Magnetic resonance direct thrombus imaging: a novel technique for imaging venous thromboemboli

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Summary
Invasive testing is now seldom required in patients with suspected venous thromboembolism (VTE). However, a corollary of noninvasive imaging is increased complexity as results are often yielded as probabilities rather than definitive answers and additional testing is frequently required following initial imaging. This creates a milieu in which misunderstandings and protocol violations are common, potentially leading to diagnostic errors. A highly accurate noninvasive imaging technique which allows immediate treatment decisions to be made is needed. Magnetic resonance direct thrombus imaging (MRDTI) is a novel technique which detects methaemoglobin in clot, allowing visualisation of thrombus without using intravenous contrast. It has two major advantages over conventional modalities which identify it as having the potential to fill this role.

Keywords
Magnetic resonance direct thrombus imaging, deep vein thrombosis, pulmonary embolism

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Introduction
Widespread availability of ultrasound and ventilation–perfusion (VQ) scanning has greatly reduced the need for invasive imaging in patients with suspected venous thromboembolism (VTE) (1, 2), yet allows treatment decisions to be made with a similar degree of safety assuming adherence to validated diagnostic pathways which may also incorporate information from a pre-test clinical probability assessment (3, 4) and plasma D-dimer estimation (5-16) (D-d). This succession of a predominantly noninvasive diagnostic paradigm represents an advance in patient care, but comes at the cost of increased diagnostic complexity: while contrast venography or pulmonary angiography usually allow immediate treatment decisions to be made, serial testing may be required after a normal initial ultrasound to detect propagating below knee deep vein thrombosis (11, 17, 18). Firstly, direct visualisation of thrombus overcomes many of the pitfalls of conventional techniques, which have either identified thrombus as a filling defect or in terms of surrogates. Secondly, simultaneous imaging of the legs and chest allows a comprehensive assessment of thrombus load, minimising the importance of overlooked subsegmental pulmonary embolism (PE) and potentially facilitating more titrated treatment. Early data suggest MRDTI is highly accurate for the detection of both deep vein thrombosis (DVT) and PE, and ongoing outcome studies are evaluating the safety of withholding treatment in suspected DVT and PE on the basis of negative MRDTI alone. If favorable, a multi-centre outcome study evaluating cost-effectiveness as well as safety would be justified. Subject to further evaluation, this technique has the potential greatly to simplify and standardise the investigation of suspected VTE.
18) (DVT), and most VQ scans are non-diagnostic (19) necessitating further investigation by one of several validated diagnostic strategies (2). Clearly, increased complexity and heterogeneity of diagnostic algorithms fosters misunderstanding, variable compliance and therefore the potential for misdiagnosis, particularly where investigations yield results in terms of probabilities rather than definitive answers (20).

A noninvasive imaging modality that was highly accurate for below and above knee DVT as well as pulmonary embolism (PE) would be highly desirable as it could provide a definitive result at the point of study, allowing immediate treatment decisions and hence simplifying and standardizing the diagnostic process. Magnetic resonance direct thrombus imaging (MRDTI), a novel application of MR technology which allows direct visualization of clot, is proving promising in this regard. This article highlights the deficiencies of currently employed noninvasive imaging techniques and explains how these could be surmounted by a technique which directly visualizes thrombus. Research to date evaluating MRDTI as a diagnostic tool for VTE is summarized, and the potential future impact of this technology on the diagnostic paradigm of VTE subject to favourable ongoing validation is discussed.

**Conventional noninvasive imaging techniques for VTE**

**Ultrasound**

While contrast venography remains the diagnostic gold standard, ultrasound is now the initial investigation of choice for clinically-suspected DVT (1), pooled data indicating a sensitivity and specificity of 96% and 98% respectively for symptomatic proximal DVT (11). However, it is less sensitive for below knee DVT so that repeat testing at one week was initially advocated in all patients with a negative initial examination to exclude the additional 1 to 2% in whom proximal DVT will become evident (2, 18). More recently, it has been shown that imaging of the calf veins is not required as long as the popliteal vein is imaged to its origin (21, 22) and that repeat imaging after an initial negative study is safely obviated when PE is absent (38). Unlike VQ scanning, spiral CT demonstrates PE as a filling defect rather than in terms of a surrogate effect on lung perfusion so that non-diagnostic scans are unusual. Moreover, appropriate interpretation of VQ-derived data, for example equating a low probability scan with a negative study (29, 36, 37), indicating that the safety of this approach is uncertain.

Experience shows that a definitive diagnosis is often not pursued following a non-diagnostic VQ scan (34, 35). In some patients treatment decisions appear to be made on the basis of an *a posteriori* 'adjustment' of pre-test probability (36), or an inappropriate interpretation of VQ-derived data, for example equating a low probability scan with a negative study (29, 36, 37). Clearly, patients failing to achieve a definitive diagnosis on VQ scanning are at risk of misdiagnosis for a variety of reasons.

**Spiral CT**

Unlike VQ scanning, spiral CT demonstrates PE as a filling defect rather than in terms of a surrogate effect on lung perfusion so that non-diagnostic scans are unusual. Moreover, alternative diagnoses may be made when PE is absent (38). However, the technique requires injection of iodinated contrast and is associated with a considerably higher radiation dose.

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While pooled data from 14 early studies revealed a mean sensitivity and specificity of 86 and 93% respectively (39), the most recent performance study in 299 patients with suspected PE revealed a less impressive sensitivity of 70%, with a specificity of 91% (40); and although an earlier outcome study (41) found only 2 (1%) episodes of clinical VTE at 3 months in 198 patients with suspected PE and a negative spiral CT in whom treatment was withheld, this did not definitively show that a negative spiral CT by itself safely excludes PE in unselected patients as 42% of these patients had also undergone lower limb ultrasound and a significant minority of patients with negative spiral CTs were excluded from follow up as they were receiving anticoagulants, in some cases possibly because of ongoing suspicion for PE despite negative imaging. More recently, Musset et al. (42) showed that anticoagulants could safely be withheld in 507 patients with low or intermediate pre-test probability, negative spiral CT and negative bilateral leg ultrasounds, 9 (1.8%) episodes of clinical VTE occurring in this subgroup over the next 3 months. Of particular note, PE was found in 4 (5.4%) of 75 patients with high pre-test probability, negative spiral CT and lower limb ultrasounds who underwent VQ scanning +/- pulmonary angiography.

Hence, while advocated by some as an imaging technique of first choice in patients with suspected PE and an abnormal chest X-ray (43, 44), and while generally accepted that treatment can be started on the basis of a positive scan, treatment should probably not be withheld on the basis of a normal spiral CT in isolation (45), although supplementary indirect CT venography of the lower limbs (46) or use of multi-slice scanning may refine overall sensitivity. Therefore, based on current evidence, many patients with suspected PE undergoing spiral CT as initial imaging will require further testing.

**Plasma D-dimers**

Over the last decade, D-d have evolved from a class of theoretically attractive exclusionary tests in suspected VTE (47, 48) to one of practical value, several clinical management studies now showing that a negative D-d test in defined low-prevalence populations with suspected VTE selected on the basis of pre-test probability or negative or equivocal noninvasive imaging effectively excludes disease (5, 6, 10, 13, 33, 49-51); in particular, imaging and treatment is obviated in patients with suspected DVT or PE who have a low pre-test probability and negative D-d test (33, 51). However, even with optimum use of D-d, most patients with suspected VTE continue to require imaging.

**MR for the detection of VTE**

**MR venography for the detection of DVT**

MR venography takes advantage of the fact that MR can distinguish between stationary and moving signal, with flowing blood appearing white and stationary clot appears dark (52), and compares favourably to contrast venography for the diagnosis of proximal DVT with a sensitivity and specificity of 97 and 93% (53). Further, it is more accurate for the diagnosis of isolated pelvic vein thromboses than standard contrast venography or ultrasound (54-56). However, there is a paucity of data for symptomatic below knee DVT, where lower sensitivity might be anticipated because of sluggish venous flow, accurate detection of clot in these veins probably requiring additional injection of contrast. The diagnostic role of this technique in clinically suspected DVT is currently limited to special situations such as suspected pelvic DVT, or in patients with plaster casts (1).

**MR / MR angiography for the detection of PE**

MR angiography or gadolinium enhanced MR angiography can be used to detect PE, and have been compared to conventional imaging techniques in several small studies which have demonstrated sensitivities of 75-100% and specificities of 420-90% (57). Pooled data from 6 studies using contrast enhancement containing 150 patients showed a mean sensitivity and specificity of 77% and 87% respectively (39). Like spiral CT, MR appears to be a reasonably reliable technique for larger central PE, but less so for smaller PEs at the segmental or subsegmental level (39, 58-62). Most recently, MR angiography was compared to pulmonary angiography in 118 patients with suspected PE and showed a sensitivity of 77% and specificity of 98% (63). Hence, it appears to have a similar accuracy to spiral CT while using safer contrast media and avoiding exposure to ionising radiation, but, like spiral CT, may not be safe as a stand-alone exclusionary test in view of imperfect sensitivity. The technique continues to evolve, and is presently regarded primarily as a research tool.

**Magnetic resonance direct thrombus imaging**

MRDTI is a recent development offering two main theoretical advantages over conventional imaging techniques. Firstly, it provides a positive image of thrombus without the need for intravenous contrast, so avoiding the potential pitfalls of previous techniques, including conventional MR, which have relied on the detection of a filling defect within flowing blood or surrogate markers for the presence of clot. Secondly, it allows simultaneous imaging of the lower limbs and chest, which allows a comprehensive ascertainment of thrombus load and harmonises with the concept that DVT and PE are not isolated diseases but part of a clinical spectrum. It is now recognized, for example, that up to half of patients with symptomatic proximal DVT but no clinical suggestion of PE have subclinical emboli on VQ scanning, though their presence does not seem to alter the prognosis (64), presumably reflecting the effectiveness of anticoagulation (65). Pursuing coterminous subclinical PE in patients with DVT may not, therefore, be justified on current evidence, but a knowledge of the peripheral thrombus load following PE could provide additional important information as
the presence or absence of proximal DVT is the chief prognostic factor for PE recurrence (27-31) and could facilitate a more titrated approach to treatment. For example, a retrospective data synthesis has shown that in patients with non-massive PE, non-high probability VQ scans, adequate cardiorespiratory reserve and negative serial ultrasounds over 2 weeks, the estimated risk of subsequent fatal and non-fatal recurrent PE is only 0% and 3% respectively in the absence of treatment, suggesting that it might be safe to withhold treatment in selected patients at high risk of bleeding despite PE, though this concept requires prospective validation (31). Finally, MRDTI also allows detection of pelvic vein and inferior vena cava thromboses which may be missed by contrast venography or ultrasound and are frequently associated with PE if present.

**How MRDTI works**

It has been known for some time that there is a stereotyped progression in the appearance of haemorrhage or thrombosis on MR at 1.5 Tesla (66, 67). Thrombus is associated with substantial T1 shortening, producing high signal intensity on T1 weighted images against a background of suppressed blood and fat which further enhances clot (68-73). This technique therefore produces a positive image of thrombus via its associated paramagnetic properties.

A T1-weighted magnetization-prepared three-dimensional gradient-echo sequence is utilized, which includes a water-only excitation radio frequency pulse to abolish the fat signal, with the effective inversion time chosen to nullify the blood signal so that clot-blood contrast is maximized. Images are acquired in the coronal plane and the technique can be performed using a standard scanner, with acquisition times for lower limb and pelvic scanning of only 7 to 10 minutes. The T1 shortening is caused by generation of methaemoglobin in thrombus which possesses strong paramagnetic properties consequent upon the 3+ ferric state of iron (74). When thrombus is formed, red cells are trapped within a mesh of platelets and fibrin. Using in vitro studies of washed red cells, we have confirmed that red cells containing methaemoglobin produce T1 shortening, the extent of which is in proportion to the level of methaemoglobin (unpublished data, Dr. B. Hunt & Professor A. Moody, see Fig. 1). This signal persists for several weeks, though for less than 6 months, presumably reflecting the removal of red cells by the macrophage system as part of the healing process (68-73). Thus information from the signal can provide data about thrombus characteristics such as volume and age (68-73, 75-77). For example, the technique has been used to show that D-d levels correlate with clot volume and surface area, and that surface

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**Figure 1:** Concentration of methaemoglobin in red cell solutions versus T1 measurements performed using magnetic resonance direct thrombus imaging

**Figure 2:** Axial section at knee level using magnetic resonance direct thrombus imaging in a patient with bilateral proximal DVT illustrating the ‘polo mint sign’
area is the more important determinant, supporting the concept that D-d generation and / or release occurs primarily at the surface of the thrombus (75); and in a study of 54 patients with symptomatic DVT confirmed by contrast venography undergoing MRDTI, clot volume was found to be a more important predictor of PE than the proximal extent of DVT. Thrombus volumes of below or above 18mls were associated with a 20% and 68% risk of PE respectively, suggesting that this threshold might have clinical application. Most PEs were subclinical, and large emboli occurred only in the latter group. In comparison, below and above knee DVTs were associated with a 29% and 58% prevalence of PE respectively (76). Furthermore, serial MRDTI evaluation of thrombus within the external iliac vein in 9 patients revealed predictable change in signal over time allowing dating of thrombus between 0 – 12, 13 – 21 and 22 – 60 days, with disappearance of signal between 6 – 12 months (77). Hence, the fact that MRDTI only detects new or recent thrombus (73, 77) raises the additional possibility that it might be useful in the diagnosis of recurrent DVT which is currently problematic using conventional techniques (78).

*In vivo*, a signal appears at the periphery of thrombus (‘polo-mint’ appearance - see Fig. 2) within a few hours of formation, gradually extending centripetally as clot matures. Positive signal appears to be generated at a faster rate in vivo than in vitro, suggesting that an active process is involved. It has been known for half a century that nitric oxide, which is produced by endothelium and monocytes, reduces deoxyhaemoglobin to produce methaemoglobin (79). We hypothesise that endothelially-derived nitric oxide may be responsible for the characteristic ‘polo-mint’ changes of “fresh” thrombus - macrophages are known to migrate into thrombus during healing (80), and would therefore contribute to this process. Signal generation does not depend on blood flow or the filling of vessels with contrast, and image interpretation requires only the detection of high signal, rather than visualisation of unaffected veins, and can be performed competently by a non-radiologist (73). Although arterial thrombus, haematoma or areas of failed fat suppression may also generate regions of high signal, these can usually be differentiated using multiplanar reconstruction. Examples of venous thromboemboli imaged using this technique are shown in figures 3-5.

**Accuracy of MRDTI for the diagnosis of DVT**

In a pilot study, MRDTI was compared to contrast venography in 18 patients with proven DVT and visualized thrombus in 17. In addition, MRDTI revealed a number of other abnormalities
not detected by contrast venography: greater proximal extent of thrombosis in 4 patients, asymptomatic contralateral DVT in 1 patient, involvement of the deep femoral vein in 5 patients and involvement of the superficial venous system in 3. The one negative study was attributed to a technically poor examination in a patient with a hip prosthesis (69, 72).

MRDTI has now been formally validated against contrast venography for the diagnosis of symptomatic DVT (73). 101 patients of all ages with suspected DVT (confirmed in 53) and onset of symptoms from between 1 and 35 days were prospectively evaluated, with ultrasound performed in discordant cases. The technique proved to be highly accurate irrespective of the extent or position of thrombosis (Table 1), though accuracy was underestimated when contrast venography alone was used as the diagnostic standard compared to the composite standard of contrast venography and ultrasound, as ultrasound revealed clot in 3 of 4 cases (isolated gastrocnemius vein thromboses in all cases) in which MRDTI was positive but contrast venography negative. Scans were interpreted by a radiologist and physician trained in the technique, and inter-observer agreement was excellent (weighted kappa statistic: 0.94) As expected, MRDTI provided additional information over and above contrast venography: 17% of patients had asymptomatic contralateral DVT and another 17% with above knee DVT were found to have more proximal extension of clot than demonstrated by contrast venography. 12% of patients undergoing MRDTI were excluded because of contraindications, claustrophobia or inconclusive results, which is similar to the proportion undergoing contrast venography in whom the procedure failed or was inconclusive (73).

Figure 5: Coronal section through chest using magnetic resonance direct thrombus from the same patient using breath hold sequence showing large embolism in right main pulmonary artery.

Table 1: Diagnostic performance of Magnetic resonance direct thrombus imaging (MRDTI) in 101 patients with clinically suspected DVT according to the standard of either contrast venography alone or a composite of contrast venography/ultrasound (73)

<table>
<thead>
<tr>
<th>Location of DVT</th>
<th>Contrast venography</th>
<th>Contrast venography / ultrasound</th>
</tr>
</thead>
<tbody>
<tr>
<td>All</td>
<td>96 / 90</td>
<td>98 / 96</td>
</tr>
<tr>
<td>Isolated calf</td>
<td>92 / 94</td>
<td>100 / 98</td>
</tr>
<tr>
<td>Femoropopliteal</td>
<td>97 / 100</td>
<td>97 / 100</td>
</tr>
<tr>
<td>Ileofemoral</td>
<td>100 / 100</td>
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Contrast venography has been established as the diagnostic gold standard for DVT by default despite suboptimal diagnostic accuracy for gastrocnemius, deep femoral and pelvic vein clots (81-84), and this study highlights the inherent difficulties when...
comparing a new diagnostic technique to an imperfect gold standard, as new techniques will always appear to produce inferior results when the diagnostic gold standard is assumed to be infallible (85).

Although not formally validated in patients with asymptomatic DVT, it is reasonable to assume a similarly high accuracy as MRDTI provides a positive image of thrombus rather than detecting a surrogate effect on venous flow, and is as sensitive for below knee DVT, which comprise the majority of asymptomatic DVT (86), as for above knee (73).

**MRDTI for the diagnosis of PE**

MRDTI also appears to be sensitive and specific for the diagnosis of PE (70, 71, 76). In one small study of 10 patients with suspected PE (confirmed in 6) undergoing MRDTI and pulmonary angiography in which 250 vessel segments were assessed, all 6 emboli were seen at the large vessel level, and 2 additional emboli were visualized by MRDTI. At the small vessel level, 1 false negative occurred so that accuracy appeared higher at the lobar level, but apparently lower beyond this. However, this could also reflect decreased sensitivity of pulmonary angiography at this level (70, 71). It should also be noted that isolated subsegmental PE comprised only 6% of events in the PIOPED study (19) and that inter-observer disagreement about their presence on pulmonary angiography was frequent.

Scanning the legs in addition to the chest increases the reliability of the technique as venographic and postmortem studies show that up to 90% of PEs are associated with lower limb or pelvic DVT (87-89) and treatment for DVT and PE is the same, thus diminishing the importance of resolving small, subsegmental PEs where the prognosis is likely to be that of the source (27-31).

Early data indicating high diagnostic accuracy of MRDTI for VTE in performance studies suggest a putative role as a diagnostic test. However, outcome studies demonstrating that treatment can be safely withheld in suspected VTE on the basis of negative MRDTI under routine conditions are required, as similar performance cannot be assumed in the less predictable domain of clinical practice, and even a small margin of error may not be acceptable with a potentially lethal disease. For example, previous studies have demonstrated that outcome is excellent when treatment is withheld in patients with suspected DVT on the basis of negative contrast venography (7) or serial ultrasound (21, 22), and in suspected PE with negative pulmonary angiography (90) or normal VQ scintigraphy (8, 15). Without similar data, routine clinical use of MRDTI would be premature and could not be recommended. In general, it is accepted that management strategies associated with a 3 month risk of clinical VTE of < 2% in ‘VTE-negative’ patients are acceptable, as a 3 month event rate of 0.6 – 1.8% is seen in patients with suspected DVT and negative contrast venography or serial ultrasound, and suspected PE and negative pulmonary angiography or normal VQ scintigraphy (7, 8, 15, 21, 22, 90). Furthermore, an overall rate of unsuspected PE of 1.5% has been demonstrated in unselected patients referred for spiral CT of the chest (91).

Two such studies are now ongoing. The safety of managing patients with suspected PE on the basis of MRDTI alone is being evaluated in the Pulmonary Embolism Diagnosis at Queen’s Medical Centre (PDQ) trial, in which patients with suspected PE have been randomized to investigation with MRDTI.
VQ scanning or spiral CT (92) (www.nottingham.ac.uk/radiology/pdq/pdq.htm). Among the first 45 patients investigated using MRDTI (93), 12 were found to be positive for PE (defined as PE and / or DVT found on imaging) and 33 were negative for PE, 4 of whom received anticoagulants for other reasons. Patients regarded as negative for PE were followed up for 3 months and no cases of recurrent VTE were diagnosed. A study evaluating the safety of withholding treatment in outpatients with clinically suspected DVT on the basis of negative MRDTI has also just begun recruiting (the topMD trial: Trial of OutPatient MRI for DVT. Personal communication, Professor A. Moody).

**The future**

If these outcome trials demonstrate that MRDTI can safely be used in the diagnostic management of PE and DVT, a further large multi-centre outcome study evaluating cost-effectiveness as well as safety would be justified. An optimal strategy would involve initial triaging of patients on the basis of the pre-test probability and D-d (33, 51), followed by MRDTI in the remainder (Fig. 6).

The cost of standard MR without contrast and a scanning time of 40 - 60 minutes is in the region of 5 times that of ultrasound and 2-3 times that of VQ or spiral CT (23, 73, 94). However, acquisition times for MRDTI are lower, which should reduce this differential. Furthermore, costs are likely to fall as the technique becomes more widely used (95). Any cost effectiveness analysis would also have to take account of the reduced need for additional imaging steps and possibly a reduced length of hospital stay compared to conventional pathways. If validated as safe and cost effective, this approach could potentially allow standardisation and substantial simplification of the diagnostic process, particularly with regard to PE, with immediate treatment decisions made in most patients following the initial session of imaging.

**Conclusion**

MRDTI avoids the pitfalls of earlier invasive and noninvasive imaging techniques which either provide a negative image of thrombus or diagnose thrombus on the basis of surrogates such as haemodynamic changes. High accuracy for below knee and pelvic as well as proximal DVT and the ability to assess the lower limbs and thorax simultaneously potentially allows immediate treatment decisions to be made in most patients, as well as providing additional prognostic information which might allow a more titrated approach to treatment. Although there are, at present, far fewer data validating MRDTI in this role than for other imaging techniques, early results are highly encouraging and have highlighted the imperfect nature of the accepted diagnostic imaging standards for VTE. However, further confirmatory data are required before the technique could be widely recommended, in particular outcome data validating the safety of withholding treatment in suspected VTE on the basis of negative MRDTI, as well as an analysis of its cost effectiveness. Subject to such data, it is possible that the combination of the pre-test probability, D-d testing and MRDTI could allow a much-needed simplification and standardization of the current diagnostic paradigm of VTE.

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