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Title: Are pulmonary embolism and deep-vein thrombosis always one disease?
Date: 2012-09-11
CHAPTER 3

Magnetic Resonance Imaging and Computed Tomography developments in imaging of venous thromboembolism

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ABSTRACT

Venous thromboembolism (VTE) is a disease that causes high morbidity and mortality in the population. At present the first-line imaging test for a suspected pulmonary embolism (PE) is computed tomography (CT) pulmonary angiography, and ultrasonography is widely used for the diagnosis of deep-vein thrombosis (DVT). Although these modalities are proven to be safe and accurate, unresolved issues remain, such as whether CT scanning in patients with a suspected PE should be extended to the legs. Another issue is the diagnosis of recurrent DVT. Magnetic resonance imaging (MRI) offers a number of advantages in the imaging of VTE. Recent developments of scanning protocols with shorter acquisition times, sometimes complemented by navigator gating or making use of endogenous contrast, offer new perspectives for the use of MRI. This review provides an overview of state of the art MRI techniques for the diagnosis of PE and DVT. Furthermore, the use of new contrast agents such as fibrin labeling to detect thrombi are addressed.
INTRODUCTION

Venous thromboembolism (VTE) is a disease with a major impact on society. With an incidence of 1 to 3 per 1000 per year, VTE causes significant morbidity and mortality in the overall population. Clinical problems include acute death from pulmonary embolism (PE), development of post-thrombotic syndrome after deep-vein thrombosis (DVT), and recurrent thrombotic events. PE is one of the common causes of cardiovascular death. The mortality rate of acute PE (15% at 3 months), exceeds the mortality rate of acute myocardial infarction.

In people with genetic risk factors such as factor V Leiden or the prothrombin mutation, the incidence of VTE increases 3-8 fold in heterozygotes. Acquired risk factors like immobilization, long-distance travel or oral contraceptive use are common and interact with genetic risk factors to further increase the risk of developing a venous thrombotic event.

At present, computed tomography pulmonary angiography (CTPA) is the first line diagnostic test for PE. The sensitivity and specificity of CTPA for diagnosis of acute PE have been reported to range from 53%-100% and 67%-100%, respectively, and may vary with the equipment used. The main disadvantages of CTPA are radiation and the need for iodinated contrast. For DVT of the legs, ultrasonography (US) has become the diagnostic modality of choice. Compared to the gold standard, contrast venography, US has a sensitivity of 96% and a specificity of 98% for the detection of proximal symptomatic DVT. For imaging of distal veins (e.g. calf veins), US is less reliable. False-positive findings tend to increase more distally. In addition, the diagnosis of recurrent DVT is a difficult topic in US. However, various limitations of the imaging modalities discussed above have led to a search for new techniques.

Magnetic resonance imaging (MRI) provides a new perspective in the imaging of VTE. Gadolinium-enhanced imaging has been an established way of thrombus imaging since the 1990s. Magnetic resonance direct thrombus imaging (MRDTI) using methemoglobin as endogenous contrast is a bright blood technique that can be used for the diagnosis of acute DVT. As research on new contrast media continues, molecular imaging comes into view. Fibrin labeling can lead to an effective way of imaging pulmonary arteries and peripheral venous thrombosis.

The aim of this review is to provide an overview of state of the art MR thrombus imaging and to contrast the MRI developments with widely used CT and nuclear medicine techniques. In this review we discuss several MR techniques, including MR angiography, MRDTI and molecular imaging.
CT Pulmonary Angiography (CTPA)

CTPA can be regarded as the new gold standard in diagnosing PE, thereby replacing pulmonary angiography. Since the introduction of multi-detector CT scanners (MDCT), the sensitivity and specificity of the CT scan for PE diagnosis have increased. From a sensitivity of 53-91% and specificity of 78-97% (single-detector CT scanner) to a sensitivity of 83-100% and specificity of 89-97% for MDCT, the diagnostic yield has markedly increased.

CTPA is an imaging modality that accurately rules out PE and in addition provides the possibility to determine alternative diagnoses such as aortic dissection, pneumonia, pneumothorax or rib fractures. This is a clear advantage over ventilation-perfusion (V/Q)-scanning and pulmonary angiography. With electrocardiogram (ECG)-gated CTPA, detailed information on the heart and coronary arteries can be obtained. This is valuable because the clinical differentiation between a cardiac event and PE is not always clear.

ECG-gated scanning acquires data at fixed time points in the cardiac cycle and thereby allows for isolation of end-systolic and end-diastolic phases. Right ventricular function can be assessed to aid the prediction of clinical outcome in patients with acute PE. Furthermore, measurement of the right ventricle to left ventricle transverse axis diameter ratio (RV/LV ratio) gives insight into the presence of right ventricular dysfunction (RVD). When the ratio is larger than one, RVD is present. A patient is diagnosed with severe RVD when the ratio exceeds 1.5. Several studies showed that CT measurement of the RV/LV ratio helps to predict mortality from PE during follow-up, and RV enlargement measured on a reconstructed CT 4-chamber view helps to predict early death. Finally, coronary artery disease can be assessed by using ECG-gated MDCT. This implies a wider triage of patients presenting with chest pain. Recently, a protocol on triple-rule-out (TRO) CT angiography was published, that involves patient selection as well as an injection and scanning protocol. Using TRO CT, a cost-effective evaluation of the coronary arteries, aorta and pulmonary arteries can be obtained for the patient with acute chest pain. As TRO CT is known to come with a relatively high radiation dose, several steps can be taken to limit radiation exposure. Scanning should be limited to incorporate the aortic arch down through the heart. In addition, prospective ECG-gating should be applied. The optimal radiation exposure then ranges from 5-9 mSv.

However, difficult issues in CTPA remain. Optimal evaluation of subsegmental pulmonary arteries is a controversial topic, although the real issue is to address clinical implications of (isolated) subsegmental PE.

The need for iodinated contrast use to obtain optimal diagnostic images with CT leads to contrast reactions in about 0.7% of patients. Reactions ranging from urticaria, severe nausea or vomiting, to facial or laryngeal edema, bronchospasm and (rarely) death have
been described. Another limitation of CT for the imaging of PE is radiation dose. In most protocols for spiral CT for PE, the effective dose is between 3 and 5 mSv, equivalent to 1-2 years of exposure to background radiation. The cancer risk associated with this exposure is approximately 150 excess cancer deaths per million people when exposed to a single CT examination for PE. Interestingly, in a systematic review on diagnosing pregnant women with a clinical suspicion for PE, CTPA has been shown to have a benefit due to the lower fetal radiation dose when compared to V/Q-scanning.

Nuclear medicine

In the field of nuclear medicine, PE diagnosis is made by V/Q-scans, or at present often by Q-scans alone. A classification of V/Q-scans in three categories that are clinically useful can be achieved by dividing the scans in high probability, normal or nondiagnostic scans. Interobserver variation can influence the results, and up to 20% of observer disagreement was found in the meta-analysis by Van Beek et al. In their meta-analysis on helical CT and V/Q-scan, a positive predictive value of 88% (95% confidence interval 84-91) for high probability V/Q-scan is found compared to pulmonary angiography. In patients with a nondiagnostic scan, however, 25% turned out to have PE proven by angiography. These patients need further diagnostic testing to safely exclude PE.

V/Q-scanning is often reserved for patients in whom motion artifact or poor right heart function limit the quality of CT examination. This modality is also useful in case of contrast allergy and in morbidly obese patients. Lung perfusion scintigraphy by means of technetium 99m-MAA (macro-aggregates of albumin) is indicated for chronic or recurrent PE, and in pediatrics. The traditional combination of a V/Q-scan is at present performed less often than the combination of a Q-scan with a chest X-ray. The most commonly used aerosol for ventilation scanning is 99mTc-DTPA. However, new radioaerosols have come to the market, one of which is 99mTc-Technegas. Technegas has decreased the problem of hotspot formation in patients with obstructive lung disease.

In addition to static perfusion scintigraphy, SPECT (single photon emission CT) has been introduced. 3D images can be acquired within the same acquisition time as static scintigraphy. Reinartz and colleagues reported a sensitivity of SPECT of 97% and specificity of 91%. A limitation of this study is that the final PE diagnosis was made based on a combination of available imaging data, clinical data, and D-dimer. Thus, the “gold standard” was not a consistent measure in all patients.

Finally, 18F-fluorodeoxyglucose (18F-FDG) positron emission tomography (PET) is mainly applied in oncologic patients, but PE can be found coincidentally. Thus far, case reports and case series have described focal FDG uptake around an intraluminal filling defect (using combined PET/CT) or a rim of FDG uptake around an area of pulmonary infarction, caused by PE. The mechanism is presumably due to the uptake of glu-
cose by activated macrophages and neutrophils in an inflammatory response around the area of pulmonary infarction.

MRI

The advantages of MRI in thoracic imaging are numerous. Besides the increasingly widespread availability of MRI systems to hospitals, no iodinated contrast is needed, no radiation exposure occurs and the examination is relatively noninvasive. With thoracic MR one can assess not only the pulmonary arteries, but (right) cardiac function can also be quantified to determine the patient’s clinical status. For patients with a previously confirmed diagnosis of PE, follow-up by means of MR is a safe method with a high diagnostic yield.

MR techniques used for diagnosing PE include MR angiography (MRA) with or without contrast-enhancement, MR perfusion imaging and real-time MR. MRA covers several advanced techniques such as contrast-enhanced high temporal resolution and noncontrast-enhanced steady state free procession (SSFP) sequences, some of the latter using navigator gating.

Due to recent technological improvements, both acquisition and reconstruction times for MRA have become shorter. Using a 3D gradient-echo sequence with a short TR and TE, breathhold time has decreased to less than 20 seconds. The introduction of parallel imaging, based on an undersampling of the K-space in the phase-encoding direction, has led to an even shorter acquisition time. Spatial resolution is high because of the shortened acquisition time, although the signal-to-noise ratio (SNR) decreases. Images are acquired in the coronal plane because in that direction the smallest number of slices are needed to cover the area of interest.\textsuperscript{114,115}

MRA

Meaney and co-workers were the first group to publish on gadolinium-enhanced MRA for the diagnosis of patients with PE.\textsuperscript{116} They found a sensitivity of 75-100\% and a specificity of 95-100\% for MRA compared to the gold standard, pulmonary angiography. Imaging was performed on a 1.5 T MRI system, using a coronal 3D spoiled gradient-echo pulse sequence. Slice thickness ranged from 3-4 millimeters. In their study, the main limitations were the small number of patients and the occurrence of breathing artifacts. Oudkerk et al. used a similar study approach, although they selected patients with a suspected PE and abnormal perfusion scan outcome.\textsuperscript{117} One dose of gadolinium contrast was given for each lung, followed by image acquisition during a separate breathhold for each lung. Images were evaluated using maximum intensity projections (MIP) and multiplanar reconstructions. An overall sensitivity of 77\% and specificity of 98\% was found in this study, although central PE sensitivity approached 100\%. The authors conclude that MRA is promising in the diagnosis of PE, but sensitivity decreases for subsegmental
emboli.\textsuperscript{117} Interobserver agreement was 91%, similar to the agreement in pulmonary angiography studies. Figure 1 shows an example of PE on a MRA image.

Traditional MRA has a longer acquisition time than CTPA, thus selective arterial phase enhancement can not be achieved.\textsuperscript{95} Therefore, it is more difficult to differentiate between arteries and veins. Another limitation, due to the fact that dyspneic patients often have difficulties holding their breath for a longer time, can be overcome by the use of navigator pulses to improve breathing artifacts.

The recently published PIOPED III study investigated MRA compared to the clinical standard of care (any combination of CTPA, V/Q-scan, pulmonary angiography, D-dimer or US) in a multicenter study, including 371 patients with diagnosed or excluded PE. Additionally, MR venography was done for the detection of DVT, the MR outcome being compared to images obtained by CT venography or ultrasound. MRA images were technically inadequate in 25% of patients. Taking into account only the technically adequate images, a sensitivity of 78% and a specificity of 99% was achieved. Adding MR venography to the MRA, changed sensitivity and specificity to 92% and 96%, respectively.\textsuperscript{118}

Contrast-enhanced MRA consists of a heavily T1-weighted gradient-echo sequence. Typically, a short TR is used to allow for short breathhold. A short TE is used to decrease background noise. An example of a contrast-enhanced MRA technique that achieves a high temporal resolution due to a multiphasic acquisition is time-resolved MRA. Scan time can be reduced to 5 seconds, thereby making this technique available for dyspneic patients. Another major benefit is the better separation of contrast between veins and arteries of the pulmonary system.\textsuperscript{119}

Figure 1. Coronal image from MRA shows focus of low signal (arrow) in the left main pulmonary artery consistent with pulmonary embolism.

Reprinted from \textit{Circulation} 109:I-15–I-21, Kanne JP, Lalani TA. “Role of computed tomography and magnetic resonance imaging for deep venous thrombosis and pulmonary embolism.” Copyright (2004), with permission from Wolters Kluwer Health.\textsuperscript{95} Courtesy of Michael B. Gotway, MD; San Francisco, Calif.
When it comes to noncontrast-enhanced MRA sequences, SSFP is a free-breathing real-time imaging technique. SSFP is useful for critically ill patients who are not capable of even a 5 second breathhold during scanning.\textsuperscript{114} Studies using this real-time technique compared with a 16-slice MDCT scan reported a sensitivity of 89% and specificity of 98%.\textsuperscript{120}

Navigator gating can be added to real-time imaging techniques in order to decrease motion or breathing artifacts in dyspneic patients. Navigator gating is a technique used to obtain the necessary images during the same phase of a patient’s respiratory cycle without the need for breathhold. Therefore, real-time imaging leads to fewer nondiagnostic studies than breathhold imaging techniques. In addition, the inherent T2-contrast allows for discrimination between embolus and surrounding blood without the use of contrast agents.\textsuperscript{120}

**Perfusion**

In MR perfusion a signal is generated based on the volume of blood in a region rather than directly imaging vascular structures. Areas of decreased or absent blood flow suggest the presence of an obstruction, thereby indirectly demonstrating PE.\textsuperscript{121} Perfusion is performed by using a 3D fast low-angle shot (FLASH) gradient-echo sequence. Single or multiple sharply delineated perfusion defects during phases of maximal (peak) parenchymal enhancement can be classified as lobar, segmental or subsegmental acute PE. Nonacute PE can be recognized by a more blurry delineation of perfusion defects. Time to peak and relative peak enhancement can be calculated by comparing pulmonary perfusion with perfusion measured in the superior caval vein.\textsuperscript{122}

Perfusion techniques can be of additional value to gadolinium-enhanced MRA. The perfusion scan can be obtained making use of the same contrast injection as required for MRA, and can be derived using post-processing methods. Breathhold during acquisition of images is needed for this sequence. In a study comparing three different MR sequences for PE diagnosis, perfusion was found to have the highest sensitivity.\textsuperscript{120} Another study comparing MR perfusion to SPECT perfusion found that both techniques showed a high agreement down to the subsegmental level, which underlines that observed abnormalities in MR perfusion sequences visualize genuine perfusion defects. Thus, the authors concluded that MR perfusion is suitable for detecting even subtle findings, essential for the analysis of subsegmental PE.\textsuperscript{123}

In clinical practice, a combination of contrast-enhanced MRA and perfusion images results in a sensitivity and specificity of over 90%, a value comparable to CTPA.\textsuperscript{124} MR perfusion can serve as a valid tool in the follow-up of patients with previously diagnosed PE. Assessment of flow as is done in MR perfusion imaging gives insight into the resolution of emboli and recovery of pulmonary flow. Perfusion is shown to be decreased in the acute PE setting, but improves when imaging patients on treatment after one week of
follow-up.\textsuperscript{122} False positive perfusion defects can be attributed to several diseases such as COPD or pulmonary scarring, similar to previously described causes of false-positive perfusion defects on V/Q scintigraphy.

\textbf{MRDTI}

The key concept behind direct thrombus imaging (DTI) is the use of endogenous contrast, due to the transformation of hemoglobin into methemoglobin in a thrombus. The DTI technique uses a T1-weighted sequence resulting in direct visualization of thrombi. T1-shortening due to methemoglobin in the thrombus leads to a higher signal than in surrounding muscle tissue. Background signal is suppressed. No filling defect is seen as in other modalities. High signal remains for up to 6 months, so differentiation between acute and chronic thrombosis can be made.\textsuperscript{125} Fraser and colleagues included 101 patients suspected of DVT in their study that compared contrast venography with MRDTI. For overall DVT diagnosis they found a sensitivity of 94-96% depending on the qualifications of the observer. Specificity ranged from 90-92%.\textsuperscript{126} MRDTI for the diagnosis of DVT will be discussed in more detail below.

However, imaging of pulmonary arteries with MRDTI turned out to be a more complicated matter than imaging DVT of the legs. Moody and co-workers started with 13 patients with PE, confirmed by pulmonary angiography or otherwise.\textsuperscript{127} Either 2D or 3D breathhold image acquisition was used. In that study, a sensitivity and specificity of 100% was achieved. Results of a randomized trial by the same study group using MRDTI have been announced but not published so far.

In our own ongoing study (K.v.L.) including patients with a proven DVT or PE, a total body MRDTI scan using a mobile table technique (Philips Medical Systems, Best, The Netherlands) is made within a week after the diagnosis has been radiologically confirmed. The PEDLAR (Pulmonary Embolism: Development, Localization And Risk factors) study aims to find the anatomical origin of a PE and to compare genetic and acquired risk factors in PE and DVT patients. Besides imaging, the protocol involves DNA collection to test for factor V Leiden and the prothrombin mutation. The moving table technique enables scanning from the calf up to the level of the jugular veins in five stations with minimum discomfort for the patient. The scanning protocol takes 20 minutes and is completed by a phase contrast volume (PCV) scan of the iliac region. The PCV is added because of possible artifacts on the DTI scan in the abdominal region, caused by movement of the filled intestines that also lead to a high signal on T1. Thus, filling defects on PCV can be used as a cross-reference for data acquired by the DTI technique.

All patients are imaged on a Philips 1.5 T MRI. The body coil is used, with the legs supported between two sandbags to prevent exorotation of the legs. The sequence is a 3DFFE with T1 enhancement. The flip angle is 15° and the shortest possible TR and TE are used, a TFE (Turbo Field Echo) prepulse with an invert time of 1200ms, and a Proset
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water selective pulse type 121 to suppress the background. The field of view is 400mm, with an 85% rectangle field of view. The matrix is 256x256 with a 70% scan percentage. Slice thickness is 2mm, 80 over contiguous slices are obtained.

Preliminary findings based on 40 patients show promising results for the imaging of DVT in the upper and lower extremities, and abdominal veins (Figs. 2-4). In addition, the subclavian veins and jugular veins can be well visualized for the evaluation of thrombi (unpublished data). Of note is that we do not use navigator gating or breathhold techniques, so imaging of the pulmonary emboli is not achieved by this scanning protocol.

**MR molecular imaging: fibrin-targeted contrast agents**

Molecular MRI can be aimed at different peptides such as serum albumins, type I collagen (elevated in fibrosis) or fibrin. Fibrin labeling is an upcoming contrast method for MR that has been studied mainly in the field of arterial thrombosis, i.e. stroke and myocardial infarction. Nevertheless, fibrin labeling can be used as a contrast method for both arterial and venous thrombosis. In general, these contrast agents are bifunctional molecules that consist of gadolinium combined with a peptide that binds to fibrin present in thrombus. Fibrin is formed from fibrinogen as the last step in the cascade of thrombus formation. Thrombin is necessary for this conversion. Moreover, fibrin functions as a mesh to form a clot structure in conjugation with platelets.

Animal models have been developed such as a fibrin-binding gadolinium-labeled peptide, EP-1873, using a model of aortic plaque rupture and thrombosis. A different peptide, EP-2104R, was applied in a model of carotid artery thrombosis in rabbits. EP-2104R does not bind to circulating fibrin, but binds specifically to fibrin in thrombi. It remains bound for several hours. Thrombus imaging was performed at several time points after thrombus generation, to verify whether a difference in thrombus age could be visualized using this contrast agent. Although thrombus signal intensity decreased with thrombus age, enhancement at 8 weeks was still present. Signal intensity was highest at the thrombus surface, and decreased in the more central part of the thrombus.

Histopathologic correlation showed that fibrin was gradually replaced by fibrous tissue. A correlation was found between thrombus enhancement and collagen content of the organizing thrombus with time. The same peptide (EP-2104R) was applied in a study in domestic swine in which DVT was induced followed by a thrombectomy procedure. The intervention was monitored with MR. After thrombectomy, dislodged thrombus fragments were visualized in the lungs. More recently, a study on in vivo thrombus formation proposed gadolinium combined with alpha-2 antiplasmin as a contrast agent. Factor VIII crosslinks alpha-2 antiplasmin via a covalent binding to fibrin. At present, studies in humans are ongoing. A phase II trial has shown that EP-2104R can be applied in humans without any adverse effects, although numbers were small (10 patients). The main focus of this study using molecular MR was on thrombi that potentially lead to
Figure 2. (left) MRDTI showing high signal representing thrombosis of the left popliteal vein and two calf veins.

Figure 3. (middle) MRDTI showing high signal representing thrombosis of the left popliteal vein ascending to the femoral vein.

Figure 4. (right) MRDTI showing high signal representing thrombosis of the right renal vein in a patient that underwent resection of the left kidney. This finding has been confirmed by a gadolinium enhanced MR of the abdomen.
stroke. A heavily T1-weighted inversion recovery black-blood gradient-echo sequence was applied and the aorta as well as the carotid arteries were imaged (Fig. 5).

**Figure 5.**

a. Molecular MR imaging of thrombus in the descending thoracic aorta in an 82-year-old female patient using inversion recovery black-blood gradient-echo imaging (IR). The high local signal amplification allows for white spot imaging of the clot (arrow).

b. Corresponding multiplanar reconstruction from contrast-enhanced multislice CT demonstrating corresponding plaque in the aortic wall. At the cranial end of the plaque a small calcification is also visible (arrowhead).


Among the presently available techniques for patients with a clinically suspected symptomatic DVT, US is the imaging modality of choice, largely replacing contrast venography. In this technique compressibility of the proximal veins is assessed. Advantages of US are the simple, accurate and noninvasive nature of the technique. Another advantage is the wide availability of US. However, US is less accurate for the diagnosis of a distal (i.e. calf vein), iliac, and inferior caval DVT. Furthermore, in patients with plaster casts and morbid obesity US can not be performed reliably.

In the last decades CT and MRI are being considered to replace US in patients in whom US is not feasible. Several issues are still unresolved, such as whether CT scanning in patients with a suspected PE should be extended to the legs. Another issue is the diagnosis of an ipsilateral recurrent DVT. In this DVT section we will address these issues, discuss the role of CT, and address the newest and most commonly used MRI techniques in the diagnosis of clinically suspected DVT. These include Direct Thrombus Imaging (MRDTI),
Venous Enhanced Subtracted Peak Arterial (VESPA) MR venography and balanced SSFP (bSSFP) techniques.

CT venography (CTV)

CTPA is the imaging modality of choice for the diagnosis of PE. However, only one study explored the performance of CTV in patients with a clinically suspected DVT. In this study CTV performed similar to contrast venography, with a sensitivity of 100% (95% CI 92-100) and a specificity of 96% (95% CI 84-98). Other studies were performed in patients with a clinically suspected PE, usually without symptoms of the legs, in which the scan was extended to the legs. In a meta-analysis the estimated pooled sensitivity of CTV was 96% (95% CI 93-98) with an estimated pooled specificity of 95% (95% CI 93.6-96.5). Of note, the heterogeneity between the studies was substantial.

CTV could be useful in patients with a suspected DVT in whom US cannot be performed or is less reliable, such as patients with morbid obesity, casts and patients with a suspected DVT in the iliac or inferior caval vein. Furthermore, patients with a suspected venous anomaly can be imaged.

A currently debated issue is the extension of the CT scan to the legs in patients with a clinically suspected PE. In a recent review, Goodman et al. discussed the advantages and disadvantages. The consideration behind performing CTV is the detection of a DVT otherwise missed by CTPA, which could be relevant because both diseases often occur concurrently. The Prospective Investigation of Pulmonary Embolism Diagnosis II (PIOPED II) showed an improvement of overall sensitivity of CT from 83% to 90% if CTV was added to CTPA. Furthermore, the extension of the CT scan allows the diagnosis of a DVT within less than 5 minutes of additional scanning time with no added iodinated contrast.

On the other hand, CTV added little to the overall diagnosis of VTE in a 3-month follow-up study, and the risk of false-positive test results, and resultant over-diagnosis and overtreatment exists. Additionally, the incidence of positive studies in patients without signs, symptoms or history of DVT is low. Finally, one needs to carefully consider whether the extra radiation exposure outweighs the benefits, especially in case of pelvic examination in younger patients. Recent studies confirm the redundancy of CTV in all patients with a clinically suspected PE and suggest it may only be useful in patients with a high probability of PE, including those with a history of VTE and possible malignancy. The incremental value of CTV was 3.4%; 0.72% in the low PE risk group and 2.6% in the high PE risk group. Another study showed noninferiority of the strategy combining D-dimer testing and CT versus the combination D-dimer testing, US and CT with a similar 3 month VTE risk of 0.3%. A recent meta-analysis confirmed these findings with a negative predictive value of 98.8% (95% CI 98.2-99.2) based on a normal CTPA as sole test compared to a negative predictive value of 98.9% (95% CI 98.0-99.4) based on a normal CTPA followed by a normal US.
In conclusion, the current literature indicates little benefit of the additional value of CTV to CTPA in patients with a suspected PE. Nonetheless, this technique could potentially be beneficial in a subset of patients, such as those with a suspected PE with a high probability and a normal pulmonary CT scan, patients with a prior DVT, or malignancy. Extra radiation burden can be minimized by limiting the scan in the proximal area to the thighs, thus excluding the pelvic veins.143

MRI

MRI of the deep venous system can be performed with and without the administration of gadolinium. Contrast can be administered directly into a peripheral vein. Newer contrast agents, that bind to albumin blood pool agents, improve peripheral imaging by the longer duration of contrast material in the vessel and by improving spatial resolution.

A meta-analysis showed a pooled estimate sensitivity of 91.5% (95% CI 87.5-94.5) and specificity of 94.8% (95% CI 92.6-96.5) for DVT diagnosis.144 The heterogeneity between the studies was substantial, including different techniques and combining the diagnosis of both proximal and distal DVT. Table 1 gives an overview of sensitivity and specificity of MRI techniques for DVT imaging compared to different modalities.

An advantage of MRI over US is the better delineation of the caval vein and pelvic veins, and MRI is therefore especially suitable in this group of patients. Furthermore, MRI allows high-quality imaging without the need for a contrast agent or radiation exposure.

Phase contrast and time of flight (TOF)

Phase contrast and TOF are two of the earliest MRI techniques evaluated for patients with a suspected DVT. Phase contrast is a nongadolinium-enhanced spin-echo technique that depends upon the phase shift of protons of flowing blood to create an image. A DVT is visualized as an area with the signal intensity of soft tissue. In case of a partially obstructive thrombus, the thrombus is surrounded by very low signal intensity. In a study by Erdman et al. this technique was assessed in 100 patients with a suspected either upper- or lower- extremity DVT and compared to contrast venography. The sensitivity was 90% with a specificity of 100% and the agreement between MRI and venography was substantial, with a kappa of 0.75.145

TOF is a gradient-echo technique that is dependent on the flow and the movement of protons in blood through the image plane. Thrombosis is visualized as a decreased signal defect within the venous lumen or a low intensity defect surrounded by the high signal intensity from flowing blood. Thrombosis within the inferior caval vein and the iliac and femoropopliteal veins can be visualized with a high degree of accuracy.145-148 The sensitivity for the femoropopliteal segments is 97% with a specificity of 93% compared to contrast venography.149
**Table 1.** Sensitivity and specificity of MRI techniques for acute DVT diagnosis.

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<th>First author</th>
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<td>Westerbeek</td>
<td>2008</td>
<td>43</td>
<td>Lower extremity</td>
<td>MRDTI</td>
<td>US</td>
<td>95</td>
<td>100</td>
</tr>
<tr>
<td>Pedrosa</td>
<td>2009</td>
<td>24</td>
<td>Upper and lower extremity</td>
<td>HASTE</td>
<td>Gadolinium enhanced MRV</td>
<td>100</td>
<td>91</td>
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</tbody>
</table>

* In case more sensitivity and specificity figures were mentioned in the article, we reported the sensitivity and specificity of the proximal veins.
Both techniques are now rarely used because of the long acquisition time. Furthermore, phase contrast has difficulties in imaging slow flowing blood especially when blood runs parallel with the imaged slice. The most important disadvantage of the TOF technique is the susceptibility to pulsatility artifacts and flow turbulence, which can mimic the presence of a thrombus and can lead to false-positive diagnosis.

**MRDTI**

As previously mentioned in the PE section, MRDTI is based upon the paramagnetic properties of methemoglobin, which gives a high signal on T1-weighted images against a suppressed background of flowing blood and fat. The intensity of this signal correlates with the amount of methemoglobin. Compared to contrast venography, MRDTI has a sensitivity of 97% for femoropopliteal DVT and a specificity of 100%.

The advantage of MRDTI is the direct visualization of the thrombus without any need for contrast administration. This benefit overcomes the limitations of other techniques that detect filling defects and surrogate markers of a thrombus (e.g. flow characteristics). Additionally, this technique has potential for patients with a clinically suspected ipsilateral recurrent DVT. The diagnosis of this group of patients is difficult, because for patients with proximal DVT, persistent vein abnormalities are present in 80% and in 50% of patients at 3 months and 1 year, respectively. Therefore, when a patient with suspected recurrence has a noncompressible venous segment on US, it can be difficult to determine whether this represents new disease or a residual abnormality. A recent study using MRDTI evaluated the MR signal change over 6 months. The authors observed that after 6 months the abnormal MR signal of the acute DVT event had disappeared in all 39 patients, while in 12 patients (31%) the CUS examination was still abnormal. This study indicates that MRDTI may potentially be an accurate method to distinguish a new recurrent event from an old thrombus in patients with a suspected acute ipsilateral recurrent DVT. This is currently being evaluated in an ongoing study (Return study, M.T.).

**VESPA**

An example of a gadolinium-enhanced MRI scan is VESPA. This technique uses a 1.5 T unit and a 3D gradient-echo sequence. It involves the use of standard angiography sequences and postprocessing software. Advantages of this technique are the rapid imaging time, the complete visualization of venous anatomy, and the possibility of the use of reconstruction techniques. Furthermore, comparison between studies to monitor thrombus progression and resolution is facilitated. The MRI study is considered positive for DVT if intraluminal filling defects are seen or if nonfilling of veins is detected with a sharp cutoff. The sensitivity was 100% for both femoral and iliac veins with a specificity of 100% for the iliac veins and 97% for the femoral veins compared to contrast venogra-
The interobserver variability was almost perfect with a \( \kappa \) of 0.85 and 0.97 for femoral and iliac veins, respectively. VESPA could be used in the visualization of complex venous anatomy in case of chronic thrombosis or venous anomalies.

**bSSFP**

The bSSFP technique is a bright-blood technique. It is a fast technique and provides a very high SNR, rapid data acquisition with limited sensitivity to motion, and intrinsically high signal intensity of intraluminal blood. This technique has a lower sensitivity and specificity for the central veins (chest, abdomen, pelvis) compared to gadolinium-enhanced MR images. The sensitivity and specificity for DVT detection compared to contrast venography was 100% each for both iliac and popliteal segments and 100% and 98%, respectively, for the femoral veins. The technique showed a good interobserver agreement (\( \kappa \) 0.64). A disadvantage of this technique is the high signal intensity of background tissue.

Because of this disadvantage a new technique has been evaluated, i.e. signal targeting using alternative radiofrequency and flow-independent relaxation enhancement (STARFIRE). STARFIRE uses a 3D bSSFP pulse sequence and uses a subtraction technique in which the signal intensities of fat and muscle will be suppressed while the signal intensity of blood will be preserved. In a comparison between 2D TOF and contrast-enhanced 3D MRA, STARFIRE had the most consistent image quality. Although STARFIRE provided much better relative contrast for muscle and fat, other artifacts need to be taken into account. Because of the use of a bSSFP pulse sequence this technique should be sensitive for off-resonance effect, appearing as dark stripes on the images. Furthermore, with the use of multislab axial acquisitions, there was some signal intensity variation as the deep veins passed from one slab to the next. Although these artifacts were minor in this study, it is uncertain whether the imaging artefacts will interfere in a study that includes more patients.

**Recent MRI developments**

For several years blood pool contrast agents have been evaluated. Blood pool agents can be divided into gadolinium-based and nongadolinium-based. An advantage of the use of blood pool contrast agents over conventional gadolinium-enhanced contrast is that the former have a substantially longer intravascular half-life and produce less soft tissue enhancement. Ferumoxytol is a new contrast agent in the class of iron oxide blood pool agents. It is a semisynthetic carbohydrate-coated ultrasmall supermagnetic iron oxide. Li et al. performed a preliminary study with ferumoxytol-enhanced MRI and dual contrast mechanism. Ferumoxytol-enhanced MRI could depict the full extent of thrombus and showed small distal vein thrombi better than duplex US in some patients. The images were of better quality than precontrast TOF. Advantages of this technique
are that the SNR could be greatly improved by signal averaging over minutes, because of the longer half-life of the contrast material in the vessel. Furthermore, multiple pulse sequences could be performed and imaging could be carried out at multiple stations without loss of accuracy. The study included a limited number of patients, therefore a larger group of patients is needed to properly validate this technique.

Gadofosveset trisodium is a new gadolinium-based blood pool agent that has been used for diagnostic imaging of coronary and carotid arteries, and peripheral arterial disease. This blood pool agent has potential for imaging the venous system, however this has not been evaluated yet.

Dynamic half-Fourier single shot turbo spin echo (HASTE) is a noncontrast-enhanced technique and provides rapid T2-weighted images which are less susceptible for motion artifacts and has been used for different applications. In a recent study this technique was compared in 24 patients with a suspected upper or lower extremity DVT with gadolinium-enhanced MRI. This technique relies on the quality of nonthrombosed veins to respond to the Valsava maneuver with dilatation of the vein. Veins were analyzed for the presence of changes in caliber and signal intensity during the Valsalva maneuver. An increase of 1.5 mm in caliber of the vein had a sensitivity of 100% and specificity of 91%. Noncontrast-enhanced 0.5 T MR venography with ECG-gated 3D half-Fourier methodology has been evaluated for use in patients with metallic implants. This technique clearly demonstrated veins adjacent to metallic implants and may be promising in postsurgery patients. However, this still requires evaluation in a larger patient group.

CONCLUSIONS

This review aimed to give an overview of state of the art imaging techniques for venous thrombosis. For PE, CTPA continues to be the preferred modality in most clinical scenarios. High resolution and velocity of image acquisition as well as its potential to detect different diagnoses that may be confusing the clinical presentation offer it significant benefits over MRI. Imaging of PE with MR molecular imaging such as fibrin labeling seems a promising technique. Diagnostic evaluation for DVT is mainly done by ultrasonography, due to its high diagnostic yield and wide availability. In the currently debated issue of adding CTV to CTPA, the recent literature shows that CTV offers no additional value in all suspected PE patients. CTV could be beneficial in patients with a high probability for PE and a normal CTPA, patients with a prior DVT, or those with underlying malignancy.

The diagnosis of recurrent DVT is challenging because of the presence of residual thrombosis. Concerning MRI techniques, MRDTI looks promising in the diagnostic process of recurrent DVT. However, a clear need for more studies remains in this area. Furthermore, the development of new blood pool contrast agents and the use of MRI in patients with metallic implants need further evaluation.