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Research article

Magnetic resonance angiography imaging of pulmonary embolism using agents with blood pool properties as an alternative to computed tomography to avoid radiation exposure

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ABSTRACT

Purpose: To evaluate the feasibility and accuracy of a combined magnetic resonance angiography (MRA) - magnetic resonance venography (MRV) protocol using contrast agents with blood pool properties, gadofosveset trisodium and gadobenate dimeglumine, in the evaluation of pulmonary embolus (PE) and deep venous thrombosis (DVT) as compared to the standard clinical reference imaging modalities; computed tomography pulmonary angiography (CTPA) and color-coded Duplex ultrasound (DUS).

Materials and methods: This prospective clinical study recruited patients presenting to the emergency department with clinical suspicion for PE and scheduled for a clinically indicated CTPA. We performed both MRA of the chest for the evaluation of PE as well as MRV of the pelvis and thighs to evaluate for DVT using a single contrast injection. MRA-MRV data was compared to the clinical reference standard CTPA and DUS, respectively.

Results: A total of 40 patients were recruited. The results on a per-patient basis comparing MRA to CTPA for pulmonary embolus yielded 100% sensitivity and 97% specificity. There was a small subset of patients that underwent clinical DUS to evaluate for DVT, which demonstrated a sensitivity and specificity of 100% for MRV.

Conclusions: This single-center, preliminary study using contrast agents with blood pool properties to perform a relatively rapid combined MRA-MRV exam to image for PE and above knee DVT shows potential as an alternative imaging choice to CTPA. Further large-scale, multicentre studies are warranted.

1. Introduction

The Prospective Investigation of Pulmonary Embolism Diagnosis III (PIOPED III) study of the diagnostic performance of magnetic resonance angiography (MRA) reported a high rate of technically inadequate images, ranging from 11 to 51%, which suggested poor performance for using MRA in the diagnosis of pulmonary embolism (PE) [1,2]. In contrast, the PIOPED II study utilizing multi-detector computed tomography pulmonary angiography (CTPA) reported excellent results, with a mere 6% inconclusive rate due to poor image quality [3]. Largely based on this study, CTPA has become the mainstay for diagnosis of PE. For this purpose, CTPA is widely accepted as the non-invasive imaging modality of choice for the evaluation of PE, with reported interobserver agreement equivalent to that of ventilation/perfusion (V/Q) scans and conventional pulmonary angiography [4–7], independent of the extent of reader experience [8]. Nonetheless, CTPA has notable drawbacks, most importantly exposure of patients to ionizing radiation and nephrotoxic contrast media. Radiation is of particular concern at centers

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using CTPA combined with computed tomography venography (CTV), adding an even greater gonadal radiation dose [9].

Pulmonary embolism (PE) is a common clinical condition with an annual incidence of 4–21 out of 10,000 per year [10]. Left untreated, PE carries a 30% mortality rate, however this is significantly reduced by prompt diagnosis and treatment [10]. One can argue that given the poor clinical outcome of untreated PE, the diagnostic benefit of CTPA must outweigh the potential radiation risks. Extrapolating data from a large multicenter diagnostic study performed in twelve US emergency departments (ED) [11], approximately 1 to 2% of all ED patients undergo CTPA to rule out PE, making CTPA one of the most commonly ordered ED computed tomography exams. Based on previous studies [8,12–14], the overall prevalence of PE was only 5 to 33%. This means that the vast majority of patients who undergo a single CTPA scan have negative results, but now are potentially at increased risk of future radiation-related neoplasm. Thus, the large number of CTPA studies performed combined with the excessive number of negative studies estimated validates any effort to reduce the exposure of patients to unnecessary radiation when appropriate. This is particularly true for younger patients.

Although there is continued controversy concerning the radiation risks of medical imaging [15], there is undoubtedly a finite risk [16,17], particularly for those between 15 and 40 years of age. In these younger patients, exposure to just a single CTPA induces an estimated mean lifetime attributable risk of cancer mortality ranging from 31 to 57 out of 100,000 [16]. Documented literature suggests significant stochastic risks due to the glandular radiation dose to the female breast [18]. A single CTPA exam in females aged 17 to 19 years likely causes 57.4 more cancers per 100,000 exams, and in females aged 20 to 29 years it is likely to cause 48.7 more cancers per 100,000 [16]. In addition, a study testing peripheral blood lymphocytes to determine the relative number of phosphorylated histones before and after a CTPA study demonstrates a significant increase in areas of radiation-induced DNA damage following a CTPA exam [19]. Regardless of how one chooses to interpret the radiation risk associated with CT scanning, there is no dispute in the literature regarding the benefits of avoiding radiation exposure by using an alternative imaging modality when available [15], and this is despite the significant evolutionary improvements in modern CT scanners allowing for reduced radiation dose strategies [20–24].

PIOPED III surmised that technical factors appear more significant in producing good or poor quality images than do patient factors or reader effects [25]. It addressed differences in the number of technically adequate studies across different imaging sites participating in the study, which could have been attributable to differences in equipment, software, particular MR protocol, technologists' experience and training, level of radiologists' supervision and type of contrast media used [1,2]. PIOPED III also demonstrated significantly better sensitivity and specificity when combined MRA-pelvic MRV studies were obtained [1]. Since PIOPED III (where studies were performed between 2006–2008), there have been significant improvements in MR equipment and imaging protocols. This has led to subsequent studies showing relatively improved accuracy of MRA for the evaluation of PE compared to CTPA [26,27].

PIOPED III furthermore determined that poor vascular opacification and motion artifacts were the main culprits in classifying studies as uninterpretable [25]. This suggests that the technical success rate of MRA could be increased through improved vascular opacification [25]. One approach to achieve this goal is to use a "blood pool" contrast agent, that remains confined to the intravascular space for a relatively long duration (compared to the more commonly used "extracellular fluid" (ECF) gadolinium agents, which rapidly leave the intravascular space and distribute throughout the extracellular fluid space). In PIOPED III there was a statistically significant increase in pulmonary signal-to-noise ratio (SNR) and contrast-to-noise ratio in the studies using gadobenate dimeglumine (MultiHance, BRACCO Diagnostics, Princeton, NJ), an agent with partial protein binding that increases T1 relaxivity and is thought to have some weak blood pool properties, as compared to those using gadopentetate dimeglumine (Magnevist, Bayer HealthCare LLC, Whippany, NJ), a purely extracellular fluid (ECF) agent [25]. The closest of the available gadolinium based contrast agents to a true "blood pool" agent has been gadofosveset trisodium (Ablavar, Lantheus Medical Imaging Inc., North Billerica, MA). As stated, gadobenate dimeglumine has weak protein binding properties [28] that confer advantages in T1 shortening, but formally it is not classified as a blood pool agent. Gadofosveset trisodium has a T1 relaxivity that is approximately three times that of gadobenate dimeglumine [29], although it is administered at 30% the dose (0.03 mmol/kg vs. 0.1 mmol/kg). Recently, it has been reported that there is no significant difference in SNR and mean vessel edge sharpness between these two contrast media for steady-state angiographic imaging when acquisition begins within 5 min post injection [30]. This is felt to be due to the combination of gadobenate dimeglumine being dosed greater than is gadofosveset trisodium and having a longer intravascular half-life than other ECF agents. This study suggested that gadobenate dimeglumine behaves like a blood pool agent over at least a short duration [29–31]. The reported intravascular half-life for gadobenate dimeglumine is between 5 and 36 min, while that of gadofosveset trisodium is 30 min [30].

The purpose of our study, therefore, is to address the overall diagnostic impact of MRA at 3.0 T as compared to CTPA for the workup of PE in the ED, using either gadofosveset trisodium or gadobenate dimeglumine.

2. Methods

2.1. Study subjects

This study was approved by the local institutional ethics review board. All participants provided written informed consent. Inclusion criteria included patients with a minimum age of 18 years presenting to the ED with clinically suspected PE and undergoing evaluation by clinically indicated CTPA. Exclusion criteria were contraindication to MRI, claustrophobia, pregnancy, an estimated glomerular filtration rate (GFR) of less than 30 mL/min/1.73m^2, and unwillingness to participate in the study. Thirty consecutive patients ranging in age from 36 to 79 years and weighing from 48 to 136 kg underwent CTPA and contrast-enhanced MRA with gadofosveset trisodium. Because gadofosveset trisodium was withdrawn from the Canadian market in the course of our study, another thirteen consecutive patients ranging in age from 34 to 90 years and weighing from 66 to 110 kg underwent CTPA and contrast-enhanced MRA with gadobenate dimeglumine. Three patients (1 gadofosveset trisodium and 2 gadobenate dimeglumine) were claustrophobic and were unable to complete the MRA. Of the total forty included patients, 9 underwent clinically indicated color-coded Duplex ultrasound (DUS) of the lower limbs for comparative evaluation to MRV. The delay time between the CTPA and MRA-MRV examinations was within 72 h, with 95% of the participants having the two studies completed within 24 h.

2.2. Computed tomography pulmonary angiography

All CTPA examinations were clinically indicated and ordered for the workup of PE. These were performed on a 64-slice CT scanner (LightSpeed VCT; GE Healthcare, Milwaukee, Wis). The standardized PE protocol has been previously described [26]. The contrast medium used was iodixanol 320 mg l/mL (Visipaque, GE Healthcare Ireland, Cork, Ireland), dosed at 1 mL/kg and administered as a bolus followed by 20 mL of NaCl 0.9% (NS) injected through an 18-gauge catheter placed into an antecubital vein, both at rates of 5 mL/sec using a dual-chamber power injector (Medrad Stellant CT injector, Bayer Heath Care LLC, Whippany, NJ).

2.3. CTPA interpretation

All CTPA exams were interpreted by staff radiologists working at our institution. The exams were viewed on the McKesson diagnostic

imaging work station (McKesson Canada, Montreal, QC) and the images were reformatted in coronal and sagittal planes as required by the interpreter. The final clinical report was deemed the gold standard for this study.

2.4. Duplex ultrasonography of the lower limbs (DUS)

All the Duplex ultrasound (DUS) examinations of the lower limbs (n = 9) were performed on the Toshiba Aplio 500 Platinum system (Toshiba Medical Systems Inc., Tustin, CA). The examinations were performed by trained ultrasound technologists using standard protocol [32,33] and then verified on site by radiologists from our institution. The images were reviewed on the McKesson diagnostic imaging work station (McKesson Canada, Montreal, QC). The final clinical radiology report was used as the gold standard for this study.

2.5. Magnetic resonance angiography (MRA) and venography (MRV)

All MRA-MRV exams were performed using a clinical 3.0 T whole body MR scanner (MAGNETOM Skyra, Siemens Medical Solutions, Erlangen, Germany) equipped with up to 204 coil elements and 128 channels (204 × 128), a gradient system with a maximum gradient strength of 45 m T/m and a slew rate of 200 T/m/s. For signal reception, a combination of a 32-channel spine array coil and two 18-channel anteriorly placed body coils were used. The contrast agents utilized in this study were gadofosveset trisodium (Ablavar, Lantheus Medical Imaging Inc., North Billerica, MA) and gadobenate dimeglumine (MultiHance, Bracco Diagnostics, Princeton, NJ), with doses adhering to the package insert of each agent (0.03 and 0.1 mmol/kg respectively). A key point in this protocol was diluting the single dose of each contrast agent with NS to a total volume of 40 mL and injecting intravenously over the course of the acquisition at 2.5 mL/sec (fixed 16 s injection). This was to prevent truncation and blurring artifacts that can occur if the contrast concentration varies over the acquisition time [34]. Breath holds ranged from 12 to 20 s.

Optimal pulmonary arterial enhancement was determined by test bolus technique in the coronal plane. Intravenous injection through an 18- or 20-gauge catheter (placed at the antecubital vein) of 1.0 mL of diluted contrast medium at a flow rate of 2.5 mL/s followed by a 20 mL NS bolus at the same rate was performed during dynamic imaging acquisition at the level of the pulmonary trunk. Parameters for test bolus imaging were: TE/TR 0.97/2.6 ms; FA = 25 °; receiver bandwidth = 950 Hz/pixel; iPAT = 2; acquisition time = 58 s; FOV = 450 x 310 mm; slice thickness = 7 mm; acquisition voxel size 1.37 × 1.37 × 7 mm, and reconstruction voxel size 1.3 × 1.3 x 7 mm. Peak enhancement at the level of the pulmonary trunk was taken as the optimal delay time for magnetic resonance pulmonary angiogram (MRA). Initially, an unenhanced coronal MRA was obtained using a three-dimensional fast gradient-echo (angio 3D-FGRE) sequence to serve as a subtraction mask with the following nominal parameters: TE/TR 1.16/3.2 ms; FA = 25 °; receiver bandwidth = 580 Hz/pixel; iPAT = 4; FOV = 450 x 315 mm; slice thickness = 1.3 mm; true acquisition voxel size 1.14 × 0.9 x 2.1 mm, reconstruction voxel size 0.9 × 0.9 x 1.3 mm, scan time 12–20 sec, averaging 16 s. The MRA acquisition was obtained by injecting the remainder of the diluted contrast medium followed by 20 mL of NS using a dual-chamber power injector (Medrad Spectris Solaris EP MR Injection System, Bayer Heath Care LLC, Whippany, NJ), both at a rate of 2.5 mL/sec. A high-resolution breath-hold MRA acquisition was acquired using the identical angio 3D-FGRE sequence as for the unenhanced MRPA. Subsequently, a second-pass (with only the FA changing to 20 °) and third-pass (with only the FA changing to 15 °) MRPA acquisition was acquired as soon as the patient was able to comply for second and third breath hold. It is noteworthy that if a patient experiences difficulties breath holding, one can consider excluding either or both of the second- and third-pass sequences, particularly if the first-pass sequence is deemed of diagnostic quality. In our study, we applied this procedure technique to the last 13 patients recruited, omitting the third-pass sequence if we deemed the first- and second-pass sequences of diagnostic quality in order to shorten the exam duration and number of breath-holds without sacrificing diagnostic efficacy.

Thoracic and abdominal coronal plane 3D-MRA/MRV late phase imaging with breath hold and a fat-suppressed, 3D spoiled gradient echo technique (VIBE) was acquired following the 3 phases of MRA with the following parameters: TE/TR 1.16/3.3 ms; FA = 9 °; receiver bandwidth = 500 Hz/pixel; iPAT = 4; TA = 0.19; FOV = 400 x 400 mm; slice thickness = 1.5 mm; acquisition voxel size 1.3 × 1.3 x 1.5 mm, reconstruction voxel size 1.3 × 1.3 x 1.5 mm, average acquisition time 19 s. Free breathing coronal MRV of the pelvis and above-knee femoral veins was then acquired using the same VIBE parameters except the acquisition voxel size changing to 1.0 × 1.0 x 1.0 mm, scan time 96 s, with shallow free breathing throughout the sequence.

All acquired images were reconstructed in sagittal and axial planar views, as required by the interpreting radiologist.

2.6. MRA and MRV image analysis

Coronal source images and axial and multi-planar reformatted images were used for interpretation. Image interpretation was performed by two experienced radiologists, both unaware of patients' clinical data and clinical CTPA and DUS results. The MRA-MRV images were analyzed using eFilm Workstation 3.4 (Merge Healthcare Inc., Chicago, IL).

The criterion for PE diagnosis by MRA was the direct visualization of hypointense thrombotic material in a pulmonary artery (filling defect) distinguishable from the surrounding lung tissue (Figs. 1 and 2). Similarly, deep venous thrombosis (DVT) diagnosis was assigned to filling defect(s) in the inferior vena cava (IVC), pelvic veins and/or lower limb veins distinguishable from surrounding tissue (Fig. 3). The CT and MR studies were documented for interpretation in the following manner: Pulmonary embolus as detected by MRA was compared to CTPA and graded as either concordant or discordant. Further specification regarding lack versus presence of thrombi and location as main, lobar, segmental and subsegmental pulmonary arterial segments was documented. Above-knee DVT detected by MRV was compared to DUS as positive or negative.

The quality of the MRA was assessed as either diagnostic or non-diagnostic by each radiologist interpreting the study.

2.7. Statistical analysis

With CTPA being considered the gold standard, the sensitivity, specificity and efficiency of MRA for PE detection were calculated on a per-patient basis and per-segment basis. Due to correlated data on a per-patient basis, sensitivity, specificity and efficiency are presented for illustrative purpose without standard errors. For segmental and subsegmental pulmonary arteries, where the results between both agents were different, agents were compared using chi-square statistics. This comparison was not done on a per-patient basis due to correlated data.

With DUS being considered the gold standard, the sensitivity, specificity, and accuracy of MRV for above-knee DVT detection were calculated on a per-patient basis.

To account for agreement due to chance, kappa statistics were calculated on a per-segment basis to estimate the inter-reader agreement for detection of PE by MRA. Such kappa statistics were not calculated on a per-patient basis due to correlated data within patients.

3. Results

Of the 30 patients recruited for MRA-MRV with gadofosveset trisodium, 29 completed the exam with 1 patient unable to complete the exam due to claustrophobia. Of the 13 patients recruited for MRA-MRV with gadobenate dimeglumine, 11 completed the exam with 2 patients

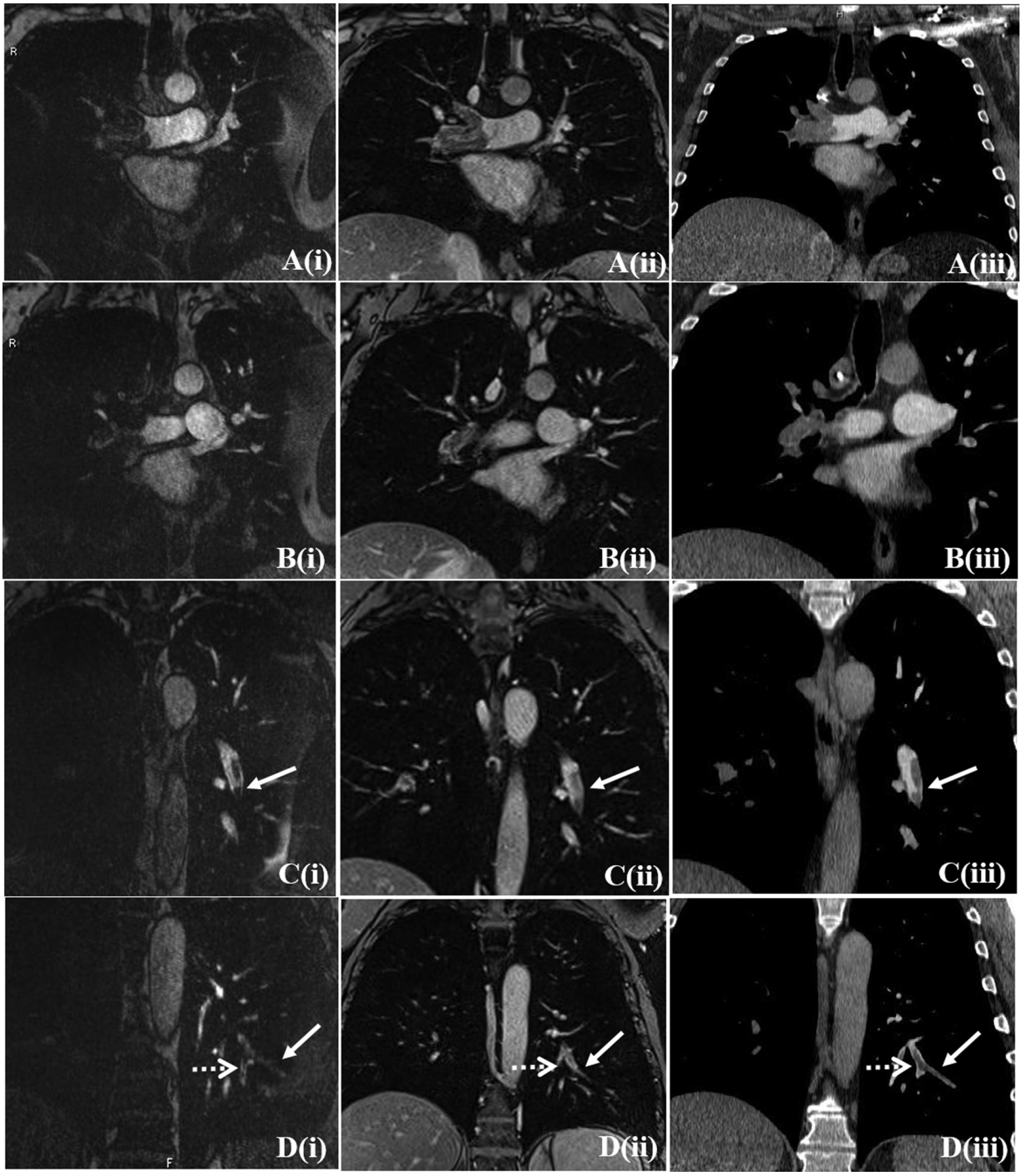

Fig. 1. MRA images obtained using gadofosveset trisodium (Ablavar, Lantheus) showing (i) first-pass angiography, (ii) late phase (VIBE) angiography and (iii) CTPA correlation of PE in: A. right main pulmonary artery, B. right upper and lower lobar arteries, C. left posterobasal segmental artery (solid arrow) and D. left posterobasal subsegmental arteries (solid and broken arrow).

dropping out for claustrophobia. The remainder of the studies were diagnostic. There were no truncation and blurring artifacts interfering with the diagnostic quality of the studies, confirming that dilution of the contrast agent with NS and injecting intravenously over the course of the acquisition was key to our protocol success [34]. Of the gadofosveset trisodium group, 4 out of 29 patients had PE. Within this same group, 6 patients underwent evaluation by DUS and 4 out of these 6 patients had DVT. In the gadobenate dimeglumine group, 3 out of the 11 patients had PE. Within in this group, 3 patients underwent DUS but none had DVT. Table 1 summarizes the results for each group. CTPA was used as the standard reference for PE and DUS as the standard reference for DVT, and these were compared to the MRA and MRV results.

One patient showed possible allergic reaction to gadobenate dimeglumine, presenting with rash approximately 15 min after injection and treated with 50 mg intravenous diphenhydramine (Benadryl, Johnson and Johnson Inc., Guelph, ON) and then observed in the emergency department for 4 h without further complications.

On a per-patient basis, the proportion of agreement between radiologists was calculated as 0.958. Results for agreement between radiologists on the per-segment basis were as follows: Main pulmonary artery proportion of agreement calculated as 1.00 (SE = N/A)

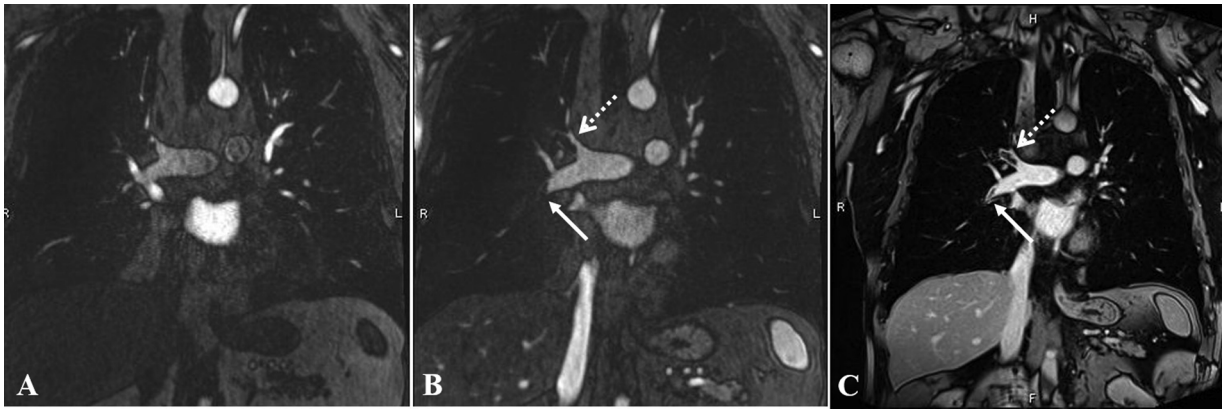

Fig. 2. MRA images obtained using gadobenate dimeglumine (MultiHance, BRACCO). A. First-pass angiography is non diagnostic due to miscalculated contrast timing, and recovered diagnostic quality images on B. second-pass angiography and C. late phase (VIBE) imaging performed at 10 min delay after contrast injection. In fact, late phase (VIBE) images showed excellent contrast of the thrombus and vessel wall. Broken arrow points to thrombus in the right upper lobar artery and solid arrow shows thrombus in the interlobar artery.

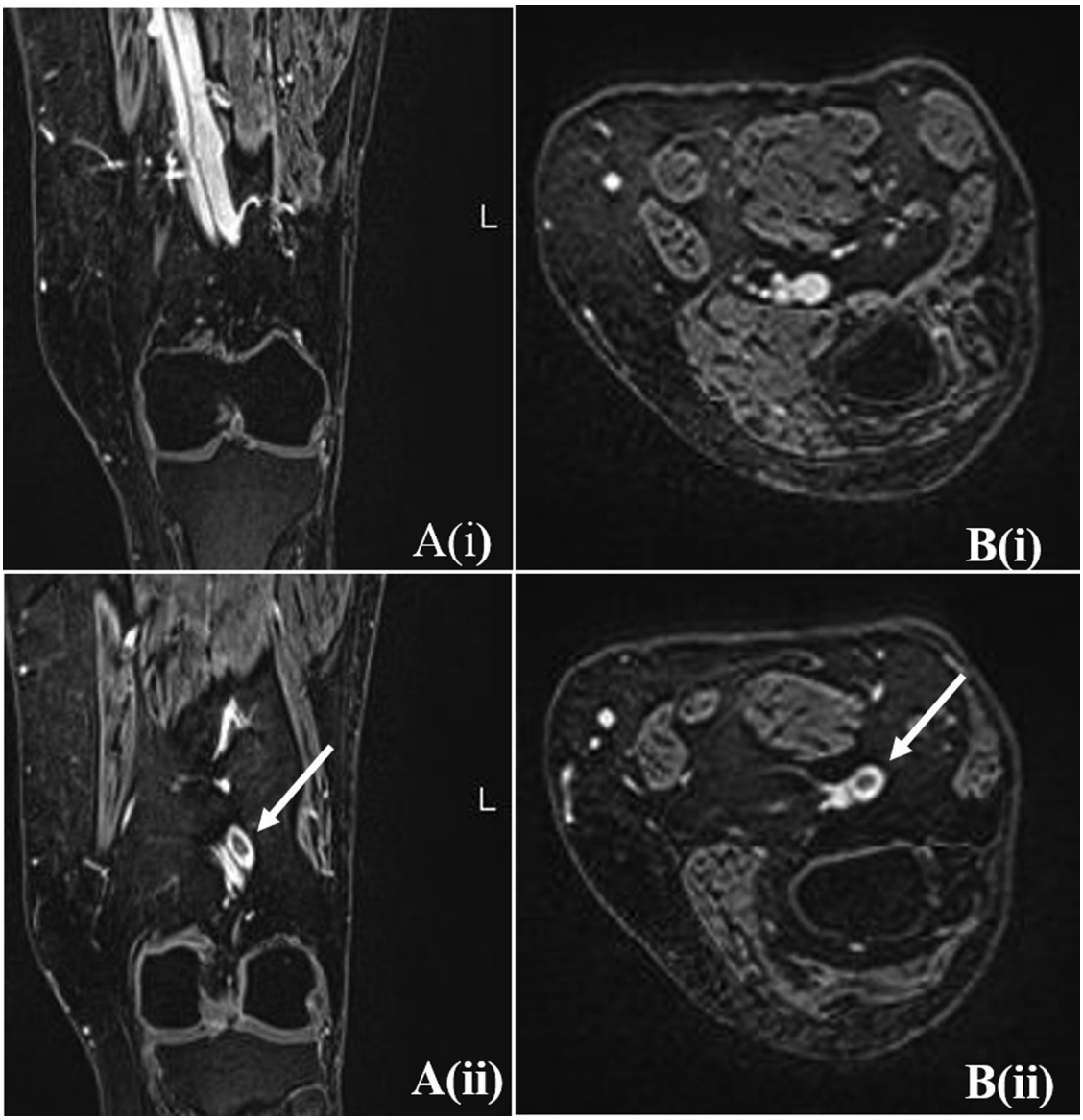

Fig. 3. MRV of the left thigh in A. coronal plane and B. axial plane showing (i) normal opacification in the superficial femoral vein and (ii) thrombus in the superficial femoral vein (solid arrow).

Table 1
Summary of statistics for MRA and MRV detection of PE and DVT using gadofosveset trisodium (Ablavar) or gadobenate dimeglumine (MultiHance).

	Blood pool agent	
	gadofosveset trisodium	gadobenate dimeglumine
MRA for PE detection		
Number of patients recruited	30	13
Number of diagnostic exams	29	11
Number of non-diagnostic exams/ claustrophobic patients	1	2
Number of patients with MRI diagnosed PE	4	3
Number of patients with CTPA diagnosed PE	4	3
Results per patient (without standard errors)		
sensitivity	0.933	1.000
specificity	0.990	1.000
efficiency	0.983	1.000
Results per segment		
Main pulmonary arteries		
sensitivity	1.000 (SE = N/A)	1.000 (SE = N/A)
specificity	1.000 (SE = N/A)	1.000 (SE = N/A)
efficiency	1.000 (SE = N/A)	1.000 (SE = N/A)
Lobar pulmonary arteries		
sensitivity	1.000 (SE = N/A)	1.000 (SE = N/A)
specificity	1.000 (SE = N/A)	1.000 (SE = N/A)
efficiency	1.000 (SE = N/A)	1.000 (SE = N/A)
Segmental pulmonary arteries		
sensitivity	1.000 (SE = N/A)	1.000 (SE = N/A)
specificity	0.960 (SE = 0.039)	1.000 (SE = N/A)
efficiency	0.966 (SE = 0.034)	1.000 (SE = N/A)
Subsegmental pulmonary arteries		
sensitivity	0.667 (SE = 0.272)	1.000 (SE = N/A)
specificity	1.000 (SE = N/A)	1.000 (SE = N/A)
efficiency	0.966 (SE = 0.034)	1.000 (SE = N/A)
MRV for DVT		
Number of patents	6	3
Number of patients with MRI-diagnosed DVT	4	0
Number of patients with DUS-diagnosed DVT	4	0
sensitivity	1.000 (SE = N/A)	N/A
specificity	1.000 (SE = N/A)	1.000 (SE = N/A)
efficiency	1.000 (SE = N/A)	N/A

corresponding to a kappa statistic of 1.00 (SE = 0.000, p = 0.014); lobar pulmonary artery proportion of agreement calculated as 1.00 (SE = N/A) corresponding to a kappa statistic of 1.00 (SE = 0.000, p = 0.014); segmental pulmonary artery proportion of agreement calculated as 0.8333 (SE = 0.152) corresponding to a kappa statistic of 0.667 (SE = 0.287, p = 0.083); and subsegmental pulmonary artery proportion of agreement calculated as 1.00 (SE = N/A) corresponding to a kappa statistic of 1.00 (SE = 0.000, p = 0.014). The kappa statistic for presence or absence of DVT was calculated at 1.000 (SE = 0.000, p = 0.008).

On a per-patient basis (Table 1), results for gadofosveset trisodium (Ablavar) and gadobenate dimeglumine (Multihance) were similar in evaluating for PE. Figs. 1 and 2 show examples of first-pass and late-phase imaging on patients undergoing MRA with gadofosveset trisodium and gadobenate dimeglumine, respectively. The sensitivity was 93.3% for gadofosveset trisodium and 100% for gadobenate dimeglumine. The specificity for gadofosveset trisodium was 99% and for gadobenate dimeglumine was 100%. Interestingly, even though gadofosveset trisodium is known to have a longer intravascular half-life than gadobenate dimeglumine, there was one case in this study where the timing for the gadobenate dimeglumine first-pass angiography sequence was mistimed (too early), yet the exam remained diagnostic due to the images obtained in second- and third-pass, as well as late-phase imaging that well demonstrated the PE (Fig. 2). This further illustrates the potential of gadobenate dimeglumine as an alternative contrast to gadofosveset trisodium due to its blood pool properties. Out of the total of 7 PE positive cases, the case shown in Fig. 2 was the only case that was not seen, even retrospectively, on fist-pass imaging. This was due to poor contrast timing. Late phase imaging, however, increased reader diagnostic confidence in 5 out of the 7 PE cases, as the location and extent of the thrombus was better seen when the vessel wall was enhanced, which occurs in the late phase imaging acquisition.

On a per-segment basis (Table 1), combining both agents, the results were as follows. At the level of the main and the lobar pulmonary arteries, the overall analysis provided a sensitivity and specificity of 100%. At the level of the segmental pulmonary arteries, the sensitivity was 100% and the sensitivity was 97% (SE = 0.030). At the level of the subsegmental pulmonary arteries, the sensitivity was 75% (SE = 0.217) and specificity was 100%. When comparing contrast agents, results were identical at the level of the main and the lobar pulmonary arteries. At the segmental and subsegmental pulmonary arteries, there were small differences, but these differences were not statistically significant (p = 0.533).

Six of the patients in the group injected with gadofosveset trisodium underwent evaluation by DUS. Of these 6 patients, 4 patients were diagnosed with DVT. MRV compared to the standard reference DUS produced a sensitivity of 100% and a specificity of 100%. The gadobenate dimeglumine group did not have any patients diagnosed with DVT. Within this group, 3 patients underwent DUS. MRV did however provide 100% specificity for absence of DVT.

4. Discussion

The results of our study suggest that MRA at 3.0 T with either gadofosveset trisodium or gadobenate dimeglumine, contrast agents with blood pool properties, performs comparably to CTPA for the diagnosis of acute PE. Our study addressed the feasibility and accuracy of our combined MRA-MRV protocol using a single dose contrast agent to detect PE (with CTPA being considered the reference standard) and DVT (with DUS being considered the reference standard). The success of our imaging protocol is that it is not very time consuming, allows for both PE and DVT evaluation simultaneously and provided consistent diagnostic quality exams. The latter is attributable to the use of contrast agents with blood pool properties allowing for late phase imaging which does not rely on timing of the acquisition in relation to the contrast administration to produce a diagnostic study (Fig. 2). In addition, unlike standard first-pass MRA that only shows the lumen of the vessel, late phase imaging allows for the vessel walls to be visualized, providing contrast outlining the intraluminal PE and thus more readily demonstrating nonocclusive mural thrombi [26]. It should be noted that late phase imaging also opacifies the pulmonary veins, potentially adding confusion to pulmonary arterial interpretation. Venous opacification, however, is typically present and easily dealt with when interpreting CTPA studies [35]. Additionally, first-pass MRA can be used as a map of the pulmonary arterial anatomy if there is confusion on late phase imaging.

A previous study [26] at 1.5 T combining non-enhanced and contrast-enhanced pulmonary MRA sequences using gadobenate dimeglumine in patients with CTPA-proven PE reported a sensitivity of 84% and a specificity of 100% [26]. This study used a combination of MRA protocols, including nonenhanced free-induction cardiac- and respiratory-triggered true fast imaging with steady-state precession (FISP), standard bolus-triggered contrast-enhanced breath hold MRA, and contrast-enhanced recirculation-phase breath-hold low–flip angle three-dimensional (3D) gradient-echo (GRE) images to evaluated for PE in patients proven to have PE by CTPA. This protocol is more time demanding compared to the protocol we report, and it does not include evaluation for DVT by MRV. In addition, the standard bolus-triggered contrast-enhanced breath hold MRA does not dilute the contrast, so that truncation and blurring artifacts have not been addressed. Another study [27] using the extracellular contrast agent gadopentetate dimeglumine at 3.0 T demonstrated 100% specificity and 100% sensitivity on a per-patient basis. This study [27], however, did report some

false positive results in segmental and subsegmental arteries bilaterally, some of which were thought to represent chronic PE. This study did not use a blood pool contrast agent and the protocol did not dilute the contrast agent, so again the truncation and blurring artifacts were not addressed and could have accounted for some of the false positive results. A retrospective single institution study at 1.5 T using contrast-enhanced pulmonary MRA with gadobenate dimeglumine demonstrated a negative predictive value (NPV) of 97% at 3 months and 96% with one year of follow up [36]. Neither of the latter studies [26,27,36] performed concomitant magnetic resonance venography (MRV) to evaluate for DVT. A previous study [37], using gadofosveset trisodium as a contrast agent, showed excellent correlation between MRV and DUS in the detection of incidental DVT in patients undergoing an MRA of the lower limbs for clinically suspected peripheral arterial occlusive disease (PAOD).

This study differs from previously published studies in several ways. First, this was a prospective clinical study recruiting patients presenting to the emergency department with clinical suspicion for PE and therefore scheduled for a clinically indicated CTPA. Second, we performed both MRA of the chest for the evaluation of PE as well as MRV of the pelvis and thighs to evaluate for DVT following a single contrast injection. And finally, we evaluated two different contrast agents, gadobenate dimeglumine and gadofosveset trisodium.

We noted no significant difference in results whether using gadofosveset trisodium, a blood pool agent, or gadobenate dimeglumine, although our results are limited to a smaller number of patients evaluated with gadobenate dimeglumine. Although gadobenate dimeglumine is not a true blood pool agent, its sufficient intravascular half-life [28] allowed for diagnostic steady-state images of the chest and lower limbs. The described combined MRA-MRV protocol used a 3.0 T MR, could be completed within 15 min and could be analyzed by any diagnostic imaging software that supports DICOM image transfer and is able to perform multiplanar reconstruction.

This study analyzed for PE by MRA using CTPA as the reference standard, and analyzed for DVT by MRV using DUS as the reference standard. We report an excellent per-patient PE sensitivity by MRA and DVT sensitivity by MRV. On a per-segment basis, MRA showed inferior accuracy compared to CTPA in the detection of smaller subsegmental PE, which has been reported in other MRA studies as well [38]. However, there is controversy in the literature as to whether isolated subsegmental PE should be treated at all. With the advent of multi-detector CT, the proportion of patients diagnosed with isolated subsegmental PE has increased [39], yet case mortality rates remain unchanged [40]. This suggests that isolated subsegmental PE may not play a major role in the mortality of PE, and that it could be considered as “over-diagnosis” and contribute to unnecessary risk of serious bleeding complications from anticoagulation. Thus, in the cases where MRA may not identify subsegmental PE, the clinical relevance of this “miss” is controversial.

MRV proved accurate in the evaluation of above knee DVT after a single dose contrast medium injection, similar to what was described previously [37]. This additional information can be gained from a relatively small time investment of an additional sequence (no additional contrast). Furthermore, the MRV sequence covers the inferior vena cava (IVC) and common iliac veins, which can be cumbersome or non diagnostic in certain patients with DUS. Although IVC thrombosis is a rare event, a previous database study showed that symptomatic PE occurred more frequently in IVC thrombosis patients compared to lower extremity DVT patients [41]. The simultaneous (or one-stop-shop) evaluation of PE and DVT by combined CTPA and CT venography (CTV) is controversial due to the additional exposure to ionizing radiation, need for increased dose of intravenous contrast agent and studies showing decreased positive yield, possibly due to increased negative CTPA rates [42,43]. Combined MRA-MRV overcomes these undesirable consequences of simultaneous imaging, and could potentially increase confidence in a decision to not treat in cases of negative MRA [44].

It should be noted that this MRA-MRV protocol was initially conceived with the intention of using a true gadolinium-based blood pool agent; gadofosveset trisodium. During the course of the study, gadofosveset trisodium (Ablavar) was removed from the market in our country due to marketing and sales considerations, and not for reasons of poor performance or safety issues. It was for that reason that we pushed forward using the same MRA-MRV protocol using gadobenate dimeglumine, the only other contrast agent available having some blood pool properties. Validating our expectations, this agent showed comparably excellent results to gadofosveset trisodium for the evaluation of both PE and DVT. Although gadobenate dimeglumine is not a true blood pool agent, its higher T1 relaxivity compared to other ECF agents [28,29] and its sufficient intravascular half-life to sustain early steady-state imaging [31] most likely contributed to the successful results obtained in this study. The limitation of our findings is that a smaller number of patients were evaluated by gadobenate dimeglumine, however, the preliminary results do suggest that both contrast agents, gadobenate dimeglumine and gadofosveset trisodium, performed well and could possibly be exchangeable depending on the institution’s contrast media availability or preference. Diluting the weight-based dose of both contrast agents to a fixed total volume of 40 mL and injecting at 2.5 mL/s likely also contributed to the success of the study by decreasing artifacts [34]. Administering the contrast in this fashion provides a much longer bolus than simply injecting non-diluted contrast at a standard 1.5–2.0 mL/s; in our protocol the duration of the diluted contrast bolus was 16 s, closely matching the average first-pass 16 s acquisition time. This is critical, as it is well understood that with an elliptical centric MRA acquisition the higher orders of k-space (which contribute mainly to edge sharpening or spatial resolution) are acquired at the end of the acquisition. If the bolus is too short, arterial signal intensity drops toward the end of the acquisition and these higher orders of k-space are essentially filtered out, resulting in decreased spatial resolution and causing truncation and blurring artifacts [45–48].

Pertinent limitations to our study included the fact that it was a single institution study and the relatively small number of patients recruited for each contrast agent. In addition, the availability of 3.0 T MRI in certain centers is limited, particularly in the emergency setting.

Further large-scale, multicenter feasibility studies are warranted to determine whether and under what circumstances MRA can prove a comparable alternative to CTPA in the work up of PE without negatively impacting clinical outcome. As a radiology community concerned with patient safety, we have the obligation to evaluate MRA as a potential alternative option to CTPA in a select cohort of patients. If further large-scale, multicenter studies prove successful and show that MRA is comparable to CTPA in clinical practice, at least under certain circumstances, without sacrificing diagnostic and therapeutic efficacy, patients will benefit from a non-invasive and relatively safe imaging alternative that does not put them at any potential risk from ionizing radiation. This is of particular importance in young patients, and could potentially have an impact on decreasing radiation-induced cancers in future generations.

Conflict of interest

The authors of the manuscript, including Josephine Pressacco, Konstantin Papas, J Paul Finn, Jean-Marc Chauny, Alain Desjardins, Yassin Irislimane, A. Kevin Toporowicz, Chantal Lanthier, Paule Samson, Marcel Desnoyers, and Jeffrey H. Maki have no conflict of interest to disclose.

Dr. Jean Lambert has unfortunately passed away after contributing his expertise, time and interest to the design, data evaluation and

revision of this project and manuscript. He played an important part of the research study and enriched our understanding of research and statistics. We include him in our authorship as he well merits. We miss his wisdom, his witty sense of humor and his classy character.

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