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A feasibility study into the accuracy of Un-enhanced Magnetic Resonance Imaging of Pulmonary Arteries (uMRPA) in the diagnosis of Pulmonary Embolism

£1985.74 awarded

Lay Summary

A feasibility study to show whether unenhanced MRI of the pulmonary arteries (uMRPA) is able to demonstrate acute thrombus and how its accuracy compares to alternatives.

Pulmonary embolism (PE) – a wandering blood clot blocking a pulmonary artery, is a potentially fatal complication of thrombo-embolic disease. It affects a wide range of people. Diagnosis is essential as the risk of a fatal recurrence following an undiagnosed thrombo-embolic event is estimated at 30%.

PE is usually confirmed by computed tomography scan utilising radiation and an iodine injection to highlight the pulmonary arteries (CTPA). This is an extremely accurate technique (although can suffer technical failure) and safe for most patients. Patients contra-indicated for CTPA include those with significant allergies, poor kidney function and pregnancy. They are usually offered a less accurate technique or have the CT scan based on an assessment of radiation and iodine risk compared to the risk of failing to detect an embolus.

The alternative examination is lung scintigraphy, also using ionising radiation (although less dose), which is not available on emergency basis and is dependent on accurate clinical risk assessments to improve result accuracy. Laboratory tests for thrombosis are affected by patient-related factors that mimic thrombotic complications e.g. cancer, pregnancy.

If shown to be accurate, uMRPA could significantly reduce risk and improve diagnosis for this vulnerable patient group. Improved diagnostic accuracy should improve treatment options and therefore reduce complication rates for these patients. A reduction in complications should lead to shorter hospital stays and better use of NHS funds.

Principle Aim

The aim of this feasibility study is to demonstrate whether non-invasive unenhanced magnetic resonance of the pulmonary arteries (uMRPA) is a viable diagnostic alternative to lung scintigraphy for PE in patients contra-indicated for CTPA.

Primary research question:

Does uMRPA offer any improvement in sensitivity and specificity over lung scintigraphy in the diagnosis of PE? This would be achieved by quantitatively comparing reference standard imaging for PE (CTPA - Baile, King et al 2000),

against three uMRPA imaging techniques to obtain accuracy values and then comparing those with latest lung scintigraphy statistics.

Outcomes

Desired outcomes are proof that a diagnostic uMRPA examination can be undertaken within 20 minutes, with greater accuracy than alternatives. Short scan times and lack of expensive injections could be cost-effective for the NHS and less intimidating for the patient.

Data generated by this study would influence the justification and design of any major clinical trial into unenhanced MRI accuracy in the diagnosis of thrombus anywhere in the body.

Literature review & identification of knowledge gap

CTPA is recommended by the British Thoracic Society as the initial lung imaging for non-massive PE. The alternative examination - lung scintigraphy, has not been universally adopted as a reference standard because of the large percentage of indeterminate examinations (PIOPED 1990), and lack of emergency availability. CTPA is contra-indicated for some patients due to the use of radiation and iodinated contrast agents e.g. pregnancy - radiation risk (Scarsbrook, Gleeson 2007), poor renal function - contrast-induced renal nephropathy (McCullough 2008), and iodine allergy - anaphylaxis risk.

The ideal diagnostic investigation is a free-breathing technique, as PE-positive patients usually have breathing difficulties. It should differentiate acute thrombus from all other tissues and not require additional contrast enhancement or ionising radiation or have any other potential health risks to the patient. MRI has excellent tissue characterisation properties without using ionising radiation or additional contrast agents and has potential to fulfil these criteria (although there are safety issues related to the strong magnetic fields).

There have been no studies published within the last 10 years dedicated to investigating unenhanced MRI techniques in PE diagnosis, although Kluge and colleagues have conducted numerous studies using contrast-enhanced techniques. These studies, and those by others, have applied conventional radiological methods e.g. angiography and ventilation/perfusion, to MRI and so become invasive through the application of extravascular contrast agents and prone to technical failure from contrast bolus interruption (e.g. Bagga & Bis 2000, Oudkerk, van Beek et al 2002, Kluge, Luboldt, and Bachman 2006). However, with improved MR hardware, three MRI techniques could potentially demonstrate acute thrombus without extra contrast agents.

Moody, Liddicoat and Krarup (1997) suggested using the inherent MR signal characteristics of acute thrombus for positive demonstration (hyperintense on T1w images due to methaemoglobin presence, Farahani, 1999) in both DVT and PE imaging. They presented a small number of patients with a mixture of comparison tests. Assessing results with angiography alone gave 100% accuracy. A later study (Fraser, Moody et al 2002) quoted 94-96% sensitivity and 90-92% specificity in DVT studies. Previously, this sequence suffered from misregistration artefacts caused by sequential slice acquisition during multiple breath-holds. Recent advances in MR hardware, improving speed, could result in multi-slice or volume acquisition using breath-hold or free-breathing techniques.

The balanced steady-state free precession sequence (b-SSFP or MR real-time) is used to great effect in cardiac scanning, (Carr, Simonettie et al 2001).

It is a fast sequence, amenable to breath-hold use with high inherent contrast between fluid (eg blood) and other tissues. Most studies using MR in the investigation of PE use this sequence as a start point eg Kluge and colleagues found 80% sensitivity and 75% specificity to the segmental level in 2006.
Francois, Tuite et al (2009) have used a modified b-SSFP sequence to produce a volume, free-breathing, un-enhanced MR angiographic examination of the pulmonary veins (called 'Native' MRA). Accuracy for pulmonary vein demonstration was similar for both the 'Native' MRA and a control Contrast Enhanced-MRA. This technique has not yet been studied for PE diagnosis.

Methodology

This is a quantitative evaluation of the presence of acute thrombus in the pulmonary arteries - a prospective, repeated measures experiment. The data collected is univariable, nominal/categorical: merely counts of correctly and incorrectly identified thrombus. Standard reference data is generated for each subject from the CTPA examination. Subjects are further observed (within 24 hours) using up to three different MR techniques.
For optimal data collection MRI should occur immediately after CTPA to minimise errors due to clot size and position changes. This is not possible in any busy scanning department servicing a variety of clinical specialities.
Anticoagulation therapy can be initiated prior to CTPA – it does not dissolve thrombus but prevents further propagation. Therefore anti-coagulation therapy prior to MRI will not significantly affect the appearance of any thrombus load.
Stein, Yaekoub et al (2010) reviewed a large group of PE positive patients who were not anti-coagulated and who had serial CTPA to evaluate clot evolution (timings were variable). 40% completely resolved between 2-7 days although the rate of resolution varies with thrombus size and position, main vessels resolving faster than segmental branches.
In the PIOPED II study (Stein, Woodward, Weg et al, 2006) comparing CTPA, lung scintigraphy and conventional pulmonary angiography, the range of time difference between examinations was 10-97 hours (mean 40 +/- 21). Discordent results have been blamed on excessive time delays between CTPA and conventional angiography, allowing clot propogation.
This shows that speed is vital to minimise errors in thrombus identification due to changes of position but 24 hours is not an unreasonable time scale.

Method

Study Population

Subjects are systematically selected – see box 1, and provide 2 lungs for separate study.

Box 1

Inclusion Criteria

Positive for PE diagnosed by CTPA from scanner A

Exclusion Criteria

MR scanning not possible within 24 hours of CTPA

Non-adult, MR un-safe, pregnancy, unable to consent.

Recruitment and consent will be undertaken by members of a patient's clinical team, following acceptance of the CTPA referral by a member of the Cardio-thoracic radiology team.
Sample size is small to keep this feasibility study manageable in costs and time. Patients positive for PE are selected as the study aim is to show sequence potential in accurately identifying thrombus within an acceptable scan time. The study also aims to provide evidence of methodological capability prior to a larger clinical trial with sample sizes to give statistical power. 10 participants provide 20 lungs (blinded thrombus location), allowing sensitivity & specificity computation. Disease prevalence in the intermediate and high-risk category is aproximately 35% (PIOPED I had 33% global prevalence, PIOPED II had 23% with a greater proportion of low probability subjects).
The hospital generates 10 CTPA referrals per week from moderate to high probability patients (3-4 positive patients per week). With 1-2 volunteers per week, data collection should take 5-8 weeks to achieve 10 positive participants.

Data collection method
This is a clinical experiment. 10 participants (20 lungs) will undergo MRI, using up to 3 different MRI techniques, within 24 hours of their CTPA. Scanning will be undertaken by 2 radiographers. To maintain participant safety, MR scanning will not exceed the 'controlled' mode of operation and total scanning time will not exceed 45 minutes.
All participants will be scanned using all technical possibilities to provide matched data for analysis. However, data from partial completion of the MRI protocol will be included in analysis for that technique's evaluation only.
All MR and CT image sets are anonomised and randomised: each MR technique image set is then separately and randomly reviewed by 2 consultant radiologists, blinded to previous imaging results, but with access to clinical information. Image sets are read using the PE Scoring Model, based on PIOPED II criteria, for objective quantification. Image review will occur no earlier than 2 weeks after the last participant is scanned to reduce reader bias.
The PE Scoring Model is based on the PIOPED II diagnostic criteria:-
An intraluminal defect with sharp interfaces within the lumin of a blood vessel, producing :-
a) complete arterial occlusion
b) central arterial defect surrounded by blood
c) peripheral intraluminal filling defect with acute angles to the vessel wall.

Data analysis method
Each sequence and combination will have accuracy statistics (sensitivity, specificity) generated on a per-embolism basis. The lack of power dictated by the small sample size means that confidence intervals are meaningless. Accuracy statistics will be compared with best available information for lung scintigraphy and lung SPECT scintigraphy to test the primary hypothesis. Inter-observer variability will be assessed by Kappa to provide a measure of analysis agreement.

Ethical implications of study

To assess patient opinion and volunteer potential, a number of symptomatic patients were asked their opinions on this proposal. Patients were concerned about the MRI environment especially if they were having breathing difficulties. Patients who are more likely to volunteer will probably have only small segmental PEs, which will affect the conspicuity of lesions.

This proposal has been discussed with colleagues who are keen to explore alternatives to lung scintigraphy (cardio-thoracic radiologists - one of whom is a co-applicant, and a referring clinician with a strong interest in research).

All participants' rights, as stipulated by the Declaration of Helsinki, are maintained. All participants will have a full explanation of the procedure from clinical staff trained in Good Clinical Practice (GCP) methods prior to voluntarily consenting. No harm is being done (MR at 1.5T, has not yet been proven unsafe for non-contra-indicated patients – Shellock - MR Safety website) and no treatment is being withheld, delayed or affected by the additional scanning. MR scanning will be undertaken in accordance with hospital local rules and Medicines & Healthcare products Regulatory Agency (MHRA) guidelines to maintain participant safety. All data is anonomised for patient confidentiality.

Potential Impact of Study

The potential of incorrect diagnosis and therefore treatment is hard to quantify: an undiagnosed pulmonary embolism can progress to fatality (in 30% of patients according to Dalen & Alpert, 1975), but there is also a 3% fatality risk associated with anti-coagulation therapy (Levine, Raskob, Beyth, Kearon, Schulman 2004).

Accuracy statistics vary for lung scintigraphy and CTPA depending on clinical probability scores, PIOPED II reporting sensitivity of 83% for CTPA. Ohno, Higashino et al quoted 67% sensitivity for planar scintigraphy in 2004.

If uMRPA compares favourably with lung scintigraphy in costs and duration and performs better then there are savings of economy for the NHS and in mortalities for patients.

Dissemination strategy

The study will be reported using the STARD (Bossuyt, Reitsma et al 2003) and QUADAS (Whiting, Rutjes et al 2003) guidelines to ensure compatibility with systematic review procedures.

The results will be published via the UK radiological and radiographic community, using journals ('British Journal of Radiology' – BJR and 'Radiography') and poster presentation at United Kingdom Radiological Conference (UKRC). Published papers receive a unique identifying number – the PMID citation reference, which can be traced by the international community via PubMed, Embase etc. This would ensure that this information was accessible and visible to a large proportion of the UK and international radiological community.

References

Bagga H, Bis KG, 2000. ‘MR Imaging and MR Angiography of Pulmonary Artery Stenosis with Tubular Hypoplasia in Pregnancy’. AJR 175:1462-1464

· Baile EM, King GG, Mueller NL, D’Yachkova Y et al 2000. ‘Spiral CT is comparable to angiography for the diagnosis of PE’. Am Journal of Respiratory and Critical; Care Medicine 161 (3):1010-1015

· Bossuyt PM, Reitsma JB, Bruns DE, Gatsonis CA et al 2003.’Towards complete and accurate reporting of studies of diagnostic accuray: the STARD initiative’. Ann. Intern. Med. 138:40-4.

· British Thoracic Society Standards of Care Committee for PE Guidelines Development Group, 2003. ‘British Thoracic Society guidelines for the management of suspected acute PE’. 2003 Thorax; 58: 470-484

· Carr JC, Simonetti O, Bundy J, Debiao L, Pereles S, Finn JP 2001. ‘Cine MRA of the Heart with Segmented True Fast Imaging with Steady State Precession.’ Radiology 219:828-834.

· Dalen JE, Alpert JS. 1975. ‘Natural history of pulmonary embolism’. Prog Cardiovasc Dis 17(4):259-70

· Farahani K 1999. ‘MRI of thermally denatured blood: Methaemoglobin formation and relaxation effects’. Magnetic Resonance Imaging 17(10): 1489-94.

· Francois CJ, Tuite D, Deshpande V, Jerecic R, Weale P, Carr JC 2009. ‘Pulmonary Vein Imaging with unenhanced 3-Dimensional Balanced Steady Stae Free Precession MR Angiography’. Radiology 250:932-939.

· Fraser JD, Moody AR, Morgan PS, Martel AL, Davidson I, 2002. ‘Diagnosis of lower-limb DVT: a prospective blinded study of MR DTI’. Annals of Internal Medicine 136 (2):89-98

· Klug A, Luboldt W, Bachman G. 2006. ‘Acute PE to the subsegmental level: Diagnostic accuracy of 3 MRI techniques compared to 16-MDCT’. AJR 187:W7-W14

· Levine MN, Raskob G, Beyth RJ, Kearon C, Schulman S 2004. ‘Hemorrhagic complications of anticoagulant treatment. The 7th ACCP Conference on antthrombotic and thrombolytic therapy’. Chest 126 (suppl3): 2875-3105

MHRA 2007. 'Safety Guidelines for Magnetic Resonance Imaging Equipment in Clinical Use'. DoH, UK.

· McCullough PA, 2008. ‘Radiocontrast-Induced Acute Kidney Injury’. Nephron Physiol 109:61-72

· Moody AL, Liddicoat A, Krarup K, 1997. ‘MR pulmonary angiography and direct imaging of embolus for the detection of pulmonary emboli’. Invest Radiol 32:431-40

· Ohno Y, Higashino T, Takenaka D et al, 2004.’MR Angiography with Sensitivity Encoding (SENSE) for suspected PE: Comparison with MDCT and Ventilation-Perfusion Scintigraphy’. AJR 183:91-98.

· Oudkerk M, van Beek EJ, Wielopolski P, van Oijen PM et al 2002. ‘Comparison of CE-MRA and conventional pulmonary angiography for the diagnosis of PE: a prospective study’. Lancet 359 (9318):1643-7.

· PIOPED Investigators 1990. ‘Value of the ventilation/perfusion scan in acute pulmonary embolism: results of the prospective investigation of pulmonary embolism diagnosis (PIOPED)’. JAMA 263:2753 –2759

· Scarsbrook AF, Gleeson FV, 2007. ‘Investigating suspected pulmonary embolism in pregnancy’. BMJ 334 (7590): 418–9

· Stein PD, Woodward PK, Weg JG, Wakefield TW et al (PIOPED II) 2006. 'Diagnostic pathways in acute pulmonary embolism: recommendations of the PIOPED II Investigators'. Am J Med 119:1048-55
· Stein PD, Yaekoub AY, Jangua M, Patel RM et al 2010. 'Resolution of Pulmonary embolism on CTPA'. AJR 194:1263-8
· Shellock FC, 2006. www. MRI safety.com. Accessed 01.05.2010
· Whiting P, Rutjes AWS, Reitsma JB, Bossuyt PM, Kleijnen J, 2003. 'The development of QUADAS: a tool for the quality assessment of studies of diagnostic accuracy included in systematic reviews'. BMC Medical Research Methodology 3:25