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Imaging Pulmonary Embolic Disease

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Abstract



Purpose of Review The purpose of this article is to review the imaging findings and current imaging techniques of acute pulmonary embolism (PE) and chronic thromboembolic disease. Special considerations are also discussed, including pregnancy, congenital heart disease, lower extremity computed tomography (CT), and the isolated subsegmental PE.

Recent Findings CT pulmonary angiography and planar ventilation/perfusion (V/Q) lung scintigraphy are the primary means of evaluating pulmonary embolic disease. Magnetic resonance angiography avoids ionizing radiation and iodinated contrast in select patients. V/Q SPECT/CT provides greater accuracy and fewer non-diagnostic exams than planar V/Q scans. Dual-energy CT may prove valuable in the diagnosis of and preoperative planning for chronic thromboembolic pulmonary hypertension. **Summary** Imaging plays a central role in identifying thromboembolic disease, but understanding the benefits and limitations when choosing the appropriate modality is imperative. Further research is needed to elucidate the role of emerging technologies in the assessment of thromboembolic disease.

Keywords Pulmonary embolism \cdot Chronic thromboembolic disease \cdot Computed tomography angiography \cdot Magnetic resonance angiography

Introduction

Acute pulmonary embolism (PE) and chronic thromboembolic disease (CTED) are potentially life-threatening conditions requiring prompt diagnosis and treatment. The hospital mortality rate for major pulmonary embolism is 30%, dropping markedly with appropriate anticoagulation [1]. Although most acute emboli resolve without sequelae following anticoagulation, some become endothelialized and lead to CTED. CTED increases pulmonary vascular resistance and may result in chronic thromboembolic pulmonary hypertension (CTEPH) [2•]. The exact incidence of CTEPH is unclear but is thought to occur after up to 3.8% of acute pulmonary embolic events and in up to 10% of patients with chronic PE

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² Department of Radiology, Division of Cardiopulmonary Imaging, University of Colorado School of Medicine, Aurora, CO, USA [3]. Imaging plays a central role in identifying patients with these conditions. The purpose of this article is to review current imaging techniques, demonstrate the imaging findings of acute PE and CTEPH, and describe special considerations in the evaluation of PE.

Clinical Considerations

Acute PE gives rise to a wide range of nonspecific symptoms, including chest pain, syncope, and dyspnea. Clinical diagnosis is therefore challenging as symptoms overlap with those of other common entities including pneumonia, congestive heart failure, aortic dissection, and obstructive airways disease [4].

Several clinical risk stratification tools help determine the pre-test probability of acute PE, such as the Wells criteria, the Geneva Prognostic index, and the Pisa model $[1, 2^{\bullet}]$. D-dimer, elevated in acute venous thrombosis, has high sensitivity and negative predictive value. When used in combination with low or intermediate pre-test probability (for example, a Wells score < 4), it effectively excludes acute PE, and the 3-month incidence of venous thromboembolism is less than 1% $[1, 2^{\bullet}, 5]$. CT pulmonary angiography (CTPA) can, therefore, be reserved for patients with high pre-test probability, or low or intermediate pre-test probability but abnormal D-dimer.

The American Heart Association classifies acute PE as high-risk (massive), intermediate-risk (submassive), or lowrisk depending on the likelihood of mortality. Massive PE is defined as sustained hypotension (systolic blood pressure < 90 mmHg for > 15 min) or requiring vasopressor support. Submassive PE is characterized by evidence of right heart strain, dilation, dysfunction, or myocardial ischemia without sustained hypotension. Low-risk PE does not cause hypotension or right heart dysfunction or enlargement [6].

CTEPH develops secondary to a combination of proximal vascular obstruction and distal arteriolar vasculopathy in nonobstructed areas. It is clinically defined as mean PA pressure \geq 25 mmHg at rest and pulmonary capillary wedge pressure < 15 mmHg with the persistence of multiple organized thrombi in the lobar, segmental, or subsegmental pulmonary arteries after at least 3 months of anticoagulation. Increased pulmonary vascular resistance leads to right ventricular (RV) dysfunction and in some cases failure with 5-year survival rates as low as 10%. Definitive treatment is pulmonary endarterectomy in select patients. This surgical procedure is only available at a few highly specialized centers [2•].

Imaging Technique and Findings

Chest Radiography

Chest radiography has a limited role in the diagnosis of PE. Typically normal in the setting of acute PE, its primary purpose is to exclude an alternative diagnosis. Subtle indirect findings suggestive of PE include decreased vascularity in the affected lung reflecting oligemia (Westermark sign), enlargement of the central pulmonary artery (Fleischner sign), peripheral dome-shaped opacity representing pulmonary infarction or hemorrhage (Hampton's hump sign), and a dilated right interlobar artery greater than 16 mm (Palla sign) [7, 8]. In CTEPH, the heart and central pulmonary arteries are more frequently enlarged. Ventilation/perfusion (V/Q) imaging also requires a chest radiograph within 12–24 h for accurate interpretation [7, 9•, 10••].

Echocardiography

Transthoracic echocardiography (TTE) is not currently recommended for hemodynamically stable patients with suspected PE. In high-risk patients, TTE has an important role in excluding other diagnoses, prognostic prediction, and identifying patients who may benefit from emergent thrombolysis. The presence of RV dysfunction, right-to-left shunt, and RV thrombus has each been linked with a roughly twofold risk of mortality [9•].

CT Pulmonary Angiography

CTPA is the gold standard for diagnosing acute PE. It is widely available, safe, and rapid with similar diagnostic accuracy as conventional angiography $[1, 6, 9^{\bullet}]$ Other advantages include the ability to risk-stratify positive cases and find alternative diagnoses in negative cases. Conventional angiography is now mainly reserved for endovascular treatment $[9^{\bullet}]$.

Technique

Optimal contrast timing is crucial to diagnostic quality. For the standard exam, 60–120 mL of intravenous contrast is administered at a rate of about 4–6 mL/s. An 18- or 20-gauge catheter in an antecubital vein is preferred [11]. Power injectable central lines with an appropriate maximum injection pressure are an alternative option to peripheral venous access [12].

Increased utilization of CT has intensified efforts to reduce radiation dose and intravenous contrast load. Reducing tube voltage is one of the most effective ways to reduce radiation dose and has the potential added benefit of reducing the amount of contrast (see "Dual-Energy CTPA" section). Postprocessing techniques with decreased image noise, such as iterative reconstruction, allow a reduction in radiation while maintaining image quality [13].

Imaging Findings

The imaging appearance of an acute PE is a central or eccentric, low-attenuation, endoluminal filling defect forming acute angles with the vessel wall (Fig. 1a). The involved vessel is usually preserved in size or slightly expanded. Complete occlusion of the artery may result in parenchymal infarction, whereas partial occlusion may result in oligemia. A central PE draping over the pulmonary trunk bifurcation, bridging the right and left pulmonary arteries, is referred to as a "saddle embolus."

Complete obstruction of one or partial occlusion of both the right and left main pulmonary arteries is typically necessary to cause right heart strain or hypotension [6]. CT features of right heart strain include RV dilation, flattening of the interventricular septum (Fig. 1b), and reflux of contrast into the inferior vena cava (IVC), hepatic veins, or azygos system. The American Heart Association defines RV dilation as an RV/left ventricular (LV) ratio of > 0.9 [14], obtained by dividing the maximal RV diameter in the axial plane by the maximal LV diameter. Measurements should be from the free wall to septal endocardium, excluding the myocardium [6]. Increased RV/ LV ratio is associated with a 2.8–7.4-fold increase in shortterm mortality, which is the strongest predictive value for 30day mortality and the most robust evidence for adverse clinical outcomes [6, 13, 15, 16]. Fig. 1 Acute pulmonary emboli with right heart dilation. a CTPA shows filling defects in the right interlobar pulmonary artery (arrow) and bilateral lower lobe segmental arteries (arrowheads).
b Right ventricular to left ventricular ratio is > 0.9, suggestive of right heart strain



Reflux of contrast into the IVC and hepatic veins is an indirect sign of acute tricuspid valve insufficiency in severe acute PE. Reflux of grade 4 or higher (into the IVC and proximal, mid, or distal hepatic veins) has been shown to have prognostic significance [16, 17]. Leftward bowing of the interventricular septum has high specificity (100%) but poor sensitivity (26%) in the prediction of RV strain and has poor interobserver agreement [16].

Pulmonary infarction is more likely with occlusive or distal PE compared with more central PE. It appears as a wedge-shaped peripheral consolidation, often with central ground-glass attenuation (the "reverse halo" or "atoll" sign) (Fig. 2). Associated pleural effusion is common [9•].

Distinguishing acute and chronic PE is critical, as treatment options and outcomes differ significantly. Organized chronic PE can appear as intraluminal bands, webs, or laminated thrombi. Laminated thrombi are intimal irregularities with obtuse angles to the vessel wall, sometimes with associated calcification (Fig. 3). Abrupt reduction in vessel size or pruning of the arterial tree is due to the retraction of organized thrombus with partial or lack of contrast opacification. If pulmonary hypertension (PH) develops, the central pulmonary arteries enlarge and may appear tortuous. Additional findings of PH include RV dysfunction (dilation, hypertrophy, and bowing of the interventricular septum), right atrial enlargement, and pleural or pericardial effusions in advanced disease. Systemic-to-pulmonary shunts may develop manifesting as dilated bronchial arteries along with occasional transpleural collateralization from intercostal and abdominal arteries [2•]. Parenchymal findings include mosaic attenuation (sharply demarcated regions of decreased attenuation, with smaller number and caliber of vessels, Fig. 4a) and scars from prior pulmonary infarctions [18].

Ventilation/Perfusion Imaging with or Without SPECT

V/Q lung scintigraphy is a nuclear medicine examination comparing ventilation (V) and perfusion (Q) to the lungs in conjunction with a chest radiograph for reference. Decreased areas of radiotracer uptake are characterized as matched (concordant), mismatched (perfusion defect with normal or less pronounced ventilation defect), or reverse



Fig. 2 Acute pulmonary emboli with pulmonary infarction. CT of the chest shows a dome-shaped peripheral opacity with central ground-glass attenuation and peripheral consolidation (arrow)





Fig. 3 Chronic thromboembolic disease. CT pulmonary angiography shows a partially calcified eccentric thrombus in the left main pulmonary artery (arrow)

Fig. 4 Chronic thromboembolic disease. **a** CT of the chest in a 72-year-old with CTEPH shows mosaic attenuation of the lungs secondary to mosaic perfusion. **B** V/Q scan in the same patient shows multiple wedge-shaped perfusion defects (arrows). Ventilation imaging (bottom row) shows mildly heterogeneous distribution of radiotracer through the lungs with radioaerosol deposition within the central bronchi, consistent obstructive airways disease



mismatched (ventilation defect with normal or less pronounced perfusion defect). Classically, a PE results in a peripheral wedge-shaped perfusion defect in a lobar, segmental, or subsegmental distribution without corresponding ventilation defect (i.e., a mismatched defect) [19].

V/Q scans are most often interpreted according to the modified Prospective Investigation of Pulmonary Embolism Diagnosis (PIOPED) II criteria. This is a probability-based interpretation system classifying results as high probability, very low probability, normal, or non-diagnostic [9•]. Modified PIOPED II has fewer categories than the original PIOPED with the aim of reducing non-diagnostic exams and was shown to be more accurate.

Perfusion imaging is performed after the intravenous injection of technetium-99m (Tc-99m-labeled macroaggregated albumin (MAA)). There are three main options for image acquisition with increasing spatial and contrast resolution: planar imaging, single-photon emission computerized tomography (SPECT), and SPECT/CT. V/Q SPECT and V/Q SPECT/CT have emerged in the last decade and are still the subject of ongoing investigation. V/Q SPECT has been reported to decrease the proportion of non-diagnostic studies in the assessment for acute PE and its use is endorsed over planar imaging by the European Association of Nuclear Medicine guidelines [20]. The addition of low-dose CT to V/Q SPECT allows both CTbased attenuation correction and anatomic CT correlation, resulting in greater accuracy (by reducing false-positive scans) and fewer non-diagnostic exams, but at the expense of increased radiation dose (especially to the breasts). V/Q SPECT and V/Q SPECT/CT are not routinely performed in the USA. More robust research and validated PE interpretation criteria of hybrid imaging are needed [20–23].

Ventilation is most often performed using aerosolized technetium-99m-labeled diethylenetriaminepentaacetic acid (DTPA) though other Tc-99m-labeled agents or radioactive noble gases such as Xenon-133 may be used [9•]. It can

sometimes be avoided if a perfusion scan is performed first and found to be normal, particularly in pregnant patients to decrease radiation dose [9•].

Ultimately, V/Q scan for the evaluation of acute PE should be reserved for select indications, such as pregnancy, iodinated contrast allergy, and renal impairment [9•]. V/Q scans should not be performed if the concomitant chest radiograph is significantly abnormal or if the patient is clinically unstable [19].

Both CTPA and V/Q scan are deemed "usually appropriate" (rating of 8 according to the ACR Appropriateness Criteria) in the assessment of suspected PH [24]. According to the American College of Cardiology working group, V/Q scan should be performed in all patients with unexplained PH to assess for CTEPH (Fig. 4B). V/Q scans have a sensitivity of 90–100% and a specificity of 94–100% for differentiation between idiopathic PH and CTEPH. A normal or lowprobability scan essentially excludes CTEPH. With a potential for false positives or non-diagnostic scans, CTPA is often obtained for confirmation, to define the anatomic extent of disease or surgical planning [21].

Dual-Energy CTPA

Dual-energy CT (DECT) acquires two nearly simultaneous datasets at low and high tube voltage levels, allowing the generation of pulmonary blood volume (PBV) maps or "iodine maps" that can be superimposed on standard CT images. PBV maps display blood volume to the lungs (rather than dynamic perfusion) and enable the detection of perfusion defects, similar to lung scintigraphy (Fig. 5) [13]. The main appeal of DECT in the chest is the combination of anatomic information from CT with the perfusion information of PBV maps into a single examination for diagnostic, prognostic, and pre-surgical evaluation of CTEPH [25].

PBV maps can be both qualitatively and quantitatively assessed for perfusion defects. The automated PBV correlates with mean pulmonary arterial pressure and pulmonary **Fig. 5** Chronic thromboembolic disease. **a** Dual-energy CT shows a thin intraluminal web in a right lower lobe segmental artery (arrow). **b** Pulmonary blood volume shows a wedge-shaped perfusion defect in the right lower lobe (arrow)



vascular resistance on right heart catheterization and thus may be used to estimate CTEPH severity. PBV maps may also improve detection of distal disease in the absence of overt intraluminal clot on CT [26]. PBV score in these patients has been shown to correlate with all-cause mortality [27]. PBV also increases after pulmonary balloon angioplasty, suggesting a role in post-treatment surveillance [28].

Despite these advantages, studies comparing PBV maps with the more established planar and V/Q SPECT have shown only modest agreement. Larger studies are needed to define the usefulness of DECT in CTEPH, particularly in light of the added post-processing and interpretation time.

The benefit of DECT in the assessment of acute PE over CT alone or V/Q scan is even less clear [25]. PBV maps have been shown to slightly increase detection of occlusive segmental and subsegmental PE compared with CT alone. However, the clinical importance of additional detected subsegmental PE remains indeterminate [29]. Growing data shows a correlation in the extent of perfusion defects on PBV maps with standard assessments of right heart strain on CT and laboratory markers as well as with adverse clinical outcomes. Radiation dose in DECT is comparable to standard CT CTA [30].

MR Pulmonary Angiography

The largest analysis of MR pulmonary angiography (MRPA) to date has been the PIOPED III study, a prospective multicenter clinical trial that found a sensitivity of 45–100% (average 78%) for acute PE on a technically adequate study. Previous studies showed sensitivities of 77–100% for the main or lobar pulmonary arteries and decreasing sensitivity for segmental (68–84%) and subsegmental arteries (0–40%) [31]. When combined with MR venogram (MRV) of the lower extremities, MRPA has a higher sensitivity (92%) and specificity (96%), though adequate diagnostic quality can be difficult to achieve [31]. Non-contrast MRPA is a less sensitive but feasible option in select patients [22].

Similar to CTPA, MRPA findings of acute PE include intraluminal filling defects and absence of vessel enhancement [8]. Occlusive or laminated thrombus detection may be more difficult in MRPA. Unlike CTPA, MRPA demonstrates lung parenchymal perfusion, and the presence or absence of perfusion defects can augment diagnosis.

While MRPA offers the advantages of avoiding iodinated contrast in patients with a severe allergy and avoiding breast radiation in young women, CTPA has higher spatial resolution, faster speed, and reduced cost [2•, 22]. MRPA is therefore not routinely utilized and should be performed at experienced centers for stable patients with contraindications to standard testing [2•, 6]. MRPA does not currently play a role in the evaluation of CTEPH in which the higher spatial resolution of CT is needed to identify often tiny weblike filling defects.

Special Considerations

Pregnancy

PE accounts for 20% of maternal deaths in the USA with about half of these deaths (52%) occurring within 24 h after the end of the pregnancy [32]. Imaging pregnant women with suspected acute PE should be aimed at avoiding or minimizing radiation dose as much as feasible. The American Thoracic Society/Society of Thoracic Radiology (ATS/STR) Committee on Pulmonary Embolism in Pregnancy published practice guidelines, which make several recommendations.

A pregnant woman with a suspected PE and signs and symptoms of deep venous thrombosis (DVT) should first undergo ultrasound of the lower extremities [33]. The ultrasound diagnosis of DVT in a patient with suspected PE is considered sufficient to start anticoagulation without further testing [2•]. If negative, chest radiograph should then be performed. If this is normal, V/Q scan is the next option. If the chest radiograph is abnormal, a V/Q scan is more likely to be non-diagnostic and a CTPA is instead recommended [33].

The choice between CTPA versus V/Q scan remains a matter of debate [10••]. For both exams, radiation dose to

the fetus is negligible, similar to background radiation throughout gestation. Radiation exposure is alternatively focused on the mother whose breasts have increased sensitivity to radiation during pregnancy. CTPA is associated with higher dose to the breasts and lungs than V/Q scan, but has fewer non-diagnostic studies [33].

Dose reduction techniques in CT include tube current modulation and decreasing the image field to limit radiation to the fetus. Radiation dose can be limited in V/Q scans by reducing Tc-99m MAA dose in perfusion imaging and excluding the ventilation scan if the perfusion is normal [10••, 33]. Contrast-enhanced MRPA should be avoided in pregnancy due to potential teratogenicity of gadolinium; however, non-contrast MRPA is feasible in some patients to exclude a central PE [33].

Lower Extremity CT Venography

Contrast-enhanced CT venography (CTV) of the lower extremities is performed by obtaining images of the iliac, femoral, and popliteal veins 3 min after the initial contrast injection for CTPA [11]. According to the American College of Radiology (ACR) Appropriateness Criteria, duplex ultrasound is the first-line exam for diagnosis of DVT with little evidence to support the use of CTV. Along with MRV, it may be considered for pelvic DVT when ultrasound is non-diagnostic or if overlying casts, surgical material, or wounds preclude the use of ultrasound [9•, 34].

Congenital Heart Disease

The Fontan procedure is the present surgical palliation for patients with various complex congenital heart diseases resulting in single ventricle physiology. The multi-staged procedure concludes with total cavopulmonary connection; the superior vena cava (SVC) is anastomosed to the pulmonary arterial system by a uni- or bi-directional Glenn shunt, and the IVC is anastomosed to the pulmonary arterial system by a Fontan shunt.

In patients referred for CTPA, achieving optimal pulmonary arterial opacification of both lungs is challenging. With a standard upper extremity contrast injection, the pulmonary arteries opacify asymmetrically, and non-opacification or reduced opacification of pulmonary artery branches in one lung may be mistaken for extensive PE. The remaining pulmonary artery branches supplied by the Fontan shunt do not opacify until later.

Optimal opacification of both pulmonary arteries is best attained by dual injection of the upper and lower extremity central veins. An alternative method involves a single injection with two separate scans—one during arterial phase and one delayed scan at about 3 min after the contrast injection when the Fontan has opacified. The ACR endorses the dualinjection method followed by a delayed scan only if the initial scan is not fully diagnostic [35].

The Isolated Subsegmental PE

Technical innovation and the pervasive use of CTPA has led to an increased incidence in PE diagnosis without a clear corresponding decline in mortality [1, 29, 36, 37]. The prognostic and clinical significance of subsegmental PE has thus become an ongoing question and subject of debate as imaging techniques advance. The lack of mortality reduction has led some authors to surmise that the incremental PE detection represents overdiagnosis [38]. Additionally, several studies have found that patients with untreated isolated subsegmental PE without DVT did not show recurrent PE or venous thromboembolism after 3 months [2•, 29, 39, 40]. It is important to note, however, that a small subsegmental PE in a critically ill patient with poor cardiopulmonary reserve can be clinically significant and should not be equated with overdiagnosis [41].

Conclusion

Acute PE and CTEPH are potentially life-threatening conditions requiring prompt diagnosis and treatment. Imaging plays a central role in identifying patients with acute pulmonary embolism and chronic thromboembolic disease, but it is important to understand the benefits and limitations when choosing the appropriate modality and protocol. In particular, special attention should be paid in the setting of pregnancy and congenital heart disease. Additionally, MRPA and lower extremity CT should be reserved for select patients. Further research is needed to elucidate the role of emerging technologies including SPECT and dual-energy CT in the assessment of patients with thromboembolic disease.

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Compliance with Ethical Standards

Conflict of Interest Joanna G. Escalon, Daniel B. Green, Tami J. Bang, and Daniel Vargas declare no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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