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STATE OF THE ART REVIEW

Imaging of Chronic Thromboembolic Disease

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Abstract
Acute pulmonary embolism (PE) is a leading cause of cardiovascular morbidity. The most common long-term complication of acute PE is chronic thromboembolic disease, a heterogenous entity which ranges from asymptomatic imaging sequelae to persistent symptoms. Chronic thromboembolic pulmonary hypertension (CTEPH) is a rare disease that can develop in this population and represents the only treatable type of pulmonary hypertension. Recognition of the characteristic findings of chronic pulmonary embolism and CTEPH provides not only diagnostic information, but is also crucial for guiding therapy. The present state-of-the-art review focuses on the multimodality imaging features of chronic pulmonary embolism. Detailed description and illustrations of relevant imaging findings will be demonstrated for ventilation/perfusion (V/Q) scan, CT scan and Dual-Energy CT and MRI and features that distinguish chronic PE from common imaging mimics.

Keywords Pulmonary embolism · Chronic thromboembolic disease · Pulmonary hypertension · Computed tomography · Dual-energy · Nuclear

Introduction

Chronic pulmonary embolism (PE) is a common occurrence following acute PE and is defined as persistence of pulmonary vascular abnormalities following appropriate therapy. Rarely, patients with chronic PE may develop pulmonary hypertension (PH), the combination of which is termed chronic thromboembolic pulmonary hypertension (CTEPH). CTEPH is a group 4 PH according to the World Symposium on Pulmonary Hypertension. CTEPH is an important cause of long-term morbidity and mortality in PE patients and remains the only potentially curable cause of pulmonary hypertension. In this article we will describe the development and gamut of chronic PE from asymptomatic residua of acute PE to CTEPH, with a focus on imaging manifestations.

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Acute PE Evolution

Acute PE is a major cause of morbidity and mortality worldwide and is the third most frequent cardiovascular disease after coronary artery disease and stroke [1]. Current guidelines recommend a minimum of 3 months of anticoagulation following an acute event. Even with optimal therapy, however, resolution of PE is frequently incomplete on imaging. A recent prospective cohort study by Marconi et al. [2] followed 183 acute PE patients with perfusion lung scintigraphy and blood gas analysis conducted at 48 h from presentation, after 1 week, and after 1, 6, and 12 months. In this study, 40% of patients had persistent perfusion defects after 6 months, with no additional improvement at 12 months. A retrospective cohort study by Choi et al. [3] followed 764 patients diagnosed with acute PE and found variable rates of observed clot resolution depending on imaging modality and criteria for complete resolution, with residual defects in 15–25% by 9–12 months. Another combined prospective and retrospective cohort study by Korkmaz et al. [4] found residual chronic PE on V/Q scan in 18.2% at 12 months.

Chronic PE

While most patients ultimately have complete resolution of their PE, the persistence of thromboemboli following acute

PE is termed as chronic thromboembolic disease (CTED). While these chronic or slowly resolving thrombi may be asymptomatic, many experience protracted symptoms which range from a functional post-PE syndrome [5] to residual or recurrent thromboembolism. The rarest and most severe long-term outcome of acute thromboembolic event is the development of CTEPH with an overall incidence following an acute thrombotic event of 1–5% [6]. However, results from the CTEPH registry [7] demonstrated that up to 25% of CTEPH patients had no history of venous thromboembolism (VTE) [8].

CTEPH

CTEPH is classified as a group 4 PH in the current classification of the World Symposium on Pulmonary Hypertension [9] and is the only potentially curable form of PH [10]. In CTEPH, the pulmonary thromboemboli have organized into fibrotic material which cause persistent obstruction and elevated pulmonary vascular resistance. In addition, in long-standing disease the unaffected areas of lung may undergo remodeling of the pulmonary arterial bed. On autopsy, the composition of these chronic PE are distinct from the acute clots and are often described as bands and webs or of irregular shapes which are firmly adherent to the vascular wall. Histologically these lesions are characterized by discrete areas of irregular intimal thickening composed of collagen, fibroblasts and few inflammatory cells, including lymphocytes and lipid-laden macrophages. In larger lesions, there may be partial recanalization via neoangiogenesis which communicate with the vasa vasorum [11].

While the causes of CTEPH are incompletely understood, clinical studies suggest an interplay between inflammation and vascular remodeling which may lead to impaired lysis and thrombosis of acute clots. Risk factors include prior splenectomy, ventriculoatrial shunts in hydrocephalus, staphylococcus infection, and chronic inflammatory disorders (osteomyelitis, inflammatory bowel disease), as well as those with non-O blood groups [12].

Diagnosis

Chronic Thromboembolic Disease

Ventilation-Perfusion (V/Q) Scintigraphy

While CT angiography has replaced V/Q scan as the most common modality for the diagnosis of acute PE, V/Q scan remains the clinical reference standard in the workup for CTED. While earlier trials comparing V/Q scan and CT in the diagnosis of CTED showed superiority of V/Q [13], more recent trials have shown comparable sensitivity and specificity between the two modalities [14]. A normal perfusion scan definitively excludes CTED with a sensitivity of 90–100% and specificity of 94–100% [15]. V/Q scan positivity for PE, relies principally on demonstrating perfusion defects that are mismatched with ventilation [16] (Fig. 1).

V/Q is limited in the setting of chronic lung disease or other comorbidities that effect baseline ventilation and/or perfusion. Misinterpretation can also occur in the setting of non-occlusive thrombi with underestimation of the degree of disease extent [17–19]. Single photon emission computed tomography (SPECT) V/Q is gaining traction, especially in Europe, in the evaluation of acute PE due to its improved sensitivity and specificity, [20] and may play a future role in the evaluation of CTED. A prospective observational study by Miles et al. [21] of 100 patients with suspected PE, 79 of whom underwent both SPECT/CT-V/Q and CTPA with 3-month follow up, found 95% agreement between the two modalities with SPECT V/Q performing at 83% sensitivity and 98% specificity. Binary (positive or negative for PE) and trinary (high, low, or intermediate probability of PE) V/Q scan interpretative strategy has added clarity compared with the standard set by the Prospective Investigation of Pulmonary Embolism Diagnosis trial (PIOPED) [22], which was a probabilistic interpretative scheme [23].

Computed Tomography

CT Pulmonary Angiography

CT pulmonary angiography (CTPA) is the current standard for diagnosis of acute PE and has been increasingly used in the diagnosis of CTED. CTPA is highly accurate for CTED diagnosis when read by an experienced cardiothoracic radiologist, however, rarity of disease and the multiplicity of findings are associated with lower diagnostic accuracy in many lower-volume settings [24]. A meta-analysis by Dong et al. [25] found pooled sensitivity and specificity of 76% and 96%, respectively, with sensitivity improved to 88% to the subsegmental pulmonary artery level. CTPA expert interpretation should delineate the extent of thrombus burden to guide therapeutic decision making. CT findings for both pulmonary hypertension and CTED/CTEPH may vary according to disease severity [26].

Chronic Thromboembolism

There are multiple distinguishing features that allow for the differentiation between acute and chronic thrombi. One main distinguishing feature is the morphology of the clots.

Eccentric filling defects or the formation of cords or webs in the vessel lumen are characteristic of chronic thromboembolism and reflect partial recanalization of a vessel following thrombosis. Acute thrombi have a distinct

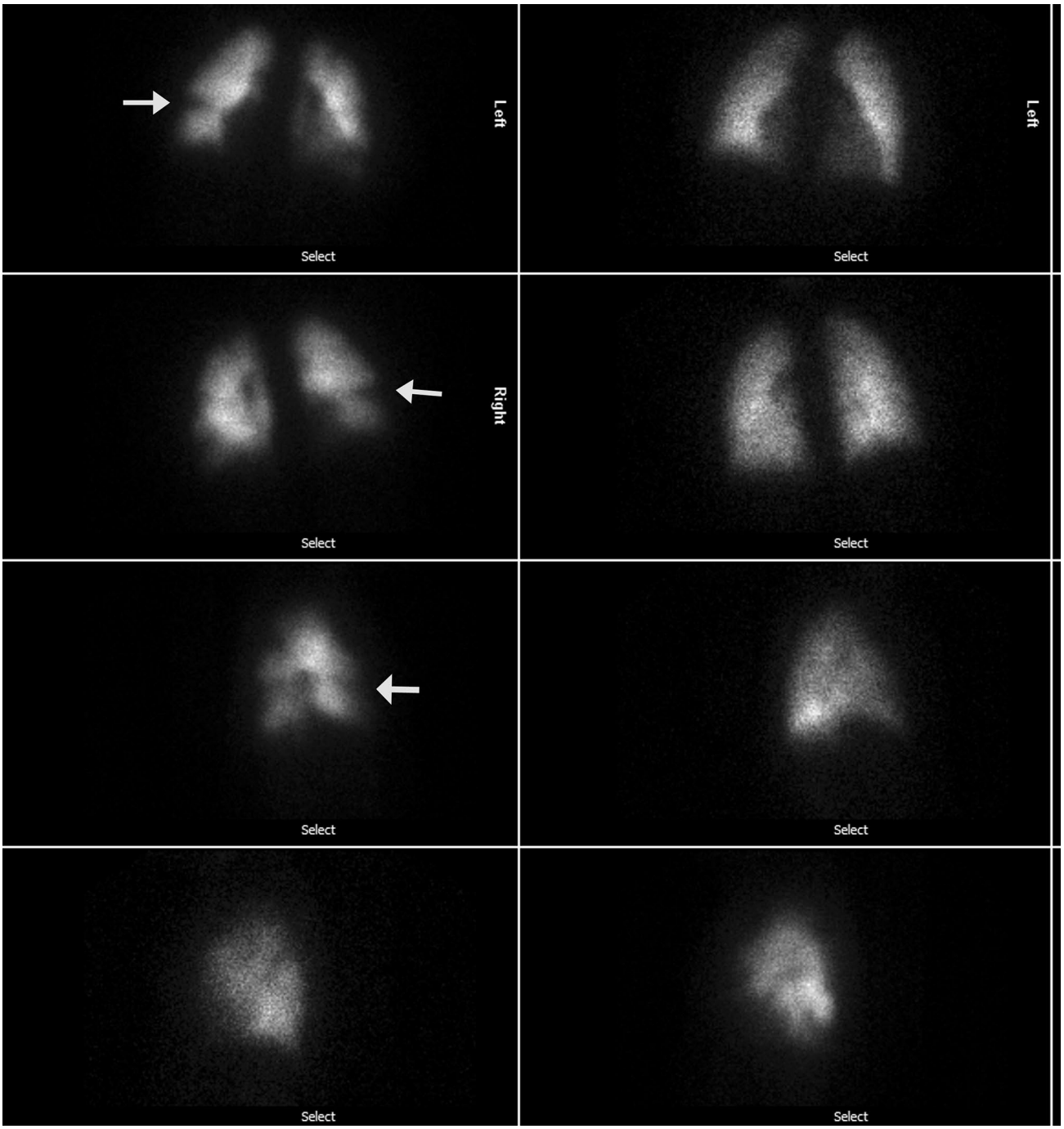

Fig. 1 32-year-old woman with known CTEPH. V/Q scintigraphy with ventilation images on the right and perfusion images on the left demonstrate persistent defects bilaterally, most notable in the right lower lobe (arrows) which are mismatched on the ventilation scan

imaging appearance and are generally more central in location, occurring at branch points with distal vascular extension [27] (Fig. 2). If the acute clots are eccentric in location, they will form an acute angle with the vessel wall, as opposed to an obtuse angle in chronic PE [28]. Another clue to help differentiate between the acute and chronic thrombi is the caliber of the affected vascular segment. In acute thromboembolism there is classically expansion of the vessel around the clot, whereas in CTED retraction or atrophy of the surrounding vessel is often seen, particularly in persistent total occlusion [2]. Focally stenotic or occluded segments may have adjacent segments of post-stenotic dilatation, while chronic complete vascular occlusion may have a convex-shaped distal vessel cut-off,

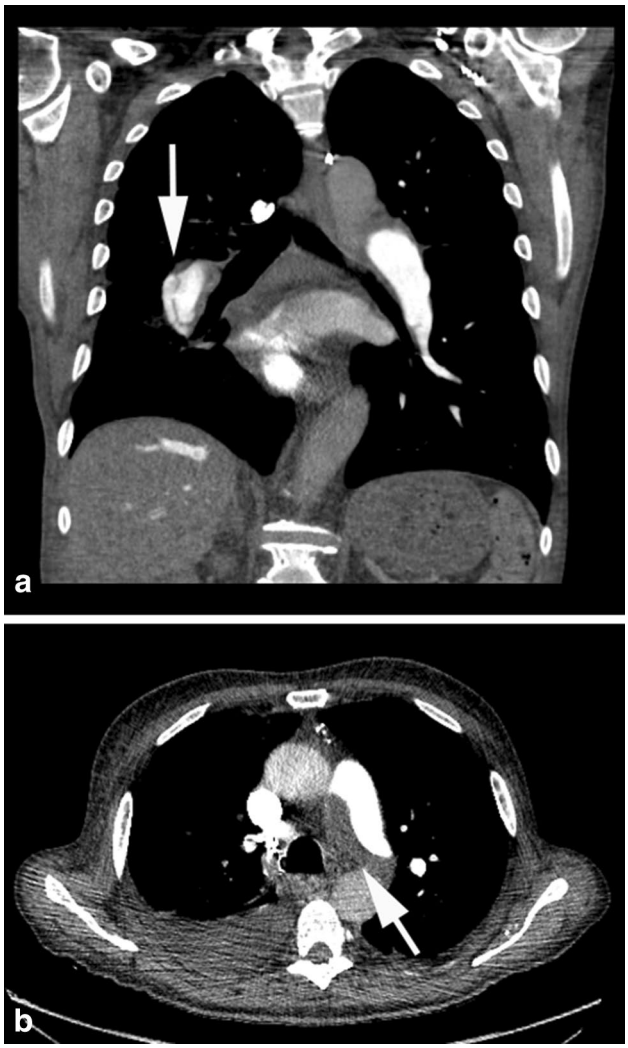

Fig. 2 63-year-old man with CTEPH. **a** Coronal chest computed tomography (CT) demonstrates a web in the right interlobar pulmonary artery (arrow), **b** axial chest CT demonstrates eccentric thrombus in the left main pulmonary artery (arrow)

previously described as a "pouch sign" on conventional pulmonary angiography [29].

Healed Lung Infarctions

While lung infarctions may have a nonspecific appearance, classic features include peripheral/pleural-based, wedge-shaped opacities which may be groundglass or consolidative and demonstrate diminished enhancement. Internal bubbly lucencies representing small foci of preserved lung, a truncated apex, and a thickened vessel leading to the apex of the infarct may also be seen [30]. Over time, the affected regions of lung retract, leaving scars or bands. Pleural thickening or trace fluid can also be present [31] (Fig. 3).

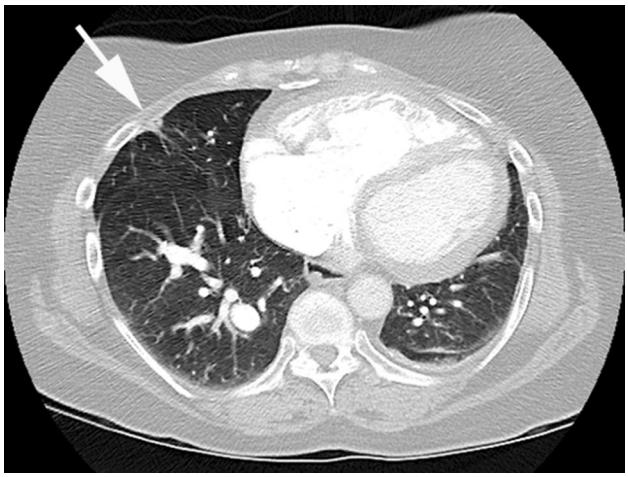

Fig. 3 62-year-old woman with a history of pulmonary embolism. Axial CT of the chest demonstrates a healed infarct in the right middle lobe (arrow)

Cylindrical Bronchiectasis

Cylindrical bronchiectasis can be seen in CTED typically affecting segmental and subsegmental bronchi adjacent to severely stenosed or thrombosed pulmonary arteries [32].

Calcified Thrombi

In a minority of patients, calcifications can be seen within chronic thrombi. Within subsegmental vessels these may appear like calcified pulmonary nodules, on axial images, however, a tubular conformation of the calcified cast can be a helpful distinguishing characteristic [33] (Fig. 4a).

Dual-Energy Computed Tomography Angiography

DECT imaging is a development founded on the principle that the attenuation of iodine can be captured at two different photon energies, one low (70–100 kV) and one high (140–150 kV) nearly simultaneously without additional radiation or iodine contrast. This dual energy capture permits creation of perfused blood volume (PBV) maps. The PBV maps provide qualitative and quantitative information on pulmonary hemodynamics, which in conjunction with the acquisition of traditional cross-sectional images, allows for both morphologic and functional pulmonary assessment. PBV maps allows for evaluation of perfusion defects (Fig. 5), which may provide a diagnosis of CTEPH even absent characteristic intravascular findings due to peripheral emboli below the resolution of CT [34, 35]. An additional advantage of DECT is the possibility of virtual nonenhanced imaging, in which the iodine can be digitally subtracted from the contrast-weighted images to reveal calcifications within

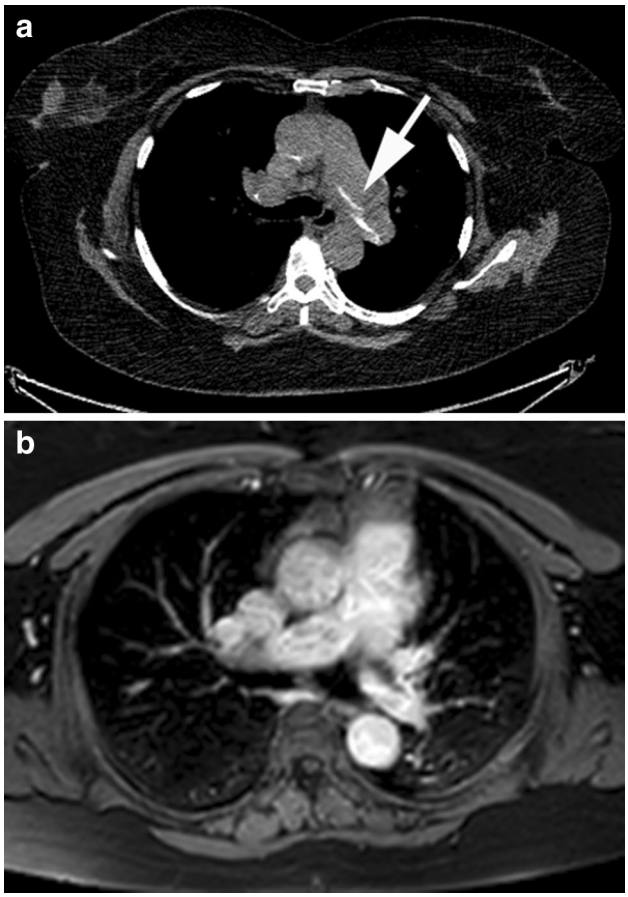

Fig. 4 68-year-old man with chronic pulmonary embolism. **a** Axial CT of the chest demonstrates chronic calcified thrombi in the left and right main pulmonary arteries (arrow). **b** Axial post contrast MR image demonstrating left main pulmonary artery eccentric thrombus

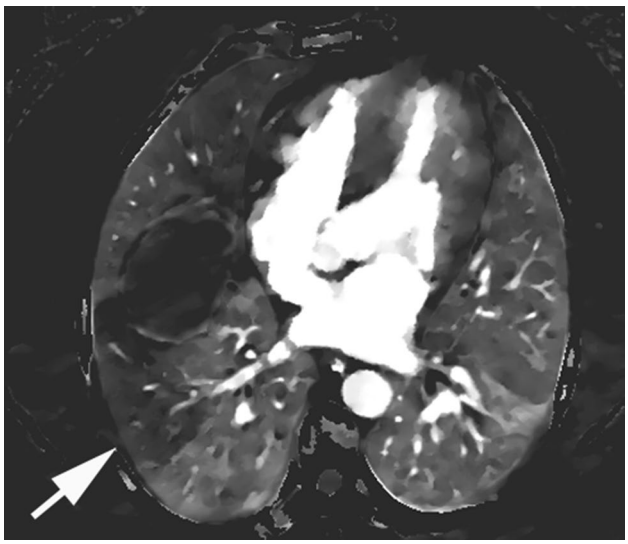

Fig. 5 32-year-old man with chronic pulmonary embolism. Pulmonary blood volume (PBV) map from a DECT of the chest demonstrates a wedge-shaped perfusion defect in the right lower lobe

chronic thrombi—a rare but characteristic finding in CTEPH [36].

Recent small and moderate sized studies have shown excellent diagnostic accuracy of DECT with sensitivity and specificities similar to that of V/Q scintigraphy. Masy et al. [37] compared DECT to V/Q, with V/Q as the reference standard, in a group of 80 patients and found excellent agreement between DECT (sensitivity 0.97, specificity 0.86) and V/Q scintigraphy (sensitivity 0.97, specificity 1). Other studies have examined the role of DECT in assessing clinical severity of CTEPH. Takagi et al. [38] analyzed 46 patients who underwent both DECT and right heart catheterization. They found a significant correlation between the lung PBV score and both mean pulmonary artery pressure (mPAP) and pulmonary vascular resistance. False negatives can occur in the setting of non-occlusive thrombi in which pulmonary perfusion of affected segments may be preserved, however, remodeling of the pulmonary vascular bed may still occur. This limitation is most pronounced in the setting of peripheral subsegmental PE which is more difficult to detect on conventional CTPA [39]. In addition, artifacts (e.g., motion, beam-hardening) can cause pseudo-defects which may be mistaken for a perfusion defect.

CTEPH

The role of CT in the setting of suspected CTEPH is multifactorial and includes the demonstration of pulmonary hypertension severity and features to help differentiate CTED while ruling out other causes, such as parenchymal lung disease. A specific diagnosis of CTEPH rather than the more common CTED can be made in the presence of multiple imaging features suggestive of new concomitant PH.

Suspected Pulmonary Hypertension

Patients with PH present with nonspecific symptoms, including fatigue, dyspnea on exertion, angina, or syncope. These initial complaints often prompt screening tests, including chest radiography and transthoracic echocardiography (TTE).

Chest Radiograph

Chest radiography is often normal early in the disease course of PH of any etiology, with characteristic findings often presenting over time as the disease progresses. Right heart enlargement may be seen by closely evaluating the cardiac borders: Right atrial enlargement causes prominence of the right heart border on the frontal radiograph, while filling of the retrosternal space on the lateral view is evidence of right ventriculomegaly. Additionally, enlargement of the main and

right and left pulmonary arteries may be seen in PH with pruning of the peripheral vessels reflecting peripheral vascular remodeling [40, 41]. Unique radiographic findings in CTEPH are limited, however, peripheral linear or wedge-shaped opacities may be seen due to chronic pulmonary infarction.

Transthoracic Echocardiography

Doppler echocardiography is considered to be the best screening test for pulmonary hypertension, which allows for calculation of systolic pulmonary artery pressure (sPAP) and ventricular pressures using the modified Bernoulli equation. TTE can also help exclude other causes of PH, including left heart dysfunction and intracardiac shunts [42].

Right Heart Catheterization

Right heart catheterization (RHC) remains the gold standard for diagnosis of PH and is required following a suggestive TTE. RHC allows for the direct measurement of pulmonary artery and capillary pressures, pulmonary resistance and cardiac output, and may help predict response to vasodilators [43]. Once a diagnosis of pulmonary hypertension has been made, additional imaging is often obtained to evaluate for an underlying causes and sequelae of PH.

Computed Tomography

Mosaic Attenuation Mosaic attenuation is a term used to describe geographic areas of lung heterogenous attenuation. It is a nonspecific finding that may be seen in small airways disease, small vessel disease and multiple parenchymal diseases [44]. Mosaic attenuation is a common finding in CTEPH, with the lucent segments reflecting hypoperfused lung and the more normal attenuation segments reflecting normal perfusion [45]. The mosaic-affected segments have been postulated to reflect extensive distal disease which suggests worse prognosis for surgical therapy [46] (Fig. 6) Additional perfusion from collateral vessels to the effected lung may contribute to focal areas of hyperattenuation. Differentiation mosaic attenuation due to CTEPH versus small airways disease can difficult and expiratory images can be helpful to identify air trapping, suggesting small airways etiology.

Enlarged Bronchial Arteries In situations of pulmonary artery circulation compromise, the bronchial arteries and their anastomotic communications to the pulmonary arteries may dilate to compensate for the pulmonary ischemia [47]. This finding is relatively specific to CTED, and in the presence of PH, highly suggestive of CTEPH; 73–100% of CTEPH patients' CTs show dilated bronchial arteries

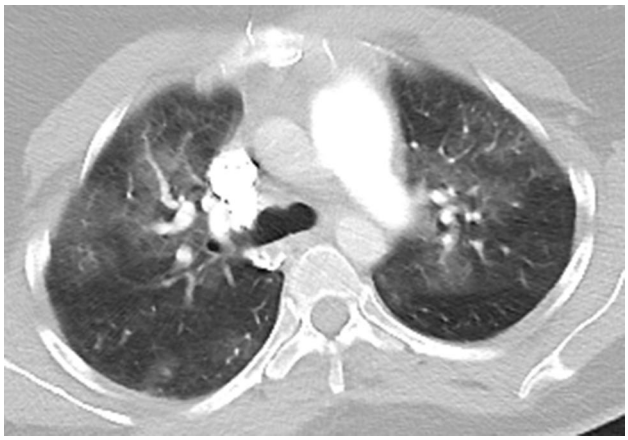

Fig. 6 32-year-old woman with CTEPH. Axial chest CT demonstrates mosaic attenuation of the lungs

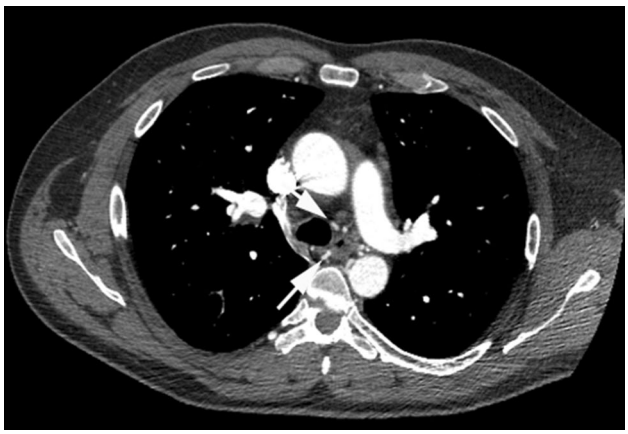

Fig. 7 43-year-old man with chronic pulmonary embolism. Axial chest CT demonstrates dilated bronchial artery collaterals (arrows)

[48, 49] (Fig. 7). Some studies have shown the presence of the bronchial artery collaterals in CTEPH to be associated with greater post-operative success [50].

Pulmonary Artery A dilated main PA can be a sign of elevated pulmonary artery pressure. The best location to evaluate for PA dilatation is just proximal to the bifurcation, perpendicular to the long axis of the vessel. Direct measurement of the PA and calculation the ratio of PA/aorta diameter are established methods. While cutoff thresholds, such as 30 mm for the PA and > 1 for PA/Aorta ratio have been identified, they are not broadly validated for various populations and should be considered within the overall clinical picture [51, 52]. (Fig. 8) Peripheral calcification within the pulmonary arteries is a specific, but insensitive sign of late-stage and severe PH (Fig. 4a) [3].

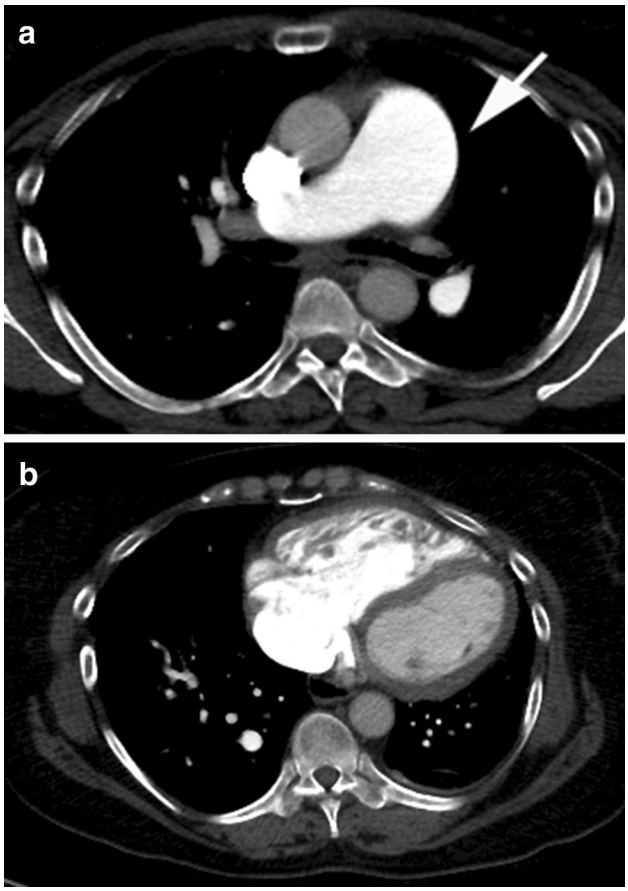

Fig. 8 62-year-old woman with CTPEH. **a** Axial chest CT demonstrates a dilated main pulmonary artery (arrow) which is suggestive of pulmonary hypertension. **b** Axial chest CT demonstrates right ventricular dilation and hypertrophy

Right Ventricular Size and Septal Configuration The right ventricle (RV) is normally smaller than the left ventricle (LV) with a thinner free wall. With longstanding elevated pulmonary artery pressures, however, the RV may progressively hypertrophy with eventual dilatation and failure if the underlying cause is not corrected [1]. A normal thickness of the RV free wall is < 4 mm and is considered to be abnormal when ≥ 6 mm. RV dilation is a sign of late-stage disease, with RV/LV diameter > 1:1 considered to be highly suggestive of pathology [53]. Straightening of the interventricular septum is a nonspecific sign of RV pressure or volume overload; however, leftward deviation of the septum is typical when mPAP ≥ 30 mmHg [54] (Fig. 8b).

Pericardial Effusion Pericardial effusions are a nonspecific finding that can be seen in PH of any etiology and is associated with a worse prognosis [55].

Centrilobular Nodules Centrilobular nodules may be seen in PH of any cause and are thought to represent recurrent pulmonary hemorrhage with subsequent macrophage ingestion of red blood cells and eventual formation of cholesterol granulomas [10].

Magnetic Resonance Imaging

MRI is gaining prominence as a modality in the evaluation of CTEPH. In addition to providing highly accurate assessment of RV morphology and function, MR allows for the evaluation of right and left atrial size, myocardial scarring, regurgitant jet velocity/volume, pulmonary venous and arterial anatomy [56]. In the setting of CTEPH, contrast-enhanced MR angiography has a high degree of accuracy in the detection of central chronic thromboemboli, including eccentric filling defects and webs/bands. In a retrospective study of 53 CTEPH patients using CTPA as a gold standard, Rajaram et al. found 98% sensitivity and 94% specificity of contrast-enhanced MRA in the detection of proximal and distal thromboemboli (Fig. 4b). The sensitivity for central vessel disease improved with the addition of proton density non-contrast MRI, and perfusion MRA showed an overall sensitivity of 92% for the diagnosis of CTED [57]. Exploratory research shows MRI evaluation of pulmonary perfusion can be performed with or without contrast, with non-contrast MRI ventilation-perfusion assessment using a Fourier decomposition. This newer method of functional assessment include longer acquisition times, low resolution, and low signal-to-noise-ratio (SNR) [58]. A recent study by Bondesson et al. [59] demonstrated improvement in SNR when a nonuniform FD was using in 11 patients and four healthy volunteers. Currently MRI is a tertiary or quaternary imaging modality in of CTEPH, but advances may lead to a larger role in the future.

Imaging Mimics

In the discussion of imaging features of any disease entity, it is important to be aware of potential mimics.

Acute Thromboembolism As discussed in the CTPA section, there are a number of imaging features that can be used to distinguish acute from chronic PE, however, there are cases where it is difficult to parse out PE chronicity.

Idiopathic Pulmonary Arterial Hypertension The characteristic filling defects of CTED may not be detectible when the disease is exclusively in distal vessels and, while secondary signs are helpful, they may be subtle or absent completely on CT. Perfusions defects, however, will be evident on V/Q scans.

Primary Sarcoma of the PA Primary PA sarcoma, a rare tumor of a cardiovascular system, presents as an intralumi-

nal filling defect on cross-sectional imaging, and can have bands and webs features suggestive of CTED. However, enhancement of the tumor is a key differentiating feature [60].

Tumor Emboli In patients with other malignancies, particularly breast, liver, renal, and gastric carcinomas, [61] tumor cells can embolize from the IVC to the central or peripheral pulmonary vasculature and cause enhancing intraluminal filling defects and perfusion defects evident on V/Q, when emboli are small and peripheral (Fig. 9).

Takayasu Arteritis/Pulmonary Vasculitis An idiopathic inflammatory large vessel arteritis, Takayasu arteritis has been classically described in young women. On CT and MR concentric mural thickening of the aorta, with wall enhancement in the acute phase is typical. Pulmonary artery involvement occurs in 50–80% [62]. Pulmonary artery findings include wall thickening, stenosis, occlusion, in situ thrombosis, and aneurysm [63] (Fig. 10). Fibrous occlusion of the central pulmonary arteries has been described in Behçet's disease, which can be mistaken for CTEPH [64].

In Situ Pulmonary Artery Thrombosis Inflammation and injury to the pulmonary artery vessel wall can occur in a number of conditions and may easily be confused with the more CTED. In situ thrombosis may occur in Eisenmenger syndrome [26], sickle cell disease, angio-invasive pulmonary aspergillosis, and trauma/surgery [65].

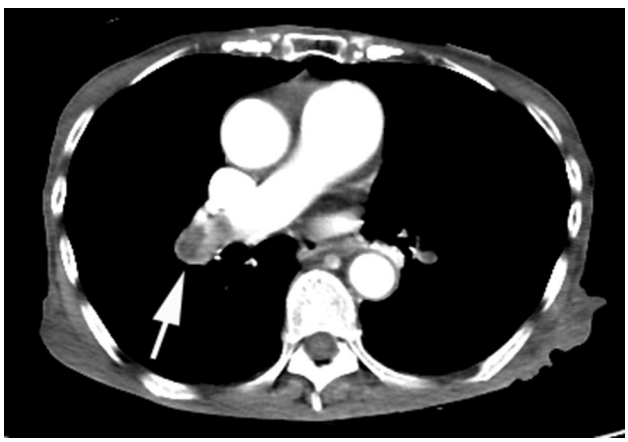

Fig. 9 80-year-old woman with abdominal cancer. Axial CT chest demonstrates enhancing filling defects in the right pulmonary artery (arrow), consistent with tumor emboli

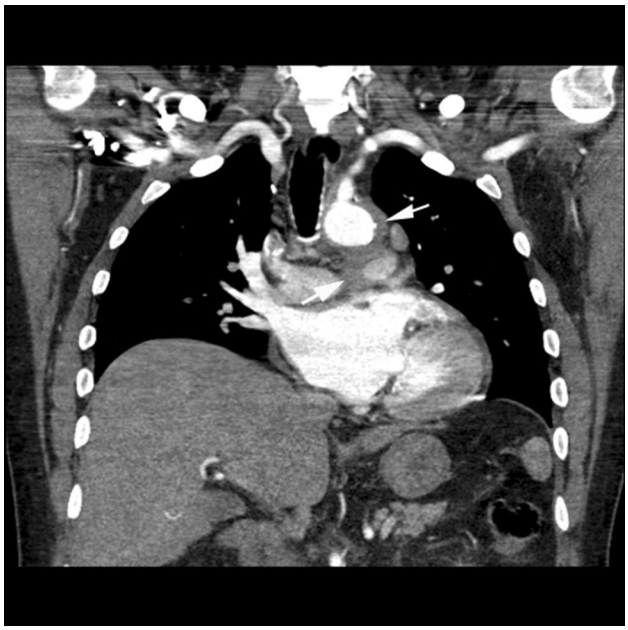

Fig. 10 60-year-old woman with Takayasu arteritis. Coronal chest CT demonstrates mural thickening involving the aorta (arrow) and pulmonary artery (arrow)

Therapy

Pulmonary Endarterectomy

The gold standard therapy of CTEPH is pulmonary endarterectomy (PEA) which offers the best opportunity for prognostic and symptomatic improvement. While the most effective treatment, only approximately 60% of patients are operative candidates [66]. Factors for determining operability include accessibility of the thrombi, severity of hemodynamic and ventilatory impairment, and comorbidities [67]. In addition, a large proportion of patients who undergo PEA experience residual or recurrent PH, found in up to 25% of patients in a recent meta-analysis by Hsieh et al. [68].

Balloon Pulmonary Angioplasty

Percutaneous balloon pulmonary angioplasty (BPA) is an emerging option for treating inoperable or recurrent CTEPH. This intravascular treatment uses small caliber balloon catheters (1.5–10 mm) in repeated sessions to dilate target lesions and achieve an appreciable reduction in mPAP [50]. Not all lesions are amenable to angioplasty. Kawakami et al. [69] reviewed 500 consecutive procedures in 97 patients and found that 'ring-like' and 'web' lesions had a higher success rate in angioplasty with fewer complications, with 'total occlusion' lesions demonstrating the lowest success rate.

Medical Therapy

All patients with CTEPH are indicated to receive lifelong oral anticoagulation. The first line therapy remains vitamin K antagonists with maintenance of an INR between two and three [70]. The newer direct oral anticoagulants remain a second line therapy secondary to limited evidence, with active ongoing research. Newer medical therapies, most notably Riociguat, has been shown to improve patient's functional status as an isolated therapy or in conjunction with BPA [71–73].

Conclusion

Chronic thromboembolic disease is common after acute PE and represents a heterogenous process ranging from asymptomatic imaging sequela to persistent symptoms signaling an increased risk of recurrent PE. CTEPH, a rare disease, develops in a small fraction of patients with prior PE. In CTEPH, imaging provides not only diagnostic information, but is also crucial in guiding therapy, including appropriate referral for pulmonary endarterectomy, the only established cure for PH. Knowledge of the range of imaging findings and distinguishing chronic PE from mimics is diagnostically crucial.

Compliance with Ethical Standards

Conflict of interest The authors declare that they have no conflict of interest.

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