Capturing venous thromboembolism: imaging and outcomes of venous thromboembolism

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PART 1

Imaging of venous thromboembolism

CHAPTER 2

Modern imaging of acute pulmonary embolism

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Abstract

The first-choice imaging test for visualization of thromboemboli in the pulmonary vasculature in patients with suspected acute pulmonary embolism (PE) is multidetector computed tomography pulmonary angiography (CTPA) – a readily available and widely used imaging technique. Through technological advancements over the past years, alternative imaging techniques for the diagnosis of PE have become available, whilst others are still under investigation. In particular, the evolution of artificial intelligence (AI) is expected to enable further innovation in diagnostic management of PE. In this narrative review, current CTPA techniques and the emerging technology photon-counting computed tomography (PCCT), as well as other modern imaging techniques of acute PE are discussed, including CTPA with iodine maps based on subtraction or dual-energy acquisition, single-photon emission CT (SPECT), magnetic resonance angiography (MRA), and magnetic resonance direct thrombus imaging (MRDTI). Furthermore, potential applications of AI are discussed.

Introduction

In patients with suspected acute pulmonary embolism (PE), multidetector computed tomography pulmonary angiography (CTPA) is the imaging test of choice. CTPA allows for adequate visualization of thromboemboli in the pulmonary vasculature down to the subsegmental pulmonary arteries, is widely available and has been validated in prospective management outcome studies.[1-3] A sensitivity of 96-100% and specificity of 97-98% have been reported for multidetector CTPA techniques.[4] With the aim of achieving high quality CTPA at the lowest radiation dose, the Canadian Society of Thoracic Radiology and the Canadian Association of Radiologists provide current and practical recommendations in their 2022 guidance, mentioning that optimal CTPA acquisition can be achieved using multidetector computed tomography (CT) with at least 16-detector rows, preferably 64-detector or greater.[5] Due to advances in hardware and post-processing techniques, radiation dose reduction has been achieved while maintaining image quality.[5,6]

In addition to the progress in radiation dose reduction, several technological advancements have been made over the past years. Multiple imaging techniques for the diagnosis of PE have become available or are currently emerging. Furthermore, artificial intelligence (AI) holds promise in various roles to improve the diagnostic management of PE. In this narrative review, we discuss current CTPA techniques and address the emerging technology photon-counting CT (PCCT), and we discuss different imaging techniques of acute PE, including CTPA with iodine maps by means of subtraction or dual-energy acquisition, single-photon emission CT (SPECT), and magnetic resonance imaging (MRI) techniques. Additionally, we describe potential roles for AI in the imaging of acute PE.

CTPA

Multidetector CTPA is routinely performed in patients with suspected PE when diagnostic imaging is indicated (see criteria regarding the appropriateness of diagnostic imaging procedures for suspected PE).[7] High quality CTPA imaging can be achieved with optimization of acquisition parameters, while considering strategies for radiation dose reduction and reduction in intravenous contrast administration. Parameters of imaging acquisition using multidetector CT include use of the smallest detector width, thin sections of 1.25 mm or less, with single inspiratory breath-suspension during the image acquisition.[5] High pitch protocols for CTPA acquisition at low kilovoltage peak (kVp), below 100 kVp, with low contrast medium volume and reduced acquisition time have been investigated and some studies suggest that diagnostic examinations of sufficient quality for evaluation of PE can be achieved with such protocols in selected (non-obese) patients.[8-11] Schönfeld et al. compared a high-pitch dual-source CTPA protocol using a contrast volume of 20 mL (pitch 3.2, scan time <1 second, no breathing commands) to "standard" CTPA with administration of 50 mL of contrast medium (single-source, pitch 1.2, scan time approximately 2 seconds, breath-hold during the scan).[12] Although the image quality of high-pitch CTPA was less than that of "standard" CTPA, the image quality was sufficient, with an effective dose of high-pitch CTPA of median 1.04 versus 1.49 for the normal-pitch CTPA calculated using a chest-specific conversion factor of $0.014\ mSv \cdot mGy^{-1}cm^{-1}$.[12] In the literature, effective radiation doses for multidetector CTPA (64- to 2x192-slice scanners) of 1.2 to 6.4 mSv are reported; notably, it is not explicitly mentioned whether the reported effective doses apply solely to the CTPA or to the entire examination.[13-16] There is also variation in published chest conversion factors, ranging from 0.014 to $0.019\ mSv \cdot Gy^{-1}cm^{-1}$.[17,18] Details regarding the effective dose of CTPA acquisition (with subtraction) performed in our current practice at Leiden University Medical Center, the Netherlands, are shown in **supplementary Table S1**; **Figure 1** shows examples of CTPA images. Foetal radiation exposure from CTPA is low.[1,5,19] With evolving CT technology resulting in reduced radiation exposure while maintaining image quality, modern CTPA imaging techniques have been found to involve low maternal radiation exposure as well.[1] CTPA is commonly performed in pregnant women.[7]

Multidetector CTPA enables the detection of contrast-filling defects in the subsegmental pulmonary arteries, however, the clinical significance of isolated subsegmental PE, and therefore the need for anticoagulant treatment, remains controversial.[1,20] The ongoing multicentre randomized placebo-controlled SAFE-SSPE trial (Surveillance versus Anticoagulation For low-risk patiEnts with isolated SubSegmental Pulmonary Embolism; NCT04263038) aims to answer the question how to manage low-risk patients with isolated subsegmental PE.[21] Furthermore, parameters can be detected on CTPA which can be used for risk stratification of patients with acute PE, such as right ventricle (RV) to left ventricle (LV) ratio as an indicator of RV dysfunction.[1] CTPA can also reveal signs suggestive of pre-existing chronic thromboembolic disease or chronic thromboembolic pulmonary hypertension (CTEPH). Dedicated reading of CTPA scans performed at diagnosis of acute PE may help to early detect CTEPH after acute PE.[22-25]

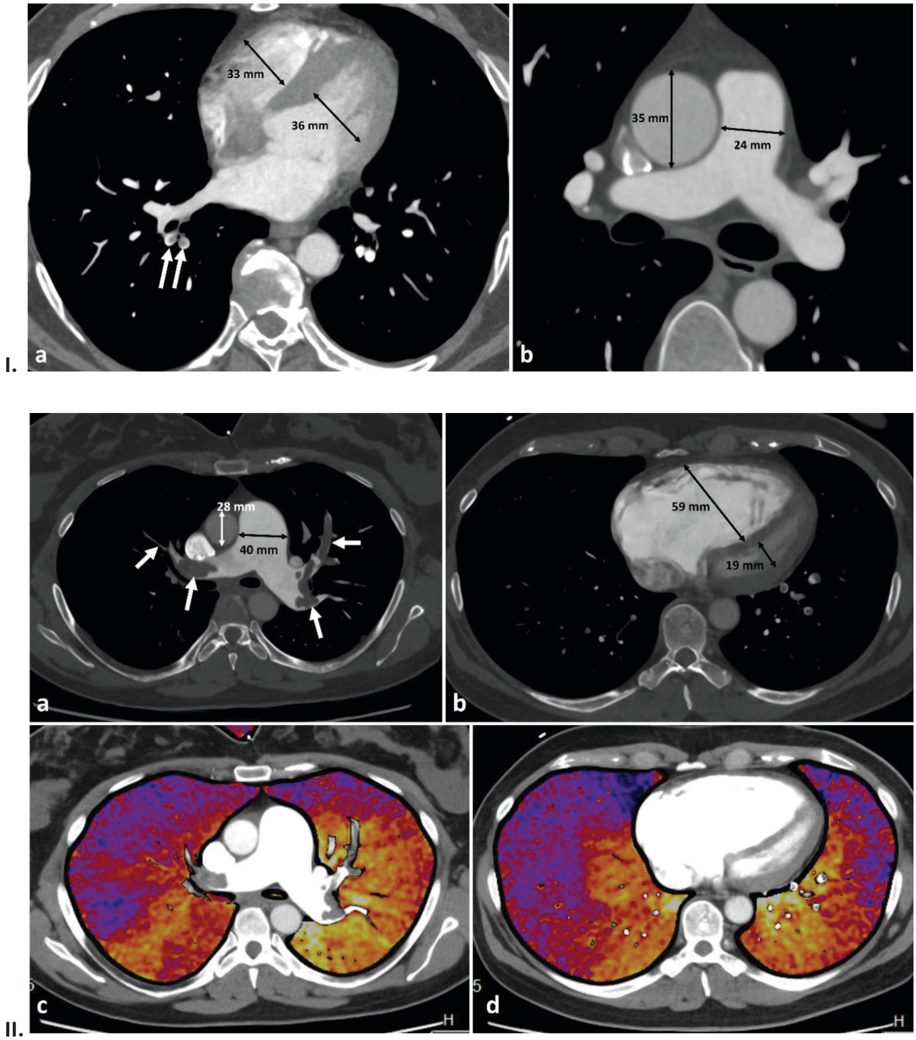
An emerging CT technology is photon-counting computed tomography (PCCT). With this technique, energy-resolving photon-counting detectors (PCDs) are used instead of energy-integrating detectors (EIDs), which enables counting individual incoming photons and differentiating photons according to their energy.[26, 27] PCCT has the potential to increase spatial resolution, reduce noise and improve contrast, and reduce radiation exposure, and also allows for the use of alternative contrast agents.[26, 28] A clinical PCD CT scanner was evaluated between October 2021 and March 2022, and showed good image quality as well as reduced radiation dose and amount of contrast agent compared with dual-energy CTPA on conventional EID CT (192-slice) scanner; 1.4 mSv versus 3.3 mSv, and 25 ml versus 50 ml of contrast medium, respectively.[29] EID scans had higher contrast-to-noise ratio than PCD scans (27.7 ± 8.6 versus 14.2 ± 4.8 for pulmonary trunk). The potential of PCCT should be confirmed in future prospective management outcome studies.

Dual-energy CT or CTPA with perfusion images

Dual-energy computed tomography (DECT) employs two distinct X-ray photon energy spectra to outline a tissue's attenuation characteristics at different photoelectric energies, thereby providing information on material composition beyond the capabilities of conventional single-energy CT.[28, 30, 31] Virtual monoenergetic images at low kilo-electronvolt (keV) levels obtained with DECT can be used for the improvement of the contrast-to-noise ratio, to reduce the amount of contrast material needed for the evaluation of PE.[30, 32, 33]

With mapping of attenuation characteristics, material decomposition images, including iodine distribution maps, can be generated.[30] Iodine maps can be used for the evaluation of perfusion defects. Iodine maps in DECT were shown to detect additional segmental and subsegmental PEs on CTPA.[34] Of 1144 CTPA examinations, a new PE diagnosis was made on 11 examinations based on review of the iodine maps. Perfusion defects assessed on iodine perfusion images obtained with DECT correlated with CTPA obstruction (Qanadli) score and ratio between RV and LV diameter.[35] Alternatively, subtraction CT can be used to evaluate pulmonary perfusion in CTPA. A pre-contrast unenhanced image set is subtracted from a contrast-enhanced image to generate a motion-corrected map representing the iodine distribution in the pulmonary parenchyma.[36, 37] The color-coded subtraction images are then superimposed on the CT images (**Figure 1 [II c, d]**; **Figure 2**).

Figure 1: Computed tomography pulmonary angiography (CTPA) images.

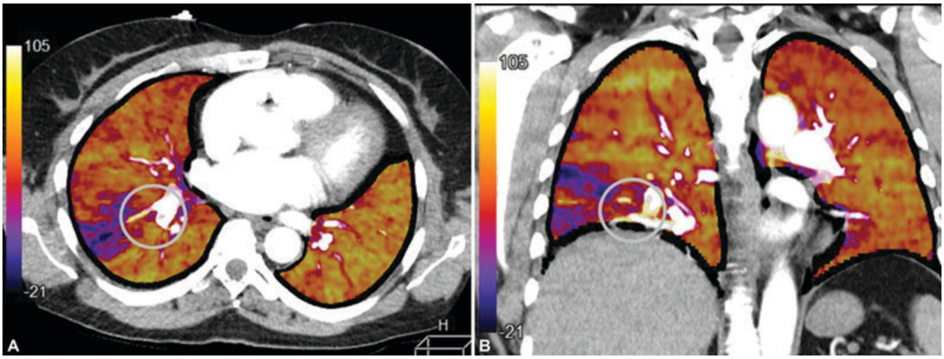


I a. 49-year-old male patient with recent ankle fracture, presenting with pain on breathing for 1 day and increased D-dimer, who was suspected of having pulmonary embolism (PE). CTPA in axial view showing segmental PEs in the posterior and lateral basal segmental arteries of the right lower lobe (white arrows). Patient had some segmental and subsegmental PEs in the right lower lobe, and some subsegmental PEs in the lingula and middle lobe. No signs of right ventricular (RV) strain, the right ventricle (RV) to left ventricle (LV) ratio is smaller than 1 (black arrows, a). **b.** Same patient, showing the diameter of the pulmonary artery that was normal (24 mm), also in relationship with the diameter of the aorta (35 mm).

II a. 39-year-old female patient presenting with acute dyspnea and D-dimer >4000, suspected of having PE. CTPA in axial view showing large central PEs, in the left and right pulmonary arteries (white arrows). Patient had extensive PEs from central extending into the subsegmental areas of all lung fields. The pulmonary artery was strongly dilated up to 40 mm, which is readily observed by comparing with the normally sized aorta of 28 mm at this age. **b.** Signs of severe RV strain with strongly dilated right ventricle, RV/LV ratio was (much) larger than 1. The interventricular septum was inversed with increased RV pressure exceeding that of the LV. **c, d.** Same patient with subtraction iodine maps at the same levels showing inhomogeneous perfusion.

The addition of perfusion images to routine CTPA was demonstrated to improve the detection of acute PE.[38] Therefore, iodine maps on top of CTPA images provide an attractive method for visualizing pulmonary perfusion. In a prospective study, the use of subtraction CT versus DECT iodine maps was compared to CTPA for the detection of PE.[38] Adding subtraction CT iodine maps to CTPA resulted in higher specificity than that of CTPA alone. Both techniques for iodine mapping showed small improvement on top of CTPA, but sensitivity did not significantly improve. Notably, whilst this study found comparable diagnostic performance and radiation dose for subtraction and dual-energy CT iodine maps, subtraction CT, unlike DECT, does not require dedicated hardware. Yet, the value of subtraction CT iodine maps for guiding management of the patient beyond the diagnosis may be limited.[37,39] To date, large prospective diagnostic or therapeutic management outcome studies investigating CT perfusion images combined with DECT or CTPA are unavailable.

Figure 2: Perfusion map fused with computed tomography pulmonary angiography.



Fused perfusion map with computed tomography pulmonary angiography: (A) axial and (B) coronal image in a patient with an acute thrombus in the right lower lobe pulmonary artery (encircled), with subsegmental reduced lung perfusion in the laterodorsal segment of the right lower lobe.

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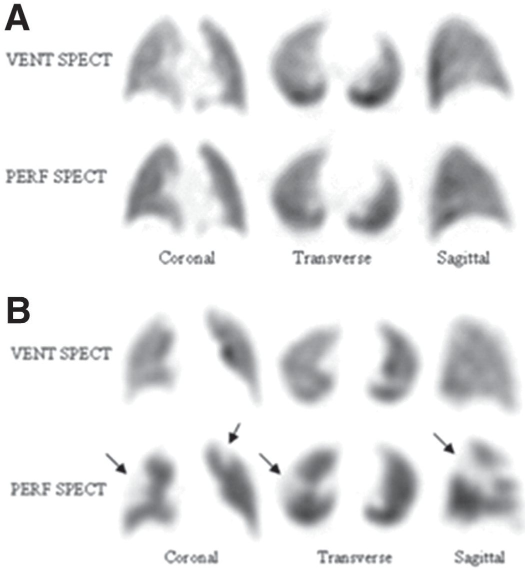
SPECT

Single-photon emission computed tomography (SPECT) is a three-dimensional technique, which provides visualization of all segments of the lung with transverse, coronal, and sagittal images, including segments previously not visible on two-dimensional planar ventilation/perfusion (V/Q) scans (**Figure 3**).[40] From planar V/Q to SPECT, and from SPECT to SPECT/CT, spatial and contrast resolution increases.[41] V/Q SPECT imaging, with or without low-dose CT, has been shown to lower the proportion of non-diagnostic scans reported to occur when performing conventional V/Q scans, to a rate of up to

5%. A sensitivity of 80-100% and specificity of 71-100% have been reported, although prospective outcome data are not available to confirm these beyond doubt.[1, 42-47]

Figure 3: Single-photon emission computed tomography (SPECT) images providing visualization of all segments of the lung in coronal, transverse, and sagittal planes.



(A) Normal ventilation and perfusion lung scan; uniform uptake in all lobes and segments. (B) Multiple mismatched ventilation and perfusion defects in a patient with multiple PE.

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Compared with planar V/Q scintigraphy, SPECT imaging increased the number of detectable defects both at the segmental and subsegmental level, and resulted in higher sensitivity and specificity (97% and 91%, respectively, compared with 76% and 85% for planar V/Q imaging found in a retrospective study).[48] However, SPECT itself was included in the reference standard in this study, and most studies that evaluated the diagnostic accuracy of SPECT have limitations in their study design. Therefore, the accuracy of V/Q SPECT compared with planar V/Q scintigraphy or CTPA has not been definitively established and should be prospectively determined using an independent reference standard.[49] Of note, a higher detection of PE compared to conventional V/Q scans may also lead to overtreatment.

According to the European Association of Nuclear Medicine (EANM) 2019 guideline on V/Q SPECT for PE diagnosis, the effective radiation dose of V/Q SPECT is approximately 2 mSv.[50] The addition of low-dose CT without contrast involves an additional radiation dose of approximately 1-2 mSv, resulting in an effective dose of around 3-4 mSv for the acquisition of V/Q SPECT/CT.[50] Two meta-analyses published in 2023 showed that the sensitivity and specificity of V/Q SPECT/CT were higher than for Q SPECT/CT, and that adding CT to the techniques improved accuracy of both V/Q SPECT and Q SPECT.[51,52] The optimal scanning technique – V/Q SPECT with or without non-enhanced CT, or Q SPECT with or without non-enhanced CT – is not yet defined. SPECT imaging techniques remain in need of validation in large prospective management outcome studies, in which patients with suspected PE and normal diagnostic test results are not treated with anticoagulants, before they can be recommended for use in guidelines.[1] The use of V/Q scanning has significantly decreased due to the widespread use of CTPA.[7] V/Q SPECT has previously been proposed for consideration in select patient groups where radiation burden is a concern, for example in pregnant women or young persons in general.[53,54] However, dose reduction strategies have resulted in continuous reduction in radiation dose of CTPA. While clinical studies are being conducted and published, technology continues to advance with improvements in image quality as well as radiation exposure. This lag in research results presents a challenge when assessing the landscape of technological possibilities for imaging of VTE.

MRI

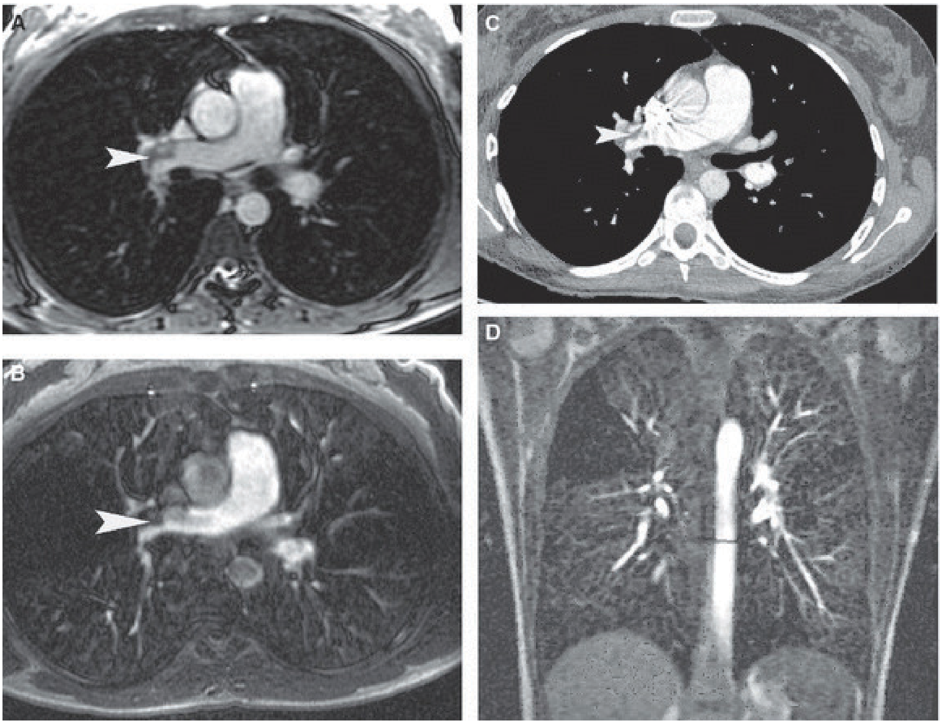
In magnetic resonance imaging (MRI) images are obtained by using a strong magnetic field and radiofrequency pulses, without involving ionizing radiation.[55] In this section, magnetic resonance angiography (MRA) and magnetic resonance direct thrombus imaging (MRDTI) are discussed.

MRA

Magnetic resonance angiography (MRA) is not yet ready for use in clinical practice where it pertains to PE detection due to insufficient sensitivity and a high proportion of inconclusive scans.[1,56,57] In addition, MR techniques are associated with low availability in urgent settings, longer study duration compared with CTPA, and high costs.[7] In the multicentre PIOPED III study that recruited patients between 2006 and 2008, diagnostic accuracy of MRA was evaluated using a reference standard based on various tests, including CTPA, V/Q scan, CT venography, venous ultrasonography, D-dimer test and clinical assessment.[58] A quarter of the patients had technically inadequate MRA scans. Sensitivity of gadolinium-enhanced MRA was 78% among participants with adequate scans, dropping to 57% when those with technically inadequate scans were included. Reasons for inadequate quality resulting in uninterpretable examinations were mostly poor vascular opacification and motion artifacts.[59] The prospective IRM-EP study evaluated MRI imaging consisting of unenhanced, perfusion and angiography sequences with gadolinium-based contrast for diagnosis of PE, with

64-detector CTPA serving as the reference method (**Figure 4**).[60] Inconclusive MRI results were found in 28-30% of the 300 included patients, mainly due to technically inadequate examinations. Overall sensitivity was 69% when considering inconclusive MRI examinations to be negative, and 79-85% for patients with conclusive MRI scans, with specificity of 99-100%. Sensitivity decreased for more distal PE location, from 97-100% for proximal PE and 68-92% for segmental PE to 21-33% for subsegmental PE. With separate evaluation of the sequences, contrast-enhanced angiography sequences showed the highest sensitivity (83-90%) and specificity (98.5-100%), but reading the sequences separately resulted in a higher proportion of inconclusive results ranging from 34-52%.[61] Given the limited sensitivity, MRA cannot be used as a stand-alone test to exclude PE.[1]

Figure 4: Magnetic resonance imaging including unenhanced, perfusion, and angiography sequences with gadolinium-based contrast.



(A) Unenhanced magnetic resonance imaging (MRI) sequence, demonstrating marginal clots within the right interlobar pulmonary artery (arrow), and (B) angiography MRI sequence, with (C) corresponding image on computed tomography angiography. (D) Perfusion MRI sequence demonstrating right-sided perfusion defect.

Still, provided sensitivity improves, MRA may provide an alternative to CTPA that is independent of ionizing radiation or iodinated contrast media.[62-68] Of note, the safety of gadolinium-based contrast during pregnancy remains uncertain as the long-term effects on foetal and neonatal outcomes are unknown,[69] and the American College of Radiology (ACR) Manual on Contrast media recommends avoiding routine administration of gadolinium-based contrast agents during pregnancy.[70] To date, use of this technique is therefore not recommended in pregnant women suspected of PE.[1, 7] As a gadolinium-free contrast agent, ferumoxytol is considered an alternative for MRA for assessment of PE during pregnancy or in case of contrast allergies.[71] Ferumoxytol is an intravenous iron supplement which is used for anaemia treatment including treatment of iron-deficiency anaemia during pregnancy and has been shown to result in good image quality when used as a contrast agent for MRA for the evaluation of PE in pregnant women.[72] However, the use of ferumoxytol is not included in the current ACR manual or clinical guidelines for diagnosis of PE.

The anticipated results of a large multicentre outcome study (IRM-EP2) evaluating the diagnostic performance of MRA in combination with venous ultrasound of the legs in patients with suspected PE may provide more ground for the use of MRA in current practice (ClinicalTrials.gov identifier NCT02059551; recruitment completed).[73]

MRDTI

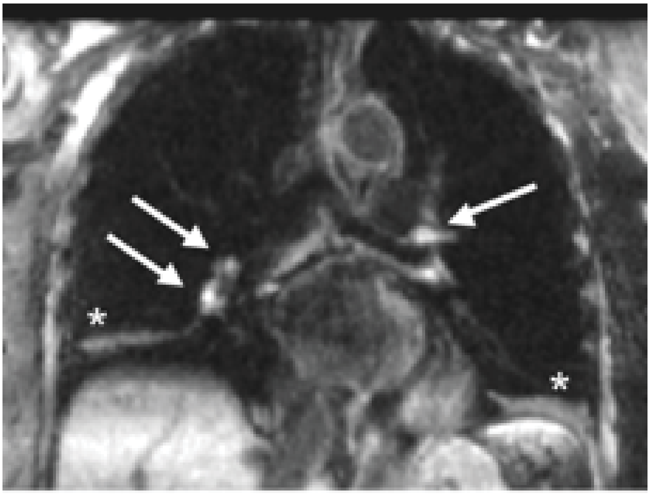
Magnetic resonance direct thrombus imaging (MRDTI) is a non-invasive technique that does not require the administration of intravenous contrast.[74-76] Thrombus detection with the MRDTI technique is based on the formation of methaemoglobin in fresh thrombus. T1 shortening caused by methaemoglobin will generate high signal intensity from the intravenous thrombus on T1-weighted sequences against the suppressed background tissues.[74-77] The high signal appears to be visible in the early stages of clot formation (described in cases within 8-12 hours and the first days after symptom onset) and changes in signal intensity over time may enable the estimation of thrombus age and the monitoring of clots in response to treatment.[75,77] The high signal intensity has been observed to plateau after approximately 3 weeks and was found to normalize during a period of 6 months.[76-79] Direct visualization of the thrombus provides information about thrombus characteristics and enables approximation of clot volume.

MRDTI imaging could overcome several difficulties experienced with techniques such as ultrasonography and CT. With MR imaging, inaccessible deep veins may be better visualized, for instance deep veins within the pelvis or in limbs that are not accessible due to plaster casts.[75] Also, MRDTI can be used as a diagnostic test in specific situations, such as suspected recurrent ipsilateral deep vein thrombosis (DVT), suspected thrombosis during pregnancy, or in case of hypersensitivity or contra-indications for contrast administration.[80-87]

MRDTI has been evaluated in clinical studies, mainly for diagnosis of DVT. In patients with acute DVT diagnosed by conventional venography, MRDTI scanning confirmed DVT in 17 out of 18 patients.[75] Furthermore, in a prospective study, MRDTI scanning of 101 patients with suspected DVT who had been subjected to venography, demonstrated overall sensitivity of two reviewers of 94-96%, specificity of 90-92%, and good interobserver reliability (k statistic 0.89-0.98).[88] In both studies, MRDTI scanning was well tolerated. As DVT and PE are manifestations of the same disease, the technique was believed to be applicable for diagnosis of PE as well (**Figure 5**).[78] MRDTI of the chest in 13 patients with suspected PE showed positive signal (i.e. area of high signal intensity on direct embolus imaging MR) in all patients with PE diagnosed using conventional pulmonary angiography or a combination of diagnostic tests including ventilation perfusion scan, lower limb ultrasound, laboratory tests, and clinical follow-up.[89] A two-dimensional gradient-echo (turbo-FLASH) breath-hold MR technique was used, that combined direct visualization of emboli by a direct imaging of embolus (DIE) sequence with an angiographic sequence for depiction of the pulmonary vasculature and clot localization. The MR technique demonstrated three additional emboli that were not detected with pulmonary angiography, which may be due to failure of the DIE technique, an obscured filling defect on pulmonary angiography by contrast in a partially occluded vessel, or dissolution of thrombus in the interval between MR and pulmonary angiography. The breath-hold MR technique was tolerated by all patients, except for one patient who had severe dyspnea. Even so, as for MRA, MRDTI is a long way from becoming a relevant diagnostic test in the routine diagnostic work-up of suspected acute PE. Limited availability of MRI, associated costs, and also lack of proper evaluation in prospective studies are the main barriers.

Moreover, the accuracy of MRDTI for smaller, (sub)segmental clots is unknown and may be insufficient; it will be challenging to equal the accuracy for the detection of PE that is achieved with current multidetector CT techniques. Given that the appearance of high signal intensity relies on methaemoglobin formation, the role of MRDTI in the acute setting (i.e. within hours after formation of methaemoglobin in acute thrombosis) could be further explored.

Figure 5: Magnetic resonance direct thrombus imaging of the chest and legs.



Upper image: Magnetic resonance direct thrombus imaging (MRDTI) demonstrating multiple bilateral pulmonary emboli (arrows) with associated lung atelectasis (*).

Lower image: MRDTI demonstrating deep vein thrombosis in the right leg.

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MRDTI may play a role in the follow-up of acute PE[90, 91]: estimating thrombus age holds the potential for the differentiation between acute and chronic PE, which can be clinically relevant given the therapeutic implications. MRDTI was shown to successfully differentiate between acute and chronic PE, as illustrated by two patient cases.[92] MRDTI showed high intensity signals that corresponded to thrombi in the pulmonary arteries, demonstrated on computed tomography pulmonary angiography (CTPA). Follow-up CTPA and MRDTI after 5 months demonstrated dissolution of the PE and absence of high intensity signals, respectively. In another patient who was diagnosed with CTEPH, thrombus observed on CTPA did not have high signal on MRDTI. Moreover, the role of MRDTI in pre-operative assessment of the presence of acute thrombosis in CTEPH was described in a case report.[93] During pulmonary endarterectomy (PEA), which is the definitive treatment for CTEPH, removal of obstructive material from the pulmonary arteries can be more challenging in the presence of subacute thrombosis of days to weeks old, since this material is strongly attached to the intima of the vessel walls and no fibrotic organization has yet occurred. In the patient case, MRDTI scan was performed one day before PEA, demonstrating a positive signal in one of the pulmonary arteries. The high signal corresponded to fresh thrombus that was removed during the surgery. No positive signal was observed in the arteries where only fibrotic chronic material was removed. Based on these findings, MRDTI could play a role in the diagnostic work-up and operability assessment of patients with CTEPH.

Artificial intelligence

Artificial intelligence (AI) may provide innovative approaches to diagnosing acute PE.[94, 95] The number of performed CTPA examinations for suspected PE has continued to increase, as well as the number of images per exam due to advancing techniques, leading to higher workload and a larger number of incidental findings.[94, 96] Based on data of a teaching hospital in the Netherlands, the number of chest CT scans for suspected PE performed during on-call hours has grown by 1360% in the period between 2006 and 2020, which may be explained by easier access to CT and overuse of (more defensive) imaging.[97] Higher examination volumes, in turn, have been found to be associated with an absolute higher number of interpretive discrepancies.[98] AI tools have the potential to improve performance, accelerate workflows for the evaluation of PE and enhance efficiency and productivity, and thus relieve the workload of radiologists.[94] Of note, advancements in medical imaging applications, including elaboration of existing applications or new imaging applications, were not shown to lead to a decrease but an increase of workload of radiologists, mostly due to increase in interpretation and post-processing time or due to the introduction of new applications in practice.[99] This underlines the importance of careful evaluation of the value of AI strategies. Before these AI tools can be widely implemented in clinical practice, the balance must tip towards the benefits.

AI may contribute to current daily practice in four ways: help ascertaining a proper indication for CTPA, classification of scans, detection of clots, and prognostication.

Indication for CTPA

AI may support the decision to order examinations for evaluation of PE, which is currently based on clinical decision rules and D-dimer tests.[100, 101] The Development and Performance of the Pulmonary Embolism Result Forecast machine learning model (PERFORM) was developed as a decision support tool for ordering CTPA.[102] Raw data from electronic medical records (EMR; including demographics, vital signs, laboratory test results, diagnoses and medication use) were transformed into feature vectors that were used to train a machine learning model for predicting PE imaging outcomes, to provide the patient-specific PE risk for patients referred for CT imaging for PE. The model was tested on EMR data obtained from two academic hospitals in the United States: training and validation of the model was performed on a dataset of 3397 CT examinations conducted for PE, followed by external validation on 240 patients. Comparisons to clinical scoring systems (Wells score, Pulmonary Embolism Rule-out Criteria [PERC], and revised Geneva score) were performed on random samples of 100 and 101 consecutive outpatients from the two hospitals. The model achieved an area under the receiver operating characteristic curve (AUROC) for predicting a subsequent PE-positive CT of 0.90 in the validation cohort and 0.71 in the external cohort.[102] In the outpatient cohorts, the model had better AUROC performance than the clinical scoring systems that are currently used in practice.

Adequate AI-based decision support for performing CTPA may help prevent unnecessary testing and overdiagnosis, and reduce costs and radiation exposure.

Classification

Another potential role for computer algorithms is categorizing and labelling images based on specific rules, which allows the classification of images as with or without PE.[95] Worklist prioritization of examinations using AI may lead to faster diagnosis of PE. This could be useful in the outpatient setting where the time to review and report outpatient CT examinations may vary and incidental PEs can be found, particularly in certain patient populations such as oncology patients.[94] AI-based prioritization of the radiologist' reading worklist of routine contrast-enhanced chest CT scans in adult patients with cancer was shown to reduce the time to diagnosis of incidental PE (from a median detection and notification time of several days to 87 minutes) as well as the rate of missed incidental PEs, from 44.8% to 2.6% when radiologists received AI assistance.[103]

Detection

Several AI models and algorithms have been developed for the detection of PE on CTPA, and studies evaluating AI algorithms have shown variability in diagnostic performance.[104-120] A meta-analysis that was published in 2021, included data from five retrospective studies and demonstrated a pooled sensitivity of 0.88 and specificity of 0.86 for AI algorithms for detection of PE on CTPA.[95,104,107-109,121] In these studies, CT scans were reviewed or annotated by radiologists to confirm PE diagnosis. However, three of the five studies were classified as having high risk of bias in at least one category of the used quality assessment tool for diagnostic accuracy studies, and none of the studies examined AI in a clinical setting. Weikert et al. evaluated a FDA-approved and CE-marked AI algorithm which was trained and validated on 28,000 CTPAs, and found high diagnostic accuracy with a sensitivity of 92.7% and a specificity of 95.5%.[104] The same AI algorithm was compared to the performance of radiologists, with the reference standard based on retrospective review of radiological reports and AI outputs by one radiologist and one information technology (IT) engineer with access to the medical records, showing that AI resulted in higher sensitivity and negative predictive value (NPV), whereas radiologists had higher specificity and positive predictive value (PPV).[122] Notably, 19 PE cases that were missed by radiologists were captured by AI (most proximal clot location: 3 lobar, 14 segmental, and 2 subsegmental), which corresponds to a correction of one missed diagnosis out of every 63 CTPA scans based on this cohort of 1202 patients. The other way around, 14 PEs were detected by radiologists but missed by AI: 3 proximal, 2 lobar, 7 segmental, and 2 subsegmental PE. Based on a survey distributed to radiologists 9 months after introduction of the AI algorithm, 72% of radiologists were positive or strongly positive that AI improved their diagnostic confidence.[122] The mean interpretation duration for a single CTPA in a cohort of patients from 2020 after AI implementation was 15.6 (SD 9.8) minutes, compared with 14.6 (SD 9.1) minutes in a pre-AI cohort from 2018.[122] Another retrospective study showed that diagnostic accuracy of this AI algorithm was higher compared to the initial radiologist report, with both higher sensitivity and specificity.[123] These findings demonstrate how AI assistance could support radiologists.

Several retrospective studies specifically evaluated computer-aided detection or AI algorithms for the detection of missed PEs.[124-126] Computer-aided detection could identify 77% of PEs that had been missed in clinical practice, according to retrospective review of CTPA scans by three radiologists who judged PE to be present while the presence of PE was not described in the report.[124] In two studies, initially missed and unreported incidental PE could be detected by AI algorithms on CT examinations that were not performed with a dedicated PE protocol (such as routine contrast-enhanced chest CTs, or abdominal and pelvic CTs that include the lung bases).[125, 126] Another algorithm could detect additional incidental PEs on conventional contrast-enhanced chest CT examinations (no CTPAs) that were not detected by radiologists, however, the algorithm also missed incidental PEs that radiologists did detect.[127] Furthermore, Ebrahimian et al. evaluated the performance of an FDA-approved, commercially available AI algorithm in CTPAs that were suboptimal due to artifacts or inadequate contrast enhancement.[128] The reference standard for presence of PE and adequacy of CTPAs was based on consensus of two radiologists who were unaware of the AI output. Among 133 suboptimal scans and 197 optimal scans, performance of the algorithm was comparable (sensitivity 100%, specificity 89%, AUC 0.89 versus sensitivity 96%, specificity 92%, AUC 0.87, respectively). On suboptimal CTPAs, the AI algorithm did not miss any PE although the PE prevalence was low (14%, versus 40% in patients with optimal CTPA).

As current evidence is based on studies with a retrospective design and may be affected by bias, prospective studies – preferably randomized – are needed to compare AI versus standard radiological practice.

Prognostication

Another task that AI algorithms can provide is the segmentation or delineation of the borders of structures, which is valuable in quantitative image analysis.[95, 129] Deep learning methods were indeed shown to accurately segment PE on CT images.[130, 131]

Clot burden quantitatively measured with a deep learning convolutional neural network method to perform clot segmentation and calculate clot volume, correlated with the clot burden assessed with Qanadli scores and Mastora scores (rho 0.82 and 0.87, respectively).[108, 132-134] Clot burden measured with a deep learning model also correlated with RV functional parameters on CTPA.[108] In a retrospective study of 101 patients with acute PE confirmed on CTPA, automated calculation of the RV/LV diameter ratio on CTPA using AI post-processing software was feasible in 87% of patients and correlated with manual analysis of RV/LV ratio (intraclass coefficient 0.78 to 0.83).[135] Use of AI may therefore contribute to the risk stratification of patients with acute PE.

Impact of clinical introduction

A sample of 440 medical imaging studies published in 2019 was evaluated in a study to assess the effect of imaging applications on the workload of radiologists. The authors demonstrated that almost half of the medical imaging applications, including AI applications, would increase the workload of radiologists, whilst 4-5% of the studied applications would reduce the workload.[99] Notably, AI applications were mainly associated with increased workload because of additional time required for post-processing and interpretation. Schmuelling et al. implemented a deep learning method for PE detection on CTPA combined with an electronic notification system at their radiology department and evaluated whether this improved the workflow.[136] Via a widget running on all reading stations, a pop-up window appeared for 60 seconds if the AI algorithm suspected a PE, to allow for immediate review of the images by the radiologist. The authors did not find a reduction in report reading and communication times, time to anticoagulation, or patient turnaround time in the emergency department. On the other hand, Batra et al. evaluated the effect of worklist prioritization based on an AI tool for flagging of suspected positive findings of acute PE on CTPA examinations and reprioritizing these to the top of the worklist, and found that report turnaround time for PE-positive CTPA examinations (i.e. time from completion of examination to available report) reduced.[137] Specifically, wait time (i.e. time from examination to initiation of report) reduced with a mean of 12 minutes for CTPA examinations positive for PE, while read time (time from report initiation to available report) did not differ between the pre-AI and post-AI periods.

Challenges

The development and implementation of AI algorithms comes with challenges. Training of deep learning algorithms requires large anonymized high-quality annotated datasets of labelled images, with accurate labelling of the pathology of interest, which may be affected by inter-reader variability.[94,138,139] Medical imaging datasets should be large and heterogenous, to limit bias due to geographical or technological factors or inherent bias e.g. based on age or gender, and avoid overfitting and underfitting.[94,139,140] Integrating non-image data, such as the indication for the examination, medical history and clinical parameters, may add rich insights but also complexity.[94,138,139] Deep learning applications should be thoroughly trained, tested and validated, with consideration of ethical and regulatory aspects and data privacy.[138-140] After successful implementation in clinical practice, appropriate monitoring and maintenance of AI tools should be ensured.[141]

Another important challenge are the costs related to AI clinical tools and licenses, that may significantly increase the CTPA examination costs. Taking a broader perspective and looking at the vast array of AI applications for CT that are currently being evaluated for any CT, integration of AI tools for multiple indications is necessary to help arriving at applications of AI that are viable in clinical practice.

In conclusion, AI could provide value in diagnosing PE, but future studies should compare AI to current standard radiological practice and address the challenges that come along with its development and implementation, including assessment of cost-effectiveness, and should further evaluate the impact of clinical introduction of AI on patient outcomes.

Conclusions

Available and emerging diagnostic strategies for detection and management of acute PE extend beyond CTPA. The potential of PCCT, perfusion iodine maps based on subtraction or dual-energy acquisition, and SPECT and MRI techniques should be confirmed in future prospective management outcome studies (**Table 1**), with attention to relevant (long-term) outcomes, including patient-centered outcomes in addition to conventional clinical outcomes.[142] Moreover, cost-benefit analyses could provide insight into the cost-effectiveness of these technologies. AI holds potential to improve workflows for the evaluation of PE, by providing support in various capacities. Further research is needed to establish which AI strategies are feasible to use in clinical practice and add value to the current diagnostic management of PE.

Table 1: Limitations and challenges associated with the imaging techniques.

Imaging technique	**Limitations**	**Challenges and future research directions**
CTPA	- Radiation exposure - Exposure to iodinated contrast	- Dose reduction strategies for continuous reduction in radiation dose - With detection of contrast-filling defects in subsegmental pulmonary arteries, unknown clinical relevance of isolated subsegmental PE *(SAFE-SSPE trial NCT04263038 is currently ongoing)*
PCCT	Compared to conventional CT: - Higher costs for PCCT hardware/software systems - Larger storage space required	- Potential of higher resolution and lower radiation dose is yet to be confirmed in future prospective management outcome studies
Perfusion iodine maps based on subtraction or DECT	- Compared to CTPA alone, sensitivity did not significantly improve, and the value of iodine maps for guiding management of the patient may be limited - DECT does require dedicated hardware	- Large prospective diagnostic or therapeutic management outcome studies investigating CT perfusion images combined with DECT or CTPA are unavailable
SPECT	- The optimal technique (V/Q SPECT vs Q SPECT, with or without non-enhanced CT) is not yet defined - Unable to provide alternative diagnosis if PE is ruled out	- SPECT imaging techniques should be validated in large prospective management outcome studies, and the accuracy of SPECT compared with planar V/Q scintigraphy and CTPA should be prospectively determined using an independent reference standard
MRA	- Insufficient sensitivity - High proportion of inconclusive scans - Limited availability (especially in urgent settings) - Longer study duration compared with CTPA - Costs associated with MRI	- Provided sensitivity improves, MRA may provide an alternative to CTPA that is independent of radiation or iodinated contrast media *(IRM-EP2 study NCT02059551 evaluating diagnostic performance of MRA combined with leg ultrasound for suspected PE is currently ongoing)* - Use of ferumoxytol as alternative for gadolinium-based contrast agents should be further evaluated before recommended in guidelines
MRDTI	- Limited availability (especially in urgent settings) - Costs associated with MRI - To date, mainly evaluated for diagnosis of deep vein thrombosis	- MRDTI for diagnosis of PE should be evaluated in prospective outcome studies - Accuracy of MRDTI for smaller, (sub) segmental clots is unknown: challenge to equal accuracy of multidetector CTPA - Appearance of high signal intensity relies on methaemoglobin formation: role of MRDTI in the acute setting (i.e. within hours) could be further explored

Abbreviations CTPA: computed tomography pulmonary angiography, PCCT: photon-counting computed tomography, DECT: dual-energy computed tomography, SPECT: single-photon emission computed tomography, MRA: magnetic resonance angiography, MRDTI: magnetic resonance direct thrombus imaging, CT: computed tomography, V/Q: ventilation/perfusion, PE: pulmonary embolism, MRI: magnetic resonance imaging, SAFE-SSPE: Surveillance versus Anticoagulation For low-risk patiEnts with isolated SubSegmental Pulmonary Embolism.

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Supplementary material

Table S1: Details regarding radiation dose of computed tomography pulmonary angiography acquisition with subtraction performed in current practice at Leiden University Medical Center.

Acquisition	DLP in mGy*cm (mean, SD)
Dual scano and scan&view	7.34 (0.78)
Helical (low-dose)	25.24 (8.44)
Sure start (contrast)	19.74 (5.48)
Helical (contrast)	112.20 (47.82)
Total	164.53 (54.60)

These data are based on a random selection of 12 CTPA scans performed during the first week of November 2023 to exclude acute PE, on Toshiba 320-slice CT scanners, CTPA protocol with subtraction acquisition at 100 kV, to illustrate radiation dose in our current practice.

Mean total effective dose: 2.30 mSv using a conversion factor of 0.014, or 3.17 mSv using a conversion factor of 0.019. Dose length product (DLP) is a measure for radiation output.

Abbreviations DLP: dose length product, mGy: milligray, SD: standard deviation, CTPA: computed tomography pulmonary angiography, PE: pulmonary embolism, CT: computed tomography, kV: kilovolt, mSv: millisievert.