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Magnetic Resonance Angiography in Pulmonary Embolism: A Review

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Introduction

The National Heart, Lung and Blood Institute defines pulmonary embolism (PE) as a potentially fatal acute obstruction to a pulmonary artery. First described in the 19th century, pulmonary embolism is one of the most common acute cardiovascular events, and results in significant morbidity and mortality. In the United States, 300,000 - 500,000 PE cases are estimated to occur annually, with an associated mortality ranging from 50,000 - 200,000.[1] The annual incidence of pulmonary embolism in Europe is estimated at 430,000.[2]

There are multiple causes of PE, with lower extremity venous thrombosis being the most common culprit. The risk of PE is known to increase with cancer, prolonged immobilization, use of oral contraceptives, cerebrovascular accidents, tobacco use and pregnancy. In fact, pulmonary embolism is the main non-obstetric cause for mortality in pregnancy, with up to five times greater risk of PE in pregnant patients as compared to non-pregnant females of similar age. Mortality from PE is variable and dependent on many factors. “High risk” pulmonary embolism, defined as that presenting with shock or hypotension, has a 30 day mortality of 16-25%.[3] In contrast, a recent meta-analysis of sub-segmental pulmonary embolism demonstrates an untreated mortality of approximately 3%.[4]

Diagnosing PE can be a challenge since the clinical presentation is non-specific and often overlaps with other clinical syndromes such as acute coronary syndrome. In testament to this, despite clinical vigilance and advanced medical imaging techniques, autopsy studies reveal that only approximately 50% of patients who die of PE are suspected of this condition pre-mortem.[5] Other than clinical and laboratory criteria, including D-Dimer levels, multiple imaging modalities are used for diagnosis of deep venous thrombosis and pulmonary embolism. These include Doppler Ultrasound and CT venography of the veins, V/Q scanning, and CT pulmonary angiography (CTPA). Over the last decade, CT pulmonary angiography has become the most accurate and commonly used imaging tool.

MR pulmonary angiography (MRPA) is an increasingly utilized modality for the diagnosis of pulmonary embolism, and in certain cases has potential advantages over CTPA. We discuss here the risks and benefits associated with the increasing use of CT pulmonary angiography and review the basics of MR pulmonary angiography and its applications.

Computed tomographic pulmonary angiography (CTPA)

CTPA is the current modality of choice for the diagnosis of PE due to its widespread availability, efficiency, rapid turnaround time and high sensitivity. One significant advantage of CT is that other life-threatening pathologies (e.g. aortic, mediastinal, pulmonary) can be conveniently detected or ruled out due to its wide field of view and use of appropriate windows and contrast timing, leading in many cases to explanatory diagnoses other than PE.

In a large meta analysis (15 studies, 3500 patients), CTPA has reported sensitivities approximating 90%, demonstrating near perfect positive and negative predictive values of 100% and 99% respectively.[6] Despite these impressive studies, CTPA is known to be imperfect. In the initial PIOPED II study that established CTPA as the imaging mainstay for PE, 51 of 824 (6%) of the studies were inconclusive due to poor image quality, with positive and negative predictive values (in the evaluable patients) of 86% and 95% respectively.[7] Reasons for imperfect CTPA included respiratory motion, flow and mixing artifacts, contrast timing problems, noise, pulmonary catheter artifacts, and streak artifact. In addition, this study has been criticized as not all patients received confirmatory pulmonary angiography – V/Q or positive lower extremity doppler for deep venous thrombosis were surrogate diagnostic criteria. Despite its flaws, it is interesting to note that in the PIOPED II data positive predictive value dropped dramatically for detecting PE in smaller vessels; 68% in segmental arteries, 25% in sub segmental arteries.[7] Other studies have shown considerable interobserver variability in CTPA, particularly for the detection of sub segmental pulmonary emboli, where CTPA was discordant in close to 50%.[8] Interestingly, while the detection of PE has convincingly increased since the advent of multi-detector CTPA, recurrent thromboembolic events after a negative CTPA have decreased, suggesting that these previously “missed” isolated emboli may not in fact be clinically significant.

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There is a growing concern that CTPA over-utilized. One study indicated an approximately fourfold rise in the use of CT for the diagnosis of pulmonary embolism over a 5 year period, but a corresponding substantial decrease in the ratio of positive studies; in ED patients the positive rate fell from 27.1 to 5.7%.[9] In the PIOPED II study, positive PE rate was 22.6%, with more recent studies showing the diagnostic yield to be on the order of 10-15%.[7,10] Thus it appears CTPA diagnostic yield rates are falling as the technique is used more often. One reason for this apparent excessive ordering of CTPA is incomplete adherence to the recommended appropriateness criteria for risk stratification as recommended by the American College of Emergency Physicians (ACEP), American College of Radiology (ACR), as well as PIOPED II.

Radiation

Computed tomography involves ionizing radiation exposure, with a typical chest CT delivering on the order of 1000 times the radiation of a chest x-ray. Average effective dose in CTPA varies by scanner type and protocol, ranging from 5.4 mSv with a lower slice detector to 10 – 20mSv in a 64-slice scanner.[11-13] In pregnancy, maternal effective doses range from 4.3 to 7.3 mSv among different studies.[14,15] Relative fetal doses are much lower, ranging from 0.02 – 0.11 depending on gestational age,[16,17] and similar to that of V/Q scans. While such fetal doses are minimal and felt to be below established risk thresholds,[18, 19] the principle of ALARA (as low as reasonably achievable) is always a primary concern within the radiology community.

The health risk due to radiation exposure from CT, while controversial, is real and known to be greatest in younger patients. Because the "real" risk of the ionizing radiation secondary to CT cannot be easily measured, much of the available data is theoretical in nature and varies considerably amongst investigators and models. A study by Woo et al. examined 1424 consecutive CTPA studies, calculating radiation dose and theoretical associated Mean Lifetime Attributable Risk of Cancer Mortality by sex and age group. Risk ranged from zero in patients greater than 90 years of age to 57.4 per 100,000 in females age 15-19.[20] Younger women (< age 40) were calculated to have the highest lifetime risk, ranging from 40 – 57 per 100,000, with men of the same age slightly less at 35 – 45 per 100,000. Compound this risk by considering Woo found a positive CTPA study in only 6.8 - 11.6%, and Heredia 5% of patients less than 40 and 45 years old respectively, meaning between 10 and 20 patients must be subjected to potentially harmful radiation in order to diagnose one PE.[20, 21] Another study noted a mean CTPA dose of 9.6 mSv, concluding even higher risk, with Mean Lifetime Attributable Risk of Cancer Mortality for a 20 year old female estimated at 300 per 100,000, dropping to 161 per 100,000 at age 40.[22] Yet another study concluded the risk of malignancy due to radiation dose after a single coronary CT, which carries similar radiation exposure and dosage to CTPA, as high as 877 per 100,000 in a 20 year old female.[23] Taking even the most conservative of these numbers amongst younger patients (risk ~50/100,000, ~10% positive rate) suggest that for every 200 pulmonary embolisms diagnosed there would be 1 associated cancer mortality. If this is even close to reality, with 300,000 – 500,000 pulmonary embolisms occurring annually in the US, many of which are in the young, the potential morbidity is not inconsequential. Thus, it is clear the radiation associated with CTPA, particularly in the young and if over utilized cannot be ignored, and the principle of ALARA is critical.

Contrast induced Nephropathy

A significant number of patients undergoing CTPA are estimated to have contraindications to iodinated contrast administration.[7] Historically, chronic kidney disease (CKD) has been considered a risk factor for i.v. iodinated contrast administration due to contrast induced nephropathy (CIN). In the original PIOPED II group, there was a 19% rate of elevated creatinine.[24] Other studies suggest CKD can be seen in 10- 25% of clinically suspected PE cases,[25-28] with an even higher percentage seen in oncology patients, ranging from 50 to 60% in one study.[29] The concept of CIN, however, is at present somewhat controversial, with a number of recent studies suggesting no or much less than commonly believed risk of CIN following i.v. administration.[30-32] While there is clear evidence that many patients who receive iodinated contrast have deterioration in renal function, this similarly occurs in patients receiving non-contrast CT, and it is questioned whether this relationship is causative vs. merely correlative.[33] A commonly used term for this association is 'post-contrast acute kidney injury' (PC-AKI), as compared to true CIN. Nonetheless, the ACR considers administration of iodinated contrast to "at risk" patients a relative (but not absolute) contraindication, and current standard of care includes periprocedural preventive measures to lessen the risk of potential CIN, including hydration, which can result in significant delay in diagnosis and eventual management of PE, in some cases by more than 10 hours.[34] Because of this, in such instances the American College of Chest Physicians suggests pre-treatment with anticoagulants when there is a high clinical suspicion for PE. This can in turn result in significant morbidity secondary to major hemorrhage.[35,36]

Allergy to Iodinated Contrast Material

Allergies to iodine contrast materials must also be considered when ordering CTPA in order to avoid potential morbidity and mortality. While severe and life-threatening iodine reactions are rare, these need to be actively prevented/treated/pretreated. In a large study of acute iodine reactions (all severities), there was a 7.4% incidence of repeat drug reaction given a history of a previous reaction, versus a 1.2% reaction rate in patients with no such history.[37] The risk of severe adverse reactions in patients with a prior history of contrast media reaction who were not treated with premedication was higher than in the patients who received premedication (14.9% and 5.6%).[37] Based on this principle, patients with history of a severe anaphylactoid reaction to iodine are generally pre-treated with steroids. This can be another factor leading to delay in obtaining emergent CTPA and can again in some circumstances lead to pre-treatment with anticoagulants. All said, there is clearly a need for an alternative strategy for the diagnosis of pulmonary embolism, particularly in young and pregnant patients, those with CKD, and those with iodine allergies.

MR pulmonary angiography

Contrast-Enhanced Magnetic Resonance Angiography is a maturing tool that has proven a viable and safe alternative to CTPA in the work up of pulmonary embolism, having no ionizing radiation and using non-nephrotoxic contrast. Many recent hardware advances, in combination with better understanding of how to best use gadolinium contrast, have led to marked improvement in diagnostic efficacy over the past several years. MRPA and comparison CTPA studies are shown in Figures 1–5.

Early small single institution reports of Contrast-Enhanced Magnetic Resonance Pulmonary Angiography (MRPA) were encouraging,[38, 39] with sensitivities 77 – 100% and specificities 95 – 98%. In these and subsequent studies, one clear trend is that MRPA sensitivity is much better for larger pulmonary arteries; segmental and more central – those typically of greatest clinical concern. Excluding sub-segmental pulmonary arteries, Oedkerk reported sensitivity ranging from 84-100%.[39] Another study demonstrated sensitivities of 68 – 100% for central and segmental arteries.[40]

Enthusiasm for MRPA was initially dampened with the publication of PIOPED III in 2010. While now somewhat dated (imaging performed 2006-2008), PIOPED III represents the largest MRPA trial to date (371 patients); a multicenter study using a variety of scanner

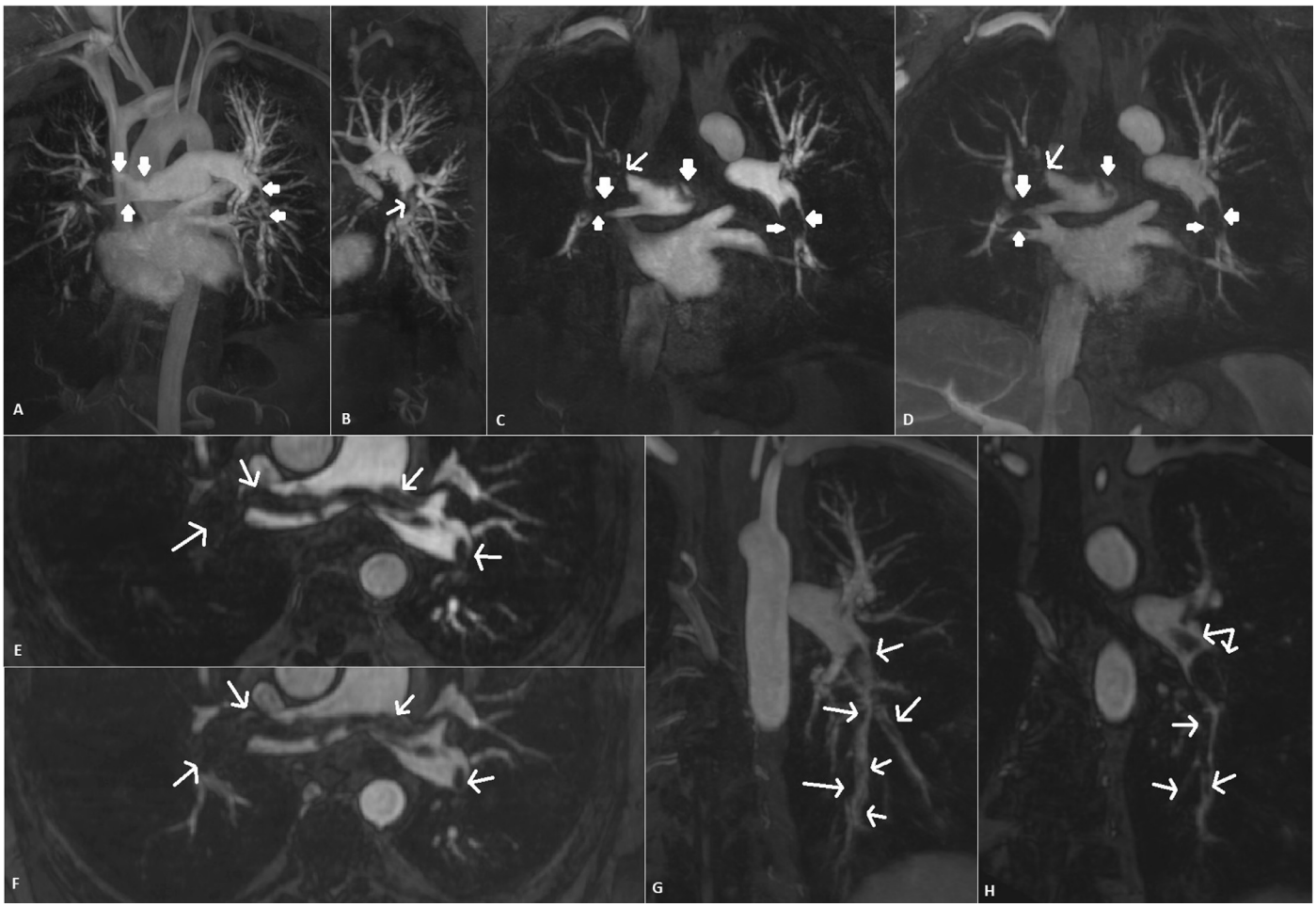

FIGURE 1. 45 year old patient with renal cell carcinoma presenting with shortness of breath. Coronal full thickness MIP *(a)* and sagittal thick MIP left hemithorax *(b)* post contrast images from MRPA. Thick MIPS are suboptimal for detecting pulmonary emboli (PE), however large central and bilateral main defects are clearly present (arrow)re seen in bilateral main, segmental and left subsegmental arteries *(arrows).* Subvolume coronal and axial MIPS in arterial and delayed phases (c/d and e/f respectively) show central PE's to better advantage (arrows). Thinner targeted oblique MIP to the right lung (g) demonstrates segmental and subsegmental vasculature, normal in the upper lobe, with multiple defects in the lower segmental arteries extending into the subsegmental arteries (arrows). These are better seen in a similarly orientated thin MPR (h) (arrows).

platforms and protocols.[24] In this study, 25% of the examinations were considered non-diagnostic (range among centers 11-52%), attributable to a combination of poor contrast opacification, motion artifact, as well as wraparound and parallel imaging artifacts. Analysis of the diagnostic studies demonstrated an overall somewhat low sensitivity of 78%, but a high specificity of 99%. This low sensitivity was largely due to the poor test characteristics of segmental and subsegmental PEs, which led to the authors concluding that MRPA should only be considered 'at centers that routinely perform it well and only for patients with contraindications to standard tests'. PIOPED III had its share of limitations that may have led to the low performance of MRA; it used a single MR technique (3D CE-MRA) with only one post-contrast acquisition, scan times were relatively long (up to 22 s), multiple MR systems and field strengths were used, timing was performed using a timing bolus, gadolinium contrast (20 - 40 mL) was administered at a fixed rate of 2 mL/s, and finally there were two blinded readers of differing experience levels selected for each case from a not entirely random pool of 13 readers, with a substantial number of non-agreements (24%) then referred to a 3rd blinded reader, suggesting considerable variability in MRPA interpretation.[41] Of note, when technically adequate, combined MRPA and lower extremity MR venography (MRV) in PIOPED III had a much greater sensitivity (92%) and similar good specificity (96%) for detecting thromboembolism.

In the years since PIOPED III, several MRPA studies have been performed suggesting significantly better diagnostic performance. A recent US study (22 positive cases per CTPA) applied multiple sequences including contrast-enhanced breath-hold MRPA, contrast-enhanced recirculation-phase breath-hold low–flip angle three-dimensional (3D) gradient echo (GRE), and non-enhanced free-induction respiratory-triggered cardiac-gated steady state free precession sequences.[42] This study demonstrated sensitivity of up to 84% and specificity of 100% using a multiple MR acquisition approach. A prospective European study (n = 274) using unenhanced, perfusion and angiographic MR concluded similar results of reasonably high sensitivity and specificity.[40] Consistent with other studies, this group reported sensitivity highest for the central pulmonary arteries (98 - 100%), decreasing for segmental (68 – 92%), and being worst for sub segmental branches (21-33%). This group found excellent interobserver agreement (K = 0.93). Another recent small study (n = 27) confirmed excellent results, evaluating positive cases on a per patient and per lobe basis.[43] Sensitivities of up to 100% were demonstrated on a per patient basis, and 83 – 85% on per lobe basis.

An alternative but perhaps more meaningful and compelling approach to evaluating the performance of MRPA as a first-line testing strategy was recently described by Schiebler et al., where instead of directly comparing MRPA with other metrics of whether or not a PE is present to test the accuracy (or efficacy) of the test, the study instead followed patient outcomes after a negative MRPA to evaluate the overall effectiveness of this diagnostic strategy.[44] In this relatively recent study of 190 patients (23 positive for PE), advances such as diluted contrast with a prolonged bolus phase, fluoroscopic bolus

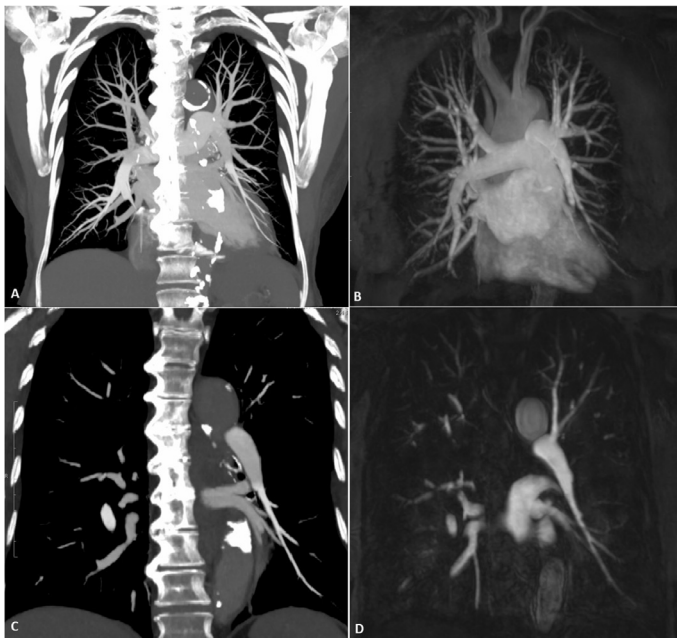

FIGURE 2. Same day CTPA and MRPA images of an 86 year old male patient with shortness of breath and elevated D Dimer level. Comparable CT vs. MR visualization of the subsegmental pulmonary arteries bilaterally on coronal thick MIP (a, b) and representative thin 5 mm MIP highlighting the left inferior pulmonary artery (c, d). No pulmonary embolism was found.

triggering, and relatively short acquisition times (~17 s) with a second post-contrast phase, 97% of the studies were considered diagnostic. Following the 167 negative patients, there was a 97% negative predictive value at 3 months, decreasing slightly to 96% at 1 year. These results demonstrate that MRA effectiveness is comparable that of CTPA studies.[6]

MRA In Pregnancy

Pulmonary embolism is the main non-obstetric cause for mortality in pregnancy. Traditional diagnostic techniques such as ventilation perfusion scan and CT scan carry considerable radiation exposure as discussed above. CTPA in pregnant patients has been reported as having comparatively inadequate contrast enhancement including

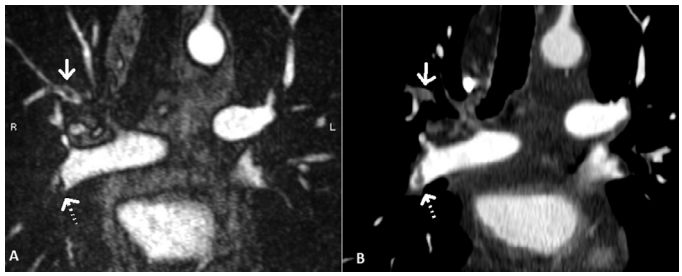

FIGURE 4. 53 year old man presents with dyspnea and DVT. Delayed phase PMRA images in coronal plane (A) and (B) coronal CTPA demonstrate PE in the anterior segmental artery of the right upper lobe (solid arrow). In addition, there is thrombus in the interlobar artery (broken arrow).

nonopacification of some pulmonary arterial segments which is a likely consequence of increased cardiac output and blood volume. Gadolinium enhanced MR angiography shows high accuracy in the general population, but should be used with care in pregnant patients as animal studies have shown association with fetal risks including growth retardation and other congenital anomalies.[45] Other MRI protocols, such as motion resistant bright blood techniques, do not utilize intravenous contrast; for example balanced steady state free precession techniques (SSFP) has been proposed as a useful approach to pregnant patients, and has even been advocated as first line diagnostic study in pregnancy or for short term follow up.[45,46] This is a relatively under-researched topic, and more investigation into non-contrast MRPA in pregnancy is needed.

Additional clinical considerations

Subsegmental Pulmonary Embolism

According to some international studies, venous thromboembolism (VTE) including PE ranges from 4-21 cases per 10,000 patients.[5] As might be expected, this incidence increases greatly (to the order of 70 per 10,000) in elderly patients 70 years of age or more. Because of the high mortality associated with larger pulmonary embolisms, there is little disagreement that these should be treated. Smaller or isolated subsegmental PEs, which are typically hemodynamically insignificant due to greater pulmonary reserves, are more controversial.

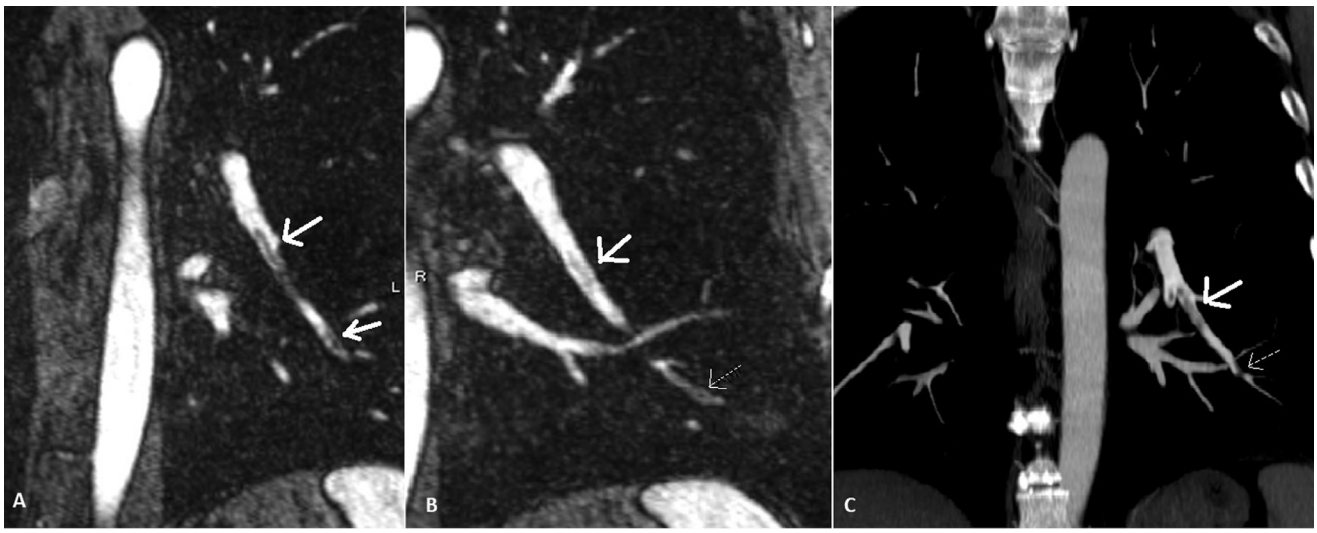

FIGURE 3. 53 year old man presenting with dyspnea and DVT. (A) Coronal source MRA images in coronal plane demonstrate pulmonary embolus in the left laterobasal segmental artery (solid arrows) with (B) subsegmental extension of thrombus (broken arrow) on delayed-phase MR angiography. (C) coronal CTPA correlation demonstrates PE in the left laterobasal segmental (solid arrow) and associated subsegmental arteries (broken arrow).

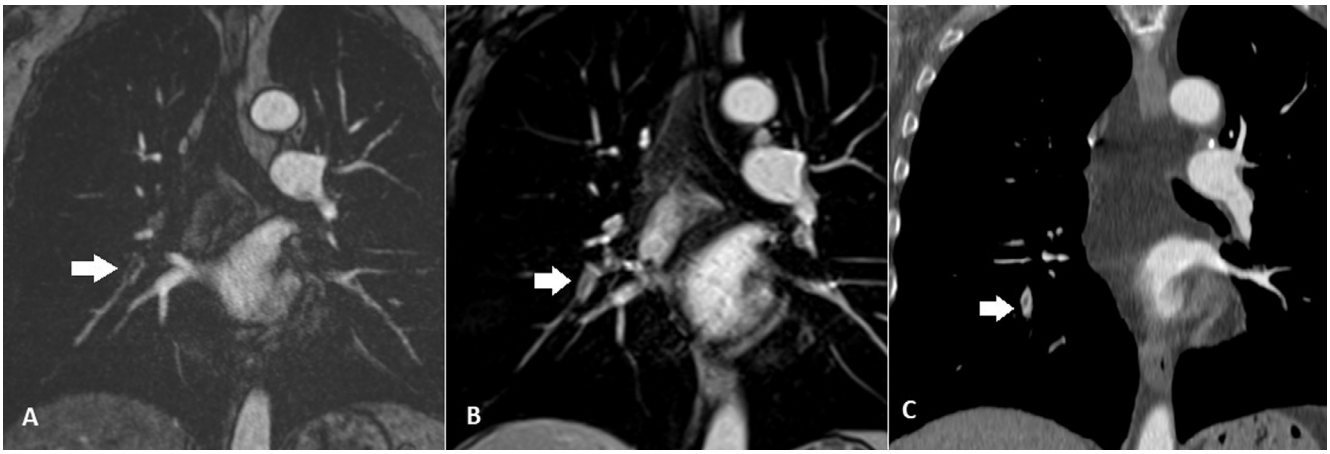

FIGURE 5. 75 year old woman presenting with dyspnea. (A) Source image coronal delayed phase PMRA, (B) late-phase (VIBE) MR and (C) coronal CTPA correlation all demonstrate right posterobasal segmental artery PE (solid arrows).

It is clear newer multi-detector CT scanners now detect a greater number of cases of isolated subsegmental pulmonary thrombus than did older generation single detector CT scanners, with one study demonstrating the incidence of subsegmental PE increasing from approximately 4.5% using a single detector scanner to more than 9% with multidetector CT.[47] At the same time, studies show considerable discordance in radiologist's diagnosis of isolated subsegmental pulmonary embolism.[8]

How and even whether to treat sub segmental pulmonary emboli, particularly when isolated, remains a subject of debate. A 2016 CHEST guideline and expert panel report advocates for clinical surveillance instead of anticoagulation for clinical scenarios in which a subsegmental pulmonary embolism is diagnosed without evidence of proximal DVT, and therefore the risk of recurrence is low.[48] Additionally, cases with low probability V/Q scans have been found to be safely managed without anticoagulation. In the study by Eyer,[49] 25 of 67 isolated subsegmental PE's were not treated with anticoagulation, and follow-up of both the treated and untreated patients demonstrated no cases of recurrent PE. Furthermore, while the detection of subsegmental PE has convincingly increased since the advent of multi-detector CTPA, the benefits of anticoagulation for subsegmental PE have been difficult to demonstrate in this cohort, suggesting that subsegmental isolated emboli may represent overdiagnosis without clinical significance. Despite this information, most patients with positive subsegmental thrombus on CTPA are treated with anticoagulation.[49]

Anticoagulation Therapy Risks For Subsegmental PE

Anticoagulation therapy can lead to major bleeding, with approximately 2% of anticoagulated patients developing a clinically significant hemorrhage. While anticoagulation for PE remains a standard of care among all patients with VTE, the risks from anticoagulation may actually outweigh the benefits conferred in select PE subpopulations. As an example, a recent study suggests patients with subsegmental emboli are more likely to experience complications of anticoagulation than adverse outcomes from the embolism itself.[50]

While controversial, the emerging standard to not treat subsegmental PE with anticoagulation opens the door to potential benefits offered by increased utilization of MRPA through avoidance of overdiagnosis of what may be clinically insignificant PEs with a CTPA. These are the PEs that might have been missed, for example, in the Schiebler study that showed excellent effectiveness with a MRA strategy.[44] Thus, MRPA may be a particularly advantageous strategy in younger patients with few comorbidities in whom radiation poses additional risk and who are less likely to have recurrence of disease.

Conclusion

Pulmonary MRA for the diagnosis of PE is a now relatively mature modality with comparable efficacy to CT for clinically significant central and segmental PE, although likely with a greater chance of missing a subsegmental PE. Subsegmental pulmonary emboli, however, have indeterminate clinical risk and significance, and the need for anticoagulation is controversial. We believe that with greater understanding of the risks, benefits and alternatives to CTPA, treating clinicians as well as patients may begin to prefer MRPA as an alternative first-line approach, especially among young and pregnant patients, as well as those with low eGFR and iodinated contrast allergies.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1067/j.cpradiol.2018.08.001.

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