter, thrombus echogenicity and Doppler venous flow in patients with previous venous thrombosis. ThrombRes 2006;117:241-7.
24. van Langevelde K, Sramek A, Vincken PW, van Rooden JK, Rosendaal FR, Cannegieter SC. Finding the origin of pulmonary emboli with a total-body magnetic resonance direct thrombus imaging technique. Haematologica 2013;98:309-15.
25. Le Gal G, Righini M, Sanchez O, et al. A positive compression ultrasonography of the lower limb veins is highly predictive of pulmonary embolism on computed tomography in suspected patients. ThrombHaemost 2006;95:963-6.
26. Righini M, G. LG, Aujesky D, et al. Complete venous ultrasound in outpatients with suspected pulmonary embolism. J ThrombHaemost 2009;7:406-12.
27. Nazerian P, Vanni S, Volpicelli G, et al. Accuracy of point-of-care multiorgan ultrasonography for the diagnosis of pulmonary embolism. Chest 2014;145:950-7.
28. Mathis G, Blank W, Reissig A, et al. Thoracic ultrasound for diagnosing pulmonary embolism: a prospective multicenter study of 352 patients. Chest 2005;128:1531-8.
29. Koenig S, Chandra S, Alaverdian A, Dibello C, Mayo PH, Narasimhan M. Ultrasound assessment of pulmonary embolism in patients receiving CT pulmonary angiography. Chest 2014;145:818-23.
30. Flinterman LE, van H, V, Rosendaal FR, Doggen CJ. Recurrent thrombosis and survival after a first venous thrombosis of the upper extremity. Circulation 2008;118:1366-72.
31. Di Nisio M, Van Sluis GL, Bossuyt PM, Buller HR, Porreca E, Rutjes AW. Accuracy of diagnostic tests for clinically suspected upper extremity deep vein thrombosis: a systematic review. J ThrombHaemost 2010;8:684-92.
32. Baarslag HJ, van Beek EJ, Koopman MM, Reekers JA. Prospective study of color duplex ultrasonography compared with contrast venography in patients suspected of having deep venous thrombosis of the upper extremities. AnnInternMed 2002;136:865-72.
33. Kleinjan A, Di NM, Beyer-Westendorf J, et al. Safety and feasibility of a diagnostic algorithm combining clinical probability, d-dimer testing, and ultrasonography for suspected upper extremity deep venous thrombosis: a prospective management study. AnnInternMed 2014;160:451-7.
34. Acosta S, Alhadad A, Svensson P, Ekberg O. Epidemiology, risk and prognostic factors in mesenteric venous thrombosis. BrJSurg 2008;95:1245-51.
35. Rajani R, Bjornsson E, Bergquist A, et al. The epidemiology and clinical features of portal vein thrombosis: a multicentre study. AlimentPharmacolTher 2010;32:1154-62.
36. Tessler FN, Gehring BJ, Gomes AS, et al. Diagnosis of portal vein thrombosis: value of color Doppler imaging. AJR AmJ Roentgenol 1991;157:293-6.

37. Stein PD, Fowler SE, Goodman LR, et al. Multidetector computed tomography for acute pulmonary embolism. N Engl J Med 2006;354:2317-27.
38. Rathbun SW, Raskob GE, Whitsett TL. Sensitivity and specificity of helical computed tomography in the diagnosis of pulmonary embolism: a systematic review. AnnInternMed 2000;132:227-32.
39. Patel S, Kazerooni EA, Cascade PN. Pulmonary embolism: optimization of small pulmonary artery visualization at multi-detector row CT. Radiology 2003;227:455-60.
40. Quiroz R, Kucher N, Zou KH, et al. Clinical validity of a negative computed tomography scan in patients with suspected pulmonary embolism: a systematic review. JAMA 2005;293:2012-7.
41. Remy-Jardin M, Pistolesi M, Goodman LR, et al. Management of suspected acute pulmonary embolism in the era of CT angiography: a statement from the Fleischner Society. Radiology 2007;245:315-29.
42. Righini M, Le GG, Aujesky D, et al. Diagnosis of pulmonary embolism by multidetector CT alone or combined with venous ultrasonography of the leg: a randomised non-inferiority trial. Lancet 2008;371:1343-52.
43. Palacio D, Benveniste MF, Betancourt-Cuellar SL, Gladish GW. Multidetector computed tomography pulmonary angiography pitfalls in the evaluation of pulmonary embolism with emphasis in technique. SeminRoentgenol 2015;50:217-25.
44. Hall WB, Truitt SG, Scheunemann LP, et al. The prevalence of clinically relevant incidental findings on chest computed tomographic angiograms ordered to diagnose pulmonary embolism. ArchInternMed 2009;169:1961-5.
45. van Strijen MJ, Bloem JL, de MW, et al. Helical computed tomography and alternative diagnosis in patients with excluded pulmonary embolism. J ThrombHaemost 2005;3:2449-56.
46. van Es J, Douma RA, Schreuder SM, et al. Clinical impact of findings supporting an alternative diagnosis on CT pulmonary angiography in patients with suspected pulmonary embolism. Chest 2013;144:1893-9.
47. Mortele KJ, Oliva MR, Ondategui S, Ros PR, Silverman SG. Universal use of nonionic iodinated contrast medium for CT: evaluation of safety in a large urban teaching hospital. AJR AmJ Roentgenol 2005;184:31-4.
48. Anderson DR, Kahn SR, Rodger MA, et al. Computed tomographic pulmonary angiography vs ventilation-perfusion lung scanning in patients with suspected pulmonary embolism: a randomized controlled trial. JAMA 2007;298:2743-53.
49. den Exter PL, van EJ, Klok FA, et al. Risk profile and clinical outcome of symptomatic subsegmental acute pulmonary embolism. Blood 2013;122:1144-9.
50. Kearon C, Akl EA, Ornelas J, et al. Antithrombotic Therapy for VTE Disease: CHEST Guideline and Expert Panel Report. Chest 2016;149:315-52.
51. Galie N, Humbert M, Vachiery JL, et al. 2015 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension: The Joint Task Force for the Diagnosis and Treatment of Pulmonary Hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS)Endorsed by: Association for European Paediatric and Congenital Cardiology (AEPC), International Society for Heart and Lung Transplantation (ISHLT). EurHeart J 2015;46:1855-6.
52. Dong C, Zhou M, Liu D, Long X, Guo T, Kong X. Diagnostic accuracy of computed tomography for chronic thromboembolic pulmonary hypertension: a systematic review and meta-analysis. PLoSOne 2015;10:e0126985.
53. Dournes G, Verdier D, Montaudon M, et al. Dual-energy CT perfusion and angiography in chronic thromboembolic pulmonary hypertension: diagnostic accuracy and concordance with radionuclide scintigraphy. EurRadiol 2014;24:42-51.

54. Sugiura T, Tanabe N, Matsuura Y, et al. Role of 320-slice CT imaging in the diagnostic workup of patients with chronic thromboembolic pulmonary hypertension. Chest 2013;143:1070-7.
55. Hull RD, Raskob GE, Hirsh J. The diagnosis of clinically suspected pulmonary embolism. Practical approaches. Chest 1986;89:417S-25S.
56. Bailey EA, Bailey DL, Roach PJ. V/Q imaging in 2010: a quick start guide. SeminNuclMed 2010;40:408-14.
57. Bajc M, Olsson B, Palmer J, Jonson B. Ventilation/Perfusion SPECT for diagnostics of pulmonary embolism in clinical practice. J InternMed 2008;264:379-87.
58. Phillips JJ, Straiton J, Staff RT. Planar and SPECT ventilation/perfusion imaging and computed tomography for the diagnosis of pulmonary embolism: A systematic review and meta-analysis of the literature, and cost and dose comparison. EurJ Radiol 2015;84:1392-400.
59. Thomas SM, Goodacre SW, Sampson FC, van Beek EJ. Diagnostic value of CT for deep vein thrombosis: results of a systematic review and meta-analysis. ClinRadiol 2008;63:299-304.
60. Baldt MM, Zontsich T, Stumpflen A, et al. Deep venous thrombosis of the lower extremity: efficacy of spiral CT venography compared with conventional venography in diagnosis. Radiology 1996;200:423-8.
61. Baarslag HJ, Koopman MM, Reekers JA, van Beek EJ. Diagnosis and management of deep vein thrombosis of the upper extremity: a review. EurRadiol 2004;14:1263-74.
62. Kim H, Chung JW, Park JH, et al. Role of CT venography in the diagnosis and treatment of benign thoracic central venous obstruction. Korean J Radiol 2003;4:146-52.
63. Ageno W, Squizzato A, Togna A, et al. Incidental diagnosis of a deep vein thrombosis in consecutive patients undergoing a computed tomography scan of the abdomen: a retrospective cohort study. J ThrombHaemost 2012;10:158-60.
64. Ageno W, Dentali F, Squizzato A. How I treat splanchnic vein thrombosis. Blood 2014;124:3685-91.
65. Coutinho JM, Stam J. How to treat cerebral venous and sinus thrombosis. J ThrombHaemost 2010;8:877-83.
66. Stam J. Thrombosis of the cerebral veins and sinuses. N Engl J Med 2005;352:1791-8.
67. Virapongse C, Cazenave C, Quisling R, Sarwar M, Hunter S. The empty delta sign: frequency and significance in 76 cases of dural sinus thrombosis. Radiology 1987;162:779-85.
68. Poon CS, Chang JK, Swarnkar A, Johnson MH, Wasenko J. Radiologic diagnosis of cerebral venous thrombosis: pictorial review. AJR AmJ Roentgenol 2007;189:S64-S75.
69. Khandelwal N, Agarwal A, Kochhar R, et al. Comparison of CT venography with MR venography in cerebral sinovenous thrombosis. AJR AmJ Roentgenol 2006;187:1637-43.
70. Linn J, Ertl-Wagner B, Seelos KC, et al. Diagnostic value of multidetector-row CT angiography in the evaluation of thrombosis of the cerebral venous sinuses. AJNR AmJ Neuroradiol 2007;28:946-52.
71. Ozsvath RR, Casey SO, Lustrin ES, Alberico RA, Hassankhani A, Patel M. Cerebral venography: comparison of CT and MR projection venography. AJR AmJ Roentgenol 1997;169:1699-707.
72. Erdman WA, Jayson HT, Redman HC, Miller GL, Parkey RW, Peshock RW. Deep venous thrombosis of extremities: role of MR imaging in the diagnosis. Radiology 1990;174:425-31.
73. Polak JF, Fox LA. MR assessment of the extremity veins. SeminUltrasound CT MR 1999;20:36-46.
74. Catalano C, Pavone P, Laghi A, et al. Role of MR venography in the evaluation of deep venous thrombosis. Acta Radiol 1997;38:907-12.
75. Fraser DG, Moody AR, Davidson IR, Martel AL, Morgan PS. Deep venous thrombosis: diagnosis by using venous enhanced subtracted peak arterial MR venography versus conventional venography. Radiology 2003;226:812-20.

76. Sampson FC, Goodacre SW, Thomas SM, van Beek EJ. The accuracy of MRI in diagnosis of suspected deep vein thrombosis: systematic review and meta-analysis. EurRadiol 2007;17:175-81.
77. Saha P, Andia ME, Modarai B, et al. Magnetic resonance T1 relaxation time of venous thrombus is determined by iron processing and predicts susceptibility to lysis. Circulation 2013;128:729-36.
78. Fraser DG, Moody AR, Morgan PS, Martel AL, Davidson I. Diagnosis of lower-limb deep venous thrombosis: a prospective blinded study of magnetic resonance direct thrombus imaging. AnnInternMed 2002;136:89-98.
79. Westerbeek RE, VAN Rooden CJ, Tan M, et al. Magnetic resonance direct thrombus imaging of the evolution of acute deep vein thrombosis of the leg. J ThrombHaemost 2008;6:1087-92.
80. Tan M, Mol GC, VAN Rooden CJ, et al. Magnetic resonance direct thrombus imaging differentiates acute recurrent ipsilateral deep vein thrombosis from residual thrombosis. Blood 2014;124:623-7.
81. Botnar RM, Perez AS, Witte S, et al. In vivo molecular imaging of acute and subacute thrombosis using a fibrin-binding magnetic resonance imaging contrast agent. Circulation 2004;109:2023-9.
82. Sirol M, Fuster V, Badimon JJ, et al. Chronic thrombus detection with in vivo magnetic resonance imaging and a fibrin-targeted contrast agent. Circulation 2005;112:1594-600.
83. Spuentrup E, Botnar RM, Wiethoff AJ, et al. MR imaging of thrombi using EP-2104R, a fibrin-specific contrast agent: initial results in patients. EurRadiol 2008;18:1995-2005.
84. Stein PD, Chenevert TL, Fowler SE, et al. Gadolinium-enhanced magnetic resonance angiography for pulmonary embolism: a multicenter prospective study (PIOPED III). AnnInternMed 2010;152:434-3.
85. Revel MP, Sanchez O, Couchon S, et al. Diagnostic accuracy of magnetic resonance imaging for an acute pulmonary embolism: results of the 'IRM-EP' study. J ThrombHaemost 2012;10:743-50.
86. Ley S, Ley-Zaporozhan J, Pitton MB, et al. Diagnostic performance of state-of-the-art imaging techniques for morphological assessment of vascular abnormalities in patients with chronic thromboembolic pulmonary hypertension (CTEPH). EurRadiol 2012;22:607-16.
87. Baarslag HJ, van Beek EJ, Reekers JA. Magnetic resonance venography in consecutive patients with suspected deep vein thrombosis of the upper extremity: initial experience. Acta Radiol 2004;45:38-43.
88. Kreft B, Strunk H, Flacke S, et al. Detection of thrombosis in the portal venous system: comparison of contrast-enhanced MR angiography with intraarterial digital subtraction angiography. Radiology 2000;216:86-92.
89. Ayanzen RH, Bird CR, Keller PJ, McCully FJ, Theobald MR, Heiserman JE. Cerebral MR venography: normal anatomy and potential diagnostic pitfalls. AJNR AmJ Neuroradiol 2000;21:74-8.
90. Isensee C, Reul J, Thron A. Magnetic resonance imaging of thrombosed dural sinuses. Stroke 1994;25:29-34.
91. Yang Q, Duan J, Fan Z, et al. Early Detection and Quantification of Cerebral Venous Thrombosis by Magnetic Resonance Black-Blood Thrombus Imaging. Stroke 2015.
92. Furie B, Furie BC. Mechanisms of thrombus formation. N Engl J Med 2008;359:938-49.
93. Rondina MT, Lam UT, Pendleton RC, et al. (18)F-FDG PET in the evaluation of acuity of deep vein thrombosis. ClinNuclMed 2012;37:1139-45.
94. Le Roux PY, Robin P, Delluc A, et al. Performance of 18F fluoro-2-desoxy-D-glucose positron emission tomography/computed tomography for the diagnosis of venous thromboembolism. ThrombRes 2015;135:31-5.
95. Hara T, Truelove J, Tawakol A, et al. 18F-fluorodeoxyglucose positron emission tomography/computed tomography enables the detection of recurrent same-site deep vein thrombosis by illuminating recently formed, neutrophil-rich thrombus. Circulation 2014;130:1044-52.

96. Klok FA, Tan M, Huisman MV. Letter by Klok et al Regarding Article, "18F-Fluorodeoxyglucose Positron Emission Tomography/Computed Tomography Enables the Detection of Recurrent Same-Site Deep Vein Thrombosis by Illuminating Recently Formed, Neutrophil-Rich Thrombus". Circulation 2015;131:e530.
97. Flavell RR, Behr SC, Brunsing RL, Naeger DM, Pampaloni MH. The incidence of pulmonary embolism and associated FDG-PET findings in IV contrast-enhanced PET/CT. AcadRadiol 2014;21:718-25.
98. Wittram C, Scott JA. 18F-FDG PET of pulmonary embolism. AJR AmJ Roentgenol 2007;189:171-6.
99. Hess S, Madsen PH, Iversen ED, Frifelt JJ, Hoilund-Carlsen PF, Alavi A. Efficacy of FDG PET/CT imaging for venous thromboembolic disorders: preliminary results from a prospective, observational pilot study. ClinNuclMed 2015;40:e23-e6.
100. Miles S, Rogers KM, Thomas P, et al. A comparison of single-photon emission CT lung scintigraphy and CT pulmonary angiography for the diagnosis of pulmonary embolism. Chest 2009;136:1546-53.