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Imaging in chronic thromboembolic pulmonary disease: Current practice and advances

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ABSTRACT

Chronic thromboembolic pulmonary disease (CTEPD) with or without pulmonary hypertension (PH) occurs when thromboemboli in pulmonary arteries fail to resolve completely. Pulmonary artery obstructions due to chronic thrombi and secondary microvasculopathy can increase pulmonary arterial pressure and resistance leading to chronic thromboembolic PH (CTEPH). Mechanical interventions and/or PH medications can improve cardiopulmonary haemodynamic, alleviate symptoms, and decrease mortality risk. Imaging is pivotal throughout the CTEPD management journey, spanning diagnosis, treatment planning, and assessing treatment outcome. With just computed tomography (CT) pulmonary angiogram and right heart catheterisation, an experienced multidisciplinary team can determine surgical candidacy in most cases. Dual energy CT, lung subtraction iodine mapping CT, and dynamic contrast-enhanced magnetic resonance imaging (MRI) offer comparable sensitivities with ventilation-perfusion scintigraphy in diagnosing CTEPD. Pulmonary angiogram with digital subtraction angiography although considered the gold standard for assessing thrombi extent and vasculature morphology is now mostly used to assess targets for balloon pulmonary angioplasty. Advancements in CT modalities and innovative MRI metrics offer better insight into CTEPD management but are limited by the availability of technology and expertise. Learning from current artificial intelligence application in medical imaging, there is promise in tapping the wealth of data provided by CTEPD imaging through automating cardiopulmonary and vascular morphology analysis.

1. Introduction

Chronic thromboembolic pulmonary disease (CTEPD) results from incomplete resolution of thromboemboli in the pulmonary arteries. Chronic thrombi leading to fibrotic obstructions and secondary microvasculopathy can cause an increase in pulmonary arterial pressure and resistance [1]. Pulmonary hypertension (PH) is currently defined as mean pulmonary arterial pressure (mPAP) of >20 mmHg and pulmonary vascular resistance (PVR) of >2 Wood units as rest [2]. When chronic thrombi and secondary microvasculopathy lead to PH this is termed as chronic thromboembolic pulmonary hypertension (CTEPH) [1]. If left untreated, CTEPH can lead to right heart failure and death [3]. Fortunately, the CTEPH multimodal treatment era has been a success story with pulmonary endarterectomy (PEA), balloon pulmonary angioplasty (BPA), and PH medical therapies improving pulmonary haemodynamic, patients' functional status and survival [4–6]. Mechanical interventions are also carefully considered with discussion on risk and benefit for selected CTEPD patients without PH to improve symptoms [2]. Imaging plays a vital role in all aspects of the CTEPD management pathway, from diagnosis and making treatment decisions, to assessing treatment outcome.

Patients usually enter the CTEPD diagnostic process with a combination of non-specific persistent cardiopulmonary symptoms post-acute pulmonary embolism (PE). Clinical suspicion with consideration of risk factors is essential as about 25 % of CTEPH diagnoses are not preceded with a clear history of acute PE [7,8]. Determining pulmonary perfusion defects with a perfusion imaging modality or direct visualization of chronic thrombi with computed tomography pulmonary angiogram (CTPA) is recommended as the initial step in radiographic diagnosis [2,9,10]. Echocardiogram is usually performed in most centres which may precede other imaging modalities to evaluate for features of PH. Patients

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Abbreviations

BPA	balloon pulmonary angioplasty
CT	computed tomography
CTEPD	chronic thromboembolic pulmonary disease
CTEPH	chronic thromboembolic pulmonary hypertension
DCE	dynamic contrast-enhanced
LSIM	lung subtraction iodine mapping
MDT	multidisciplinary team
MRI	magnetic resonance imaging
PA-DSA	selective pulmonary angiography with digital subtraction angiography
PEA	pulmonary endarterectomy
PH	pulmonary hypertension
V/Q	ventilation-perfusion

with a combination of persistent symptoms and evidence of perfusion defects or chronic thrombi on imaging will proceed to right heart catheterisation (RHC) for the gold-standard cardiopulmonary hemodynamic measurements. Further imaging assessment of vascular lesions to establish treatment approach is critical for patient selection for PEA and/or BPA. Patients with CTEPD without PH should have cardiopulmonary exercise testing which provides valuable insight to the underlying pathophysiology of dyspnoea and exercise intolerance to aid in the decision for mechanical intervention. After mechanical treatment, patients should have further imaging to reassess effects of the intervention [9]. Fig. 1 shows the diagnostic and management approach in CTEPD.

Delays in diagnosing CTEPD are common, contributed to by a knowledge gap of clinicians and the imaging community [8–11]. In this article, we review the role of imaging modalities to evaluate pulmonary vascular CTEPD features focusing on CT, ventilation-perfusion (V/Q) scintigraphy, selective pulmonary angiography with digital subtraction angiography (PA-DSA) and magnetic resonance imaging (MRI) in current practice. The strengths, challenges, and advances in these imaging modalities for: diagnosis, evaluation of treatment strategy and follow-up post intervention will be discussed. Additionally, we review the potential beneficial role of artificial intelligence (AI) to leverage the data provided by imaging in CTEPD.

2. CTEPD features

Features of chronic thrombi reflects the organization and partial recanalization of acute thrombus after at least 3 months of therapeutic anticoagulation [2,12]. Fig. 2 shows an illustration of intravascular features in CTEPD.

CTEPD characteristics on imaging can be classified into direct and indirect vascular features, parenchymal features, and cardiac features on summarized in Table 1 [9,10,12,13].

3. Computed tomography

3.1. Computed tomography pulmonary angiography

Multidetector CT are now widely available and allow quick high quality CTPA which provides excellent spatial and temporal resolution of the pulmonary vasculature and lung parenchyma [9]. The advantage of CTPA is the direct visualization of chronic thromboembolism providing a vascular blueprint of location and anatomic extent. CTPA offers excellent proximal chronic thromboembolism delineation to assess suitability and planning for PEA in pulmonary arteries with a diameter of 10–40 mm by an experienced CTEPH multidisciplinary team [2,8–10,14]. Therefore, equipped with only CTPA and RHC, diagnosis of CTEPD and decision for PEA can be made for patients with proximal distribution of the chronic clots.

3.1.1. CTEPD features on CTPA

Direct intravascular features seen includes laminated eccentric filling defects due to thrombus adherence to the vessel wall, webs/slits/bands in the pulmonary artery, chronic total occlusions (pouch or tapered lesions, and amputated vessels) and calcified thrombus (Fig. 2 and Table 1) [2,8–10,12–14]. These contrast with acute PE which are most frequently situated in the middle of the vessel, particularly at bifurcation points, with no evidence of vascular remodelling. When assessing CTPA in patients with acute PE, it is vital to look for signs of existing CTEPD in order to formulate management decisions [15,16]. Pulmonary arterial morphology including vessel tapering and post-stenotic dilatation can also be visualised in CTEPD.

Mosaic attenuation of the pulmonary parenchyma is commonly found in CTEPH. Heterogeneous lung parenchyma attenuation illustrates hypo-perfused lung due to vascular obstruction in areas of decreased attenuation and normal/increased perfusion in areas of normal/increased attenuation [13,17]. Reduced vascular calibre in the regions of hypoattenuation is a useful marker of vascular disease. In CTEPH this is due to the primary vascular occlusion and remodelling, but this can also occur in obstructive airway disease where the vascular remodelling is a secondary phenomenon. Assessment of the airways for thickening/dilation is thus important to help distinguish between these two entities.

Features of chronic thrombi and pulmonary artery morphology are similar in CTEPD without PH and in CTEPH. However, indirect vascular features including main pulmonary artery dilatation, tortuous vessels, and bronchial arteries dilatation point towards CTEPH [9,12,13,17]. Additionally, cardiac features of increased right to left ventricle ratio and tricuspid regurgitation with retrograde contrast in the inferior vena cava and the hepatic veins provide clues suggesting PH.

Sensitivity and specificity in detecting CTEPH depends on the location of chronic thromboembolism and varies between studies. In a meta-analysis the pooled sensitivity and specificity were 88 % and 90 % (total arteries), 95 % and 96 % (main and lobar arteries) and 88 % and 89 % (segmental arteries) respectively [18]. Fig. 3 show features of CTEPD and PH on CTPA.

3.1.2. Challenges with CTPA in CTEPD

CTPA interpretation to identify CTEPD features requires an experienced and trained radiologist to avoid falsely low sensitivity. In a study assessing the original reports of CTPA with visible features of CTEPH, only 26 % of the original radiology reports diagnosed CTEPH, with 63 % describing pulmonary arterial abnormalities in isolation with no mention of PH or CTEPH, 53 % reporting signs of PH, and 6 % documenting mosaic attenuation [11]. Multiple conditions mimic CTEPD imaged on CTPA including pulmonary vasculitis, fibrosing mediastinitis, pulmonary artery sarcoma and congenital pulmonary artery abnormalities, further highlighting the importance of an experienced CTEPH multidisciplinary team for decision-making [2,9,10].

Distal subsegmental pulmonary artery disease can be difficult to identify therefore potentially resulting in underestimation of CTEPD clot burden on CTPA alone [10]. In these cases, mosaic perfusion pattern provides a valuable clue indicating possible CTEPD. Current guidelines states that even a negative high quality CTPA does not exclude CTEPH during the diagnostic process as visualization of distal subsegmental pulmonary artery disease can be missed [2,9,10,14]. Therefore, perfusion imaging such as planar V/Q or V/Q single-photon emission computed tomography (SPECT) should be considered where there is a high pre-test probability (such as in the presence of PH or mosaic attenuation) despite a normal CTPA.

A relevant concern of CTPA is radiation during image acquisition and measures should be taken to minimise exposure. The European Association of Nuclear Medicine (EAMN) reported a higher effective radiation dose of CTPA (4–20 mSv) compared to V/Q scans (1.2–2 mSv) to

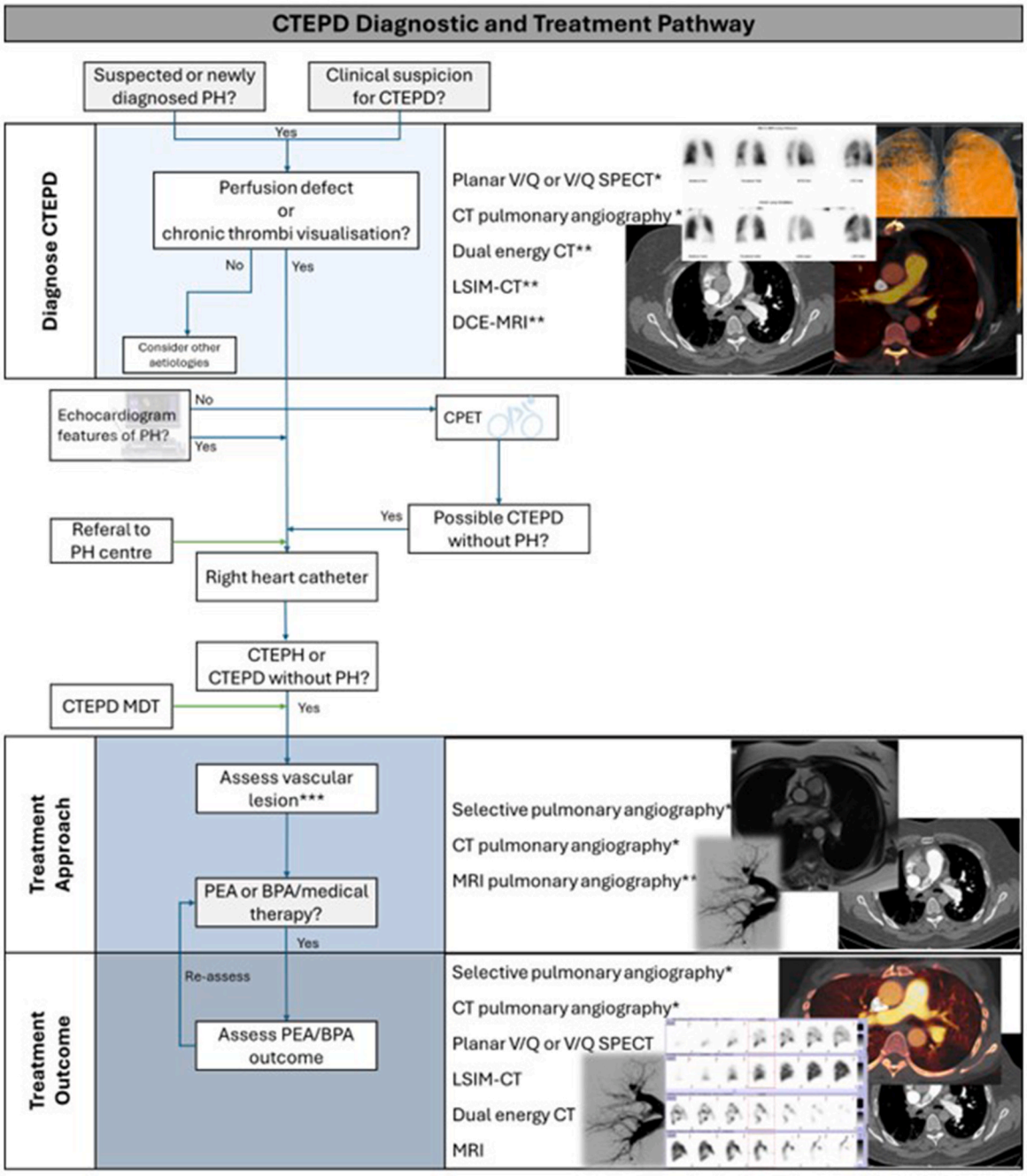

Fig. 1. Diagnostic and management approach in chronic thromboembolic pulmonary disease (CTEPD).
*Current practice.
**Can be considered as alternative according to local expertise/experience.
***In context with pulmonary hemodynamic measurements and symptoms.
BPA: balloon pulmonary angioplasty, CT: computed tomography, CPET: cardiopulmonary exercise test, DCE: dynamic contrast-enhanced, LSIM: lung subtraction iodine mapping, MDT: multidisciplinary team, MRI: magnetic resonance imaging, PEA: pulmonary endarterectomy, PH: pulmonary hypertension, V/Q: ventilation-perfusion

diagnose PE [19]. Use of modern CT using third-generation dual-source CT systems, high pitch acquisitions, low-kVp tailored to the patient, and iterative/machine learning based reconstruction can all aid in lowering radiation dose [20]. The use of iodinated contrast can be a limiting factor in patients with allergy, severe renal disease, or thyroid dysfunction. CTPA also requires intravenous access and precise timing of contrast administration to ensure peak pulmonary arterial contrast enhancement during imaging acquisition. Furthermore, to reduce motion artifact, coordinated breath holding (3–5 s) is required which can be challenging in some patients.

3.2. *Dual energy computed tomography (DECT)*

DECT is of great interest for a potential 'one-stop CTEPD imaging modality' for diagnosis and planning treatment approach. DECT brings together the advantages of CTPA and perfusion imaging in a single imaging modality by providing evaluations on parenchymal perfusion, acute vs chronic pulmonary thromboembolism, pulmonary vasculature

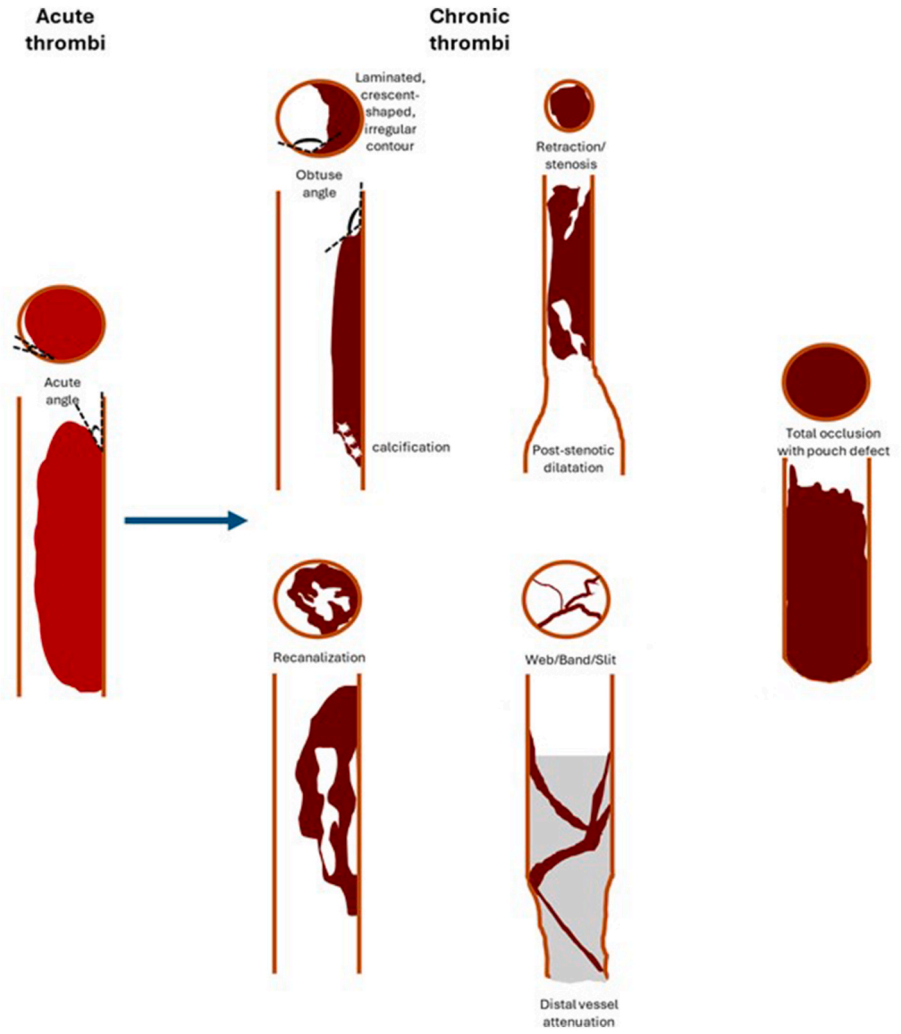

Fig. 2. Chronic thromboembolic pulmonary disease intravascular features.

Table 1
Vascular, parenchymal, and cardiac features seen on CTEPD imaging in current practice.

Direct vascular CTEPD features (CTPA, MRI, and PA-DSA)	Obtuse angles between thrombi and vessel wall Intimal irregularities Laminated thrombus Webs, bands, slits Thrombus calcification Pulmonary artery narrowing, attenuation and amputation Post-stenotic dilatation
Indirect vascular CTEPH features (CTPA, MRI, and PA-DSA)	Main pulmonary artery dilatation Tortuous pulmonary arteries Bronchial artery dilatation[a]
Parenchymal CTEPD features (CTPA, DECT, LSIM and V/Q scan)	Mosaic attenuations[b] Perfusion defect[c]
Cardiac CTEPH features (CTPA and MRI)	Dilated right heart chambers Increased right to left ventricle ratio Interventricular septal flattening Tricuspid regurgitation

CT: computed tomography, DECT: dual-energy CT, LSIM: lung subtraction iodine mapping, MRI: magnetic resonance imaging, PA-DSA: pulmonary angiogram with digital subtraction angiography, V/Q: ventilation-perfusion.

[a] Not on PA-DSA.

[b] CTPA.

[c] DECT, LSIM and V/Q scan.

morphology, and lung parenchyma changes [2,8,14]. Regional iodine distribution maps offer qualitative perfusion assessment which gives an advantage over CTPA where subtle webs and distal disease may be overlooked [9,10,12]. These show good agreement with perfusion maps from V/Q scans.

Suitability of DECT for surgical planning is shown by its high sensitivity (92–100 %) in predicting proximal disease (main and lobar pulmonary artery) which is comparable to post-PEA level of disease by the surgical Jamieson classification [21]. However, the extent of perfusion defects seen on DECT fails to be associated with the level of disease based on surgical classification.

3.2.1. *Challenges with DECT in CTEPD*

It Is important to note when interpreting DECT that unlike V/Q scan, iodine perfusion mapping can also show parenchymal perfusion through systemic collaterals shunts beyond the occluded pulmonary arteries depending on the acquisition phase [9]. Therefore, false negative results can ensue if perfusion mapping is performed with a high level of enhancement of the aorta when systemic collaterals will also be opacified.

The use of DECT in clinical practice is currently limited due to a combination of limited availability and expertise. It requires either dual source CT scanners, or third generation scanners with rapid kV switching capabilities, or spectral imaging. As a result, outside of specialised cardiothoracic centres, qualitative assessment of DECT perfusion mapping is less widely utilised [22]. There are similar limitations in DECT as

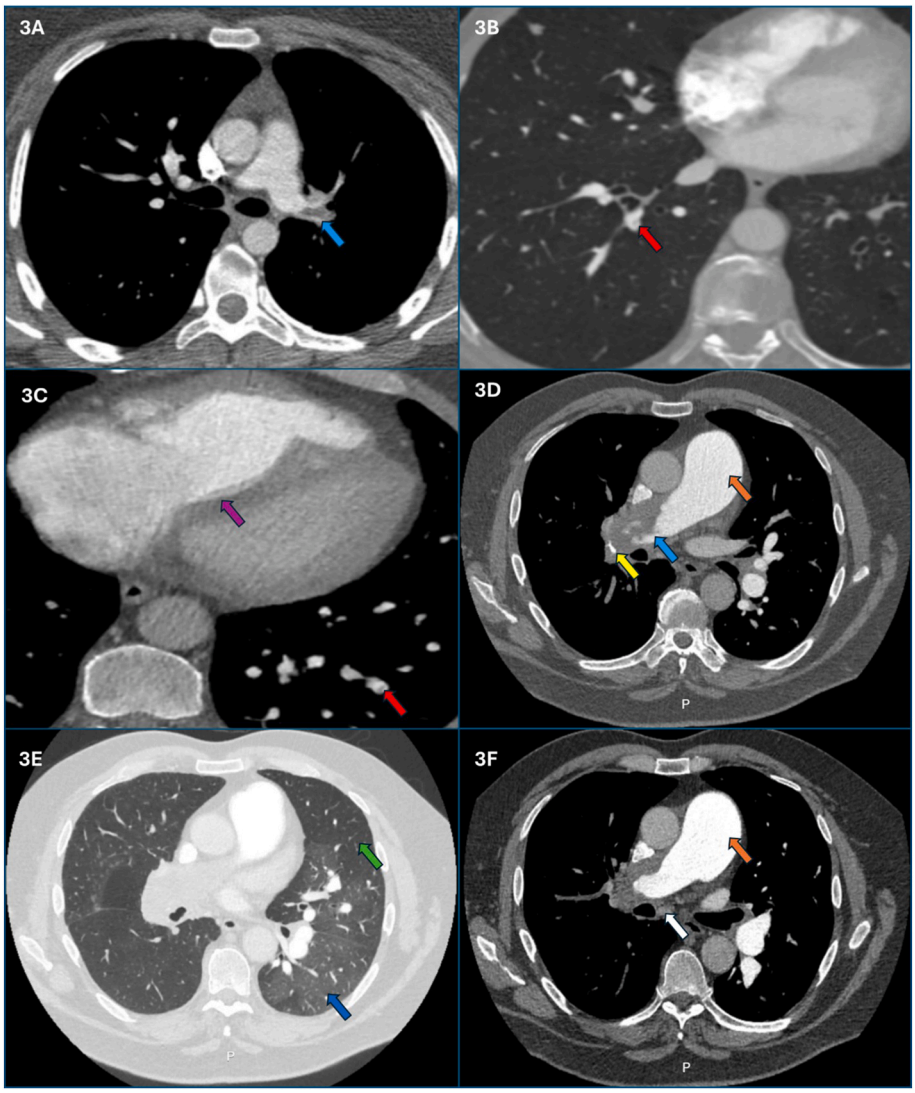

Fig. 3. Chronic thromboembolic pulmonary disease features on CTPA 3A: CTEPD without PH patient with extensive left main pulmonary artery chronic thrombi with intimal irregularity and obtuse angle (light blue arrow). Note the non-dilated main pulmonary artery. 3B: CTEPD without PH patient with pulmonary artery web/band (red arrow). Note the normal right to left ventricle ratio. 3C: CTEPH patient with dilated right heart chambers with flattening of the interventricular septum (purple arrow) and pulmonary artery web/band (red arrow). 3D: CTEPH patient with calcification (yellow arrow) in extensive occluding proximal chronic thrombi, irregular intimal contour with obtuse angle (light blue arrow) and dilated main pulmonary artery (orange arrow). 3E: CTEPH patient with mosaicism with areas of hypo-attenuation and vascular pruning in region of vascular obstruction (green arrow) and normal/hyper-attenuation in region without vascular obstruction (dark blue arrow). 3F: CTEPH patient with dilated bronchial artery (white arrow) and dilated main pulmonary artery (orange arrow). (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

encountered with CTPA including exposure to radiation, need for precise contrast administration timing, and patients' ability for breath-holding to reduce motion artifacts. While DECT results in a higher initial radiation dose, this can be offset by a reduced need for second line V/Q scans which incur a second dose of radiation.

3.3. Lung subtraction iodine mapping CT (LSIM-CT)

LSIM-CT can provide color-coded iodine distribution maps comparable to DECT [2]. LSIM-CT involves performing a non-contrast CT followed by CTPA resulting in higher contrast-to-noise ratio than DECT and improvement of image quality. As LSIM-CT is a post-processing technique, it is available on a wider range of scanners, potentially resulting in lower cost and ability to scale up availability/usage compared to the hardware required for DECT. As LSIM-CT involves two CT imaging, this result in higher radiation exposure than only performing CTPA and can result in misregistration of perfusion defects if different levels of breath hold occur between the two scans. Despite this, LSIM-CT is more accurate in diagnosing CTEPH than CTPA alone [23].

3.4. Follow up CT post mechanical intervention

Clearance of proximal chronic thrombi can be evaluated on CTPA after patients undergo PEA. Improvement of pulmonary perfusion can be evaluated on DECT and LSIM-CT after mechanical intervention but is utilised mostly post-PEA [9,22]. Iodine perfusion mapping on CT has also been shown to be useful in post-BPA assessment with high sensitivity and specificity (92 % and 99 %) comparable to PA-DSA [9,22,24]. Fig. 4 shows clearance of chronic thrombi and improvement of perfusion on CT.

3.5. CT scoring for CTEPD

The CT severity score and CT obstruction index to quantify degree of

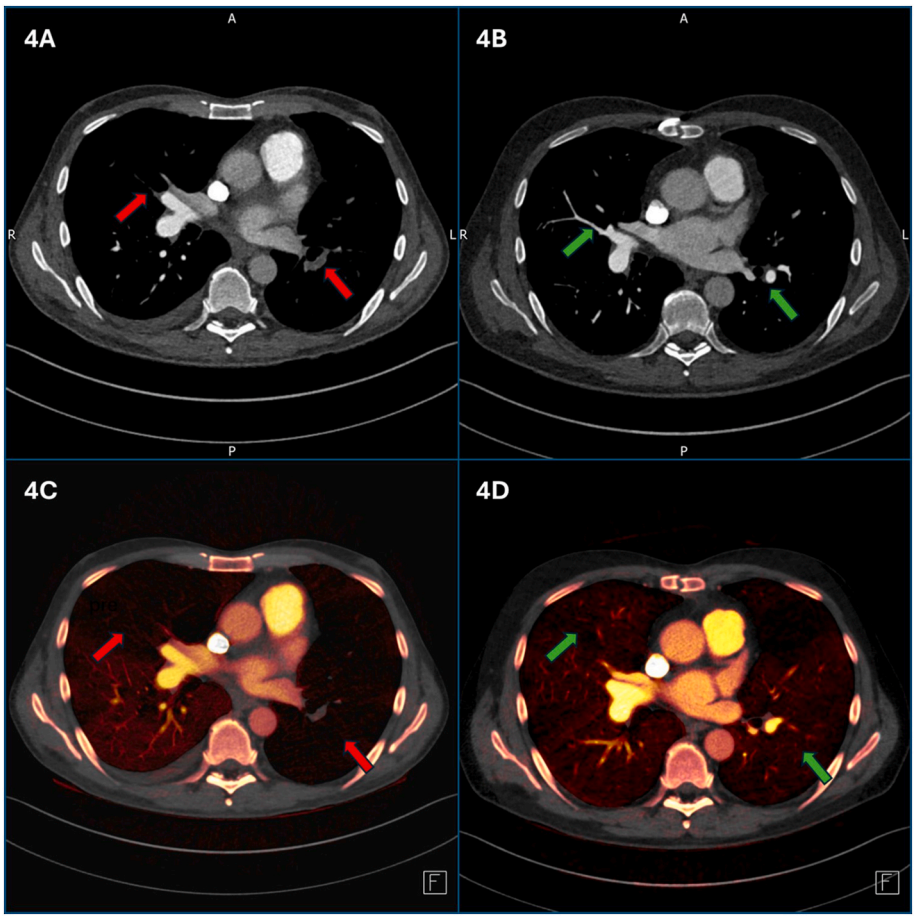

Fig. 4. CT pulmonary angiogram and dual energy CT pre and post pulmonary endarterectomy. 4A: CT pulmonary angiogram pre-PEA shows occluded pulmonary arteries (red arrows). 4B: CT pulmonary angiogram shows patent pulmonary arteries post-PEA which were previously occluded (green arrows). 4C: Dual energy CT pre-pea shows parenchymal perfusion defect in areas of occluded pulmonary arteries (red arrows). 4D: Dual energy CT shows improved parenchymal perfusion corresponding with patent pulmonary arteries post-pea (green arrows). (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

arterial obstruction on CTPA has been widely described in acute PE [25,26]. Use of these scores to quantify vascular obstruction in CTEPH have shown muted success [27,28]. Abozeed et al. attempted to qualitatively score the clot burden on CT and perfusion defect on CT iodine perfusion mapping in CTEPH. They showed the combined clot burden and perfusion defect score correlated with invasive hemodynamic measurements [29]. However, there are challenges in compiling the prediction of CTEPH severity and quantitatively describing chronic thrombi volume by location on CT for clinical application. This is contributed by poor interobserver agreement on level of disease at segmental and subsegmental level, and in the heterogenous CTEPH features seen on CTPA [30]. Furthermore, possible microvasculopathy in CTEPH is difficult to account for on CT.

4. Ventilation-perfusion scintigraphy

V/Q scintigraphy remains an integral imaging modality to rule out CTEPD in the early stages of the PH diagnostic algorithm [2,9,10]. The major limitation when V/Q scan suggests CTEPD is that further imaging in a different modality will eventually be required to assess extent of vascular lesions and pulmonary vascular anatomy to guide treatment approach [9,19].

4.1. CTEPD features on V/Q scintigraphy

CTEPD results in mismatched wedge-shaped perfusion defect where there is preserved ventilation but absent perfusion within a lung segment on V/Q scan. Most studies on sensitivity and specificity in diagnosing CTEPH had extrapolated criteria of positive V/Q scan from acute PE. Le Pennec et al. showed that the optimal threshold of 2.5 segmental mismatched perfusion defects on V/Q scans in CTEPH provided a sensitivity of 100 % and specificity of 94.7 % [31]. Fig. 5 shows mismatched perfusion defect on V/Q SPECT with low dose CT.

It is important to keep in mind that there is no correlation between the degree of perfusion defects on V/Q scan and hemodynamic severity of CTEPH [32]. Furthermore, perfusion defects seem to decrease in a longitudinal study in severe unoperated CTEPH despite worsening right ventricular function [33]. A holistic approach with good clinical judgement in the interpretation of V/Q scans is essential to ensure low rates of nondiagnostic reports in comparison to the use of probabilistic scores [19].

4.2. Challenges and strengths of V/Q scintigraphy

Planar V/Q scan which is 2-dimensional can underestimate mismatched perfusion defects with “shine-through masking” due to the superposition of abnormal areas of perfusion over regions with normal perfusion [8,19]. As a result, 3-dimensional multiplanar V/Q imaging with SPECT is now considered preferable as it can overcome some of the limitations with 2-dimensional planar V/Q scans [10,14]. V/Q SPECT initially showed better ability in detecting obstructed segments compared to now older 4 to 64-slice CTPA [34]. However, the overall

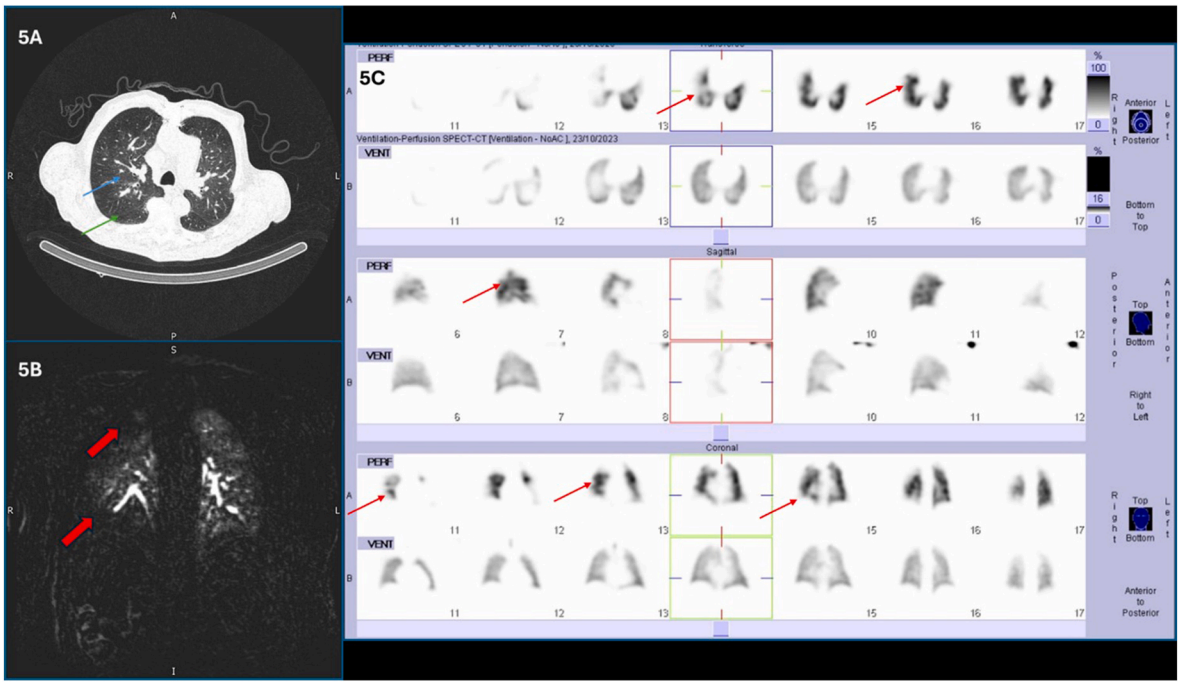

Fig. 5. Ventilation-perfusion single-photon emission computed tomography (SPECT) with low dose CT 5A: CT showing mosaicism with areas of hypo-attenuation and vascular pruning in region of vascular obstruction (green arrow) and normal/hyper-attenuation in region without vascular obstruction (blue arrow). 5B: V/Q SPECT showing perfusion defect (red arrows). 5C: V/Q SPECT showing mismatched perfusion defect (red arrows) with preserved ventilation. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

sensitivity and specificity of V/Q SPECT, planar V/Q and CTPA with second-generation dual-source CT scanner was later shown to be similar [35]. To provide better specificity in CTEPD diagnosis particularly in patients with other lung diseases, V/Q SPECT or perfusion only SPECT can be combined with low dose CT [19,36].

V/Q scan has the advantage of not requiring breath holding although limited movement during V/Q scan imaging acquisition is recommended [37]. Additionally, as contrast is not required, patients with severe renal impairment or contrast allergy can benefit from a V/Q scan as the initial imaging modality for diagnosis of CTEPD. Although radiopharmaceuticals half-life needs to be considered, precise administration timing is not necessary as in other imaging modalities.

4.3. Follow up V/Q scintigraphy post mechanical intervention

V/Q scan can assess improvement in perfusion defect post-PEA but is not as frequently used post-BPA [38]. Hyper-perfusion may be visualised on V/Q scan post-PEA in areas of reperfusion (hypo-perfused pre-PEA) and with relative photopenia in areas of previously normal perfusion pre-PEA. Perfusion post-PEA on V/Q scan will however tend to appear more homogeneous with time. As with utilizing V/Q scan for CTEPD diagnosis, imaging in another modality will ultimately be required if further mechanical intervention is deemed necessary.

5. Selective pulmonary angiography with digital subtraction angiography

PA-DSA was considered the reference standard in diagnosis and visualizing the pulmonary vasculature for surgical candidacy in CTEPD. However, PA-DSA is no longer routinely required in the assessment of CTEPD patients, particularly for PEA suitability, with the emergence of high-quality CTPA showing comparable or superior sensitivity and specificity [2,8,10,13]. PA-DSA is still required to determine suitability and viable targets for BPA. In practical terms, admission for RHC provides the perfect opportunity to perform PA-DSA concurrently using the same introducer sheath.

5.1. CTEPD features on PA-DSA

PA-DSA features of CTEPD reflect the remodelling and partial recanalization of chronic thrombi and its effect on pulmonary vascular morphology (Fig. 2 and Table 1). The suggested description of these features during PA-DSA are: ring-like stenosis (type A), bands or webs (type B), subtotal occlusion (type C), total occlusion (type D), and tortuous lesions (type E) [39]. As in CTPA, these features of chronic thrombi are similar in CTEPD without PH and in CTEPH.

PA-DSA features can also provide guidance in predicting outcome of mechanical intervention in CTEPH. Ring-like stenoses and web lesions result in higher success with lower complication rates, while total occlusions result in the lowest success rate, and tortuous lesions are associated with higher complication rates in BPA [39]. In addition, poor subpleural perfusion at $\leq$1.5 cm from the lateral pleura in all segments during the capillary phase of PA-DSA can predict distal pruning typical of microvasculopathy, resulting in worse PEA outcome with higher surgical mortality and postoperative PVR [40]. Similarly, in inoperable CTEPH, poor subpleural perfusion in the capillary phase of PA-DSA is a predictor of BPA failure with mean pulmonary arterial pressure (mPAP) $>$ 30 mmHg and a reduction in PVR of $<$30 % [41].

5.2. Challenges with PA-DSA in CTEPD

Limitations of PA-DSA includes involving an invasive procedure although considered safe even in severe CTEPH, possible contrast-induced nephrotoxicity in patients with severe renal insufficiency and motion artifact if patients are unable to efficiently breath-hold. Furthermore, there is higher radiation exposure compared to non-invasive radiological CTEPD imaging and is more resource intensive [22,42].

5.3. Follow up PA-DSA post mechanical intervention

PA-DSA concurrently with RHC remains the most frequently used imaging modality to assess potential targets for BPA [9,22]. As the number of BPA procedures can potentially continue provided there are accessible vascular lesions, the consensus-recommended hemodynamic goal is mPAP <30 mmHg [6]. PA-DSA additionally allows immediate visualization and improvement of regional pulmonary artery iodine concentrations pre- and post-BPA. Fig. 6 shows PA-DSA pre and post BPA.

6. Magnetic resonance imaging

The value of MRI is in evaluating right ventricular (RV) function and morphology, which is considered the reference standard cardiac imaging to assess PH severity of various aetiologies including CTEPH [8,9,13,14]. The diagnosis of CTEPD requires time-resolved dynamic contrast-enhanced MRI (DCE-MRI) to assess pulmonary parenchymal perfusion and MRI pulmonary angiography (MRPA) to evaluate the presence and distribution of perfusion defects and pulmonary vascular morphology.

6.1. CTEPD features on MRI

There has been varying reporting of DCE-MRI performance in identifying CTEPH, but larger studies determined good sensitivity. MRPA identifies the same features of chronic thrombi and pulmonary arterial morphology in CTEPD as in CTPA. MRPA can better recognise pulmonary artery stenosis, post-stenosis dilatation and complete obstruction compared to 64-slice CTPA [43]. In contrast, CTPA is superior to MRPA in identifying pulmonary wall adherent chronic thrombi and intra-luminal webs and bands. MRPA has also been found to be poorer in identifying subsegmental disease compared to CTPA and PA-DSA [44].

6.2. Challenges and strengths of MRI

The advantage of DCE-MRI/MRPA is its capability in assessing vascular abnormalities without subjecting patients to ionizing radiation or requiring the use of iodine-based contrast agents. However, DCE-MRI/MRPA is susceptible to motion and respiratory artifacts potentially compromising image fidelity. MRI also requires relatively longer acquisition durations. Patient related limitations include claustrophobia, ferromagnetic objects, and breath-holding. Additionally, use is currently limited due to requiring appropriate expertise and experience in the complex image acquisition, post-processing, and diagnostic interpretation [10,14]. Furthermore, DCE-MRI/MRPA for CTEPH is currently considered as not cost-effective [10].

7. Advances in CTEPD imaging

7.1. CT

7.1.1. Dual energy CT

Qualitative assessment of iodine distribution mapping defect on DECT to evaluate pulmonary perfused blood volume (PBV) shows correlation with invasive RHC measurements [45]. This can be further improved with automated quantification of PBV using DECT post-processing software to provide non-invasive insight to CTEPH severity [46,47]. However, lack of standardised protocols for consistent and reproducible PBV images acquisition and prospective validation limits its use to quantitatively describe CTEPH severity [14].

7.1.2. Cone-beam CT and C-arm CT

Advanced CT modalities/techniques allows higher spatial resolution and ability to better delineate distal CTEPH lesions [8–10,14]. Cone-beam CT (CBCT) and C-arm CT (CACT) are acquired with an angio-suite C-arm and catheter directed iodinated contrast into the main pulmonary artery [22]. CBCT provides better enhancement of the pulmonary arteries resulting in more web-like stenoses detection compared to 64-slice multidetector CTPA [48]. CBCT/CACT also provide enhanced information on vascular structure and subsegmental lesions compared to PA-DSA alone for BPA planning [22,49]. Additionally, CBCT/CACT can be used to mark BPA targets to provide a 3-dimensional vascular road map in combination with real-time fluoroscopy allowing better guidance of complex pulmonary vascular anatomy [50]. However, CBCT is invasive, susceptible to motion artifacts and does not provide high-quality imaging of lung parenchyma [22]. Furthermore, availability is a significant limiting factor.

7.1.3. ECG-gated CTPA

ECG-gated CTPA allows clearer vascular imaging with less pulsation artifacts and require less effective radiation dose [8,14]. ECG-gated 320-slice CTPA therefore can provide improved sensitivity and specificity, 97 % (main and lobar arteries) and 86 % and 95 % (segmental arteries), in diagnosing CTEPH [51].

7.2. MRI

Quantitative measurement of perfusion on DCE-MRI have shown promise and correlates with PBV on DECT [52]. Quantitative perfusion

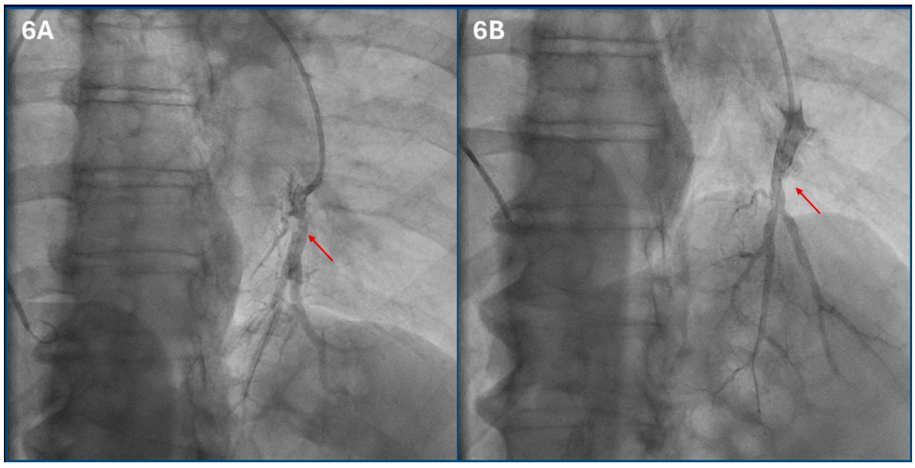

Fig. 6. Selective pulmonary angiography with digital subtraction angiography.
PA-DSA pre-BPA (6A) and reperfusion of pulmonary artery (red arrows) post-BPA (6B).

by evaluating pulmonary blood flow (PBF) on DCE-MRI illustrates regional improvement post-PEA in the lower lobes which correlates with 6-min walk distance [53]. Similarly, quantitative PBF on DCE-MRI demonstrates improvement post-BPA and correlates with NTproBNP and MRI-derived hemodynamic measurements [54]. However, MRI features as non-invasive alternative to RHC are still not sufficiently reliable for translation to clinical use due to small number of comparable studies, small cohorts, paucity of prospective studies, and delays between MRI and invasive RHC [8,10,14].

7.3. Cardiac imaging

Cardiac imaging with MRI can provide metrics on cardiac remodelling and reverse remodelling in CTEPD [8,9,14,53]. This is in addition to echocardiogram routinely used for screening of PH. However, it is out of the scope of this review.

8. Artificial intelligence in CTEPD imaging-current evidence and prospects

Applying AI in medical imaging entails leveraging machine learning (ML) algorithms and methodologies to analyse images for assisting in the interpretation, diagnosis, and treatment of diverse diseases and conditions. AI is already used widely in medical research especially in cancer imaging [55]. ML allowing less interobserver variation and efficient automatic segmentation has even seen some success in translation to clinical application [56]. These successes provide a stepping-stone and precedence that perhaps ML can be applied on medical imaging in CTEPD and PH in general.

ML can be used for automated segmentation of pulmonary vessels with differentiation of arteries and veins. It can also help in quantifying pulmonary vascular morphology on CTPA. Automated segmentation and assessment of pulmonary vessels on CTPA have shown that lower arterial and venous small vessel volume, higher large arterial volume and increased pulmonary artery tortuosity can be used to distinguish between pulmonary arterial hypertension (PAH) and patients without PH [57]. Similarly, small-vessel volume fraction, vascular density, artery to vein volume ratio of the larger vessels and pulmonary artery tortuosity can differentiate CTEPH from patients without PH [58]. Pienn et al. has also recently used ML on CTPA in a mixed PH cohort to demonstrate arteries over veins ratio with diameters between 6 and 10 mm correlated with PH prognostic markers [59]. Of particular interest is the capitalization of automated segmentation of pulmonary vessels by ML to demonstrate improvement of pulmonary arterial blood distribution in PAH patients treated with seralutinib (an inhaled platelet-derived growth factor receptor, colony stimulating factor 1 receptor and c-KIT inhibitor undergoing Phase 3 clinical trial) on CT [60]. Knowledge acquired through these ML-based automated segmentation and pulmonary vascular morphology assessment on CTPA, which were mostly in PAH cohorts, could potentially be transferred to CTEPD. However, this will require robust research methodology and prospective validation.

The automation of cardiac MRI measurements in PH patients has evolved significantly in recent years but have not been validated in CTEPH [61,62]. However, there is a significant gap in harnessing ML for automated assessment of DCE-MRI/MRPA which is of value in CTEPH diagnosis and decision-making.

Application of ML in CTEPD research has challenges including being a relatively rare disease resulting in small single centre cohorts, difficulty in assessing heterogeneity of vascular lesions, defining poor treatment outcome, and evaluating microvasculopathy. With current advances and acceptance of value in ML, this is the optimal time for further research on CTEPD imaging on large cohorts with prospective validation. Of particular interest is the ML-based CTPA features evaluation to non-invasively assess treatment outcome and residual PH. An automated mapping on location and volume of chronic thrombi can aid in treatment approach decisions. Additionally, analysing medical imaging data with the help of ML to better describe differences in pulmonary vascular morphology between various PH aetiologies are also intriguing.

9. Conclusion

Imaging in CTEPD is crucial for diagnosis, evaluating treatment approach and assessing treatment outcomes. Utilizing only CTPA and RHC, most patients can be accurately diagnosed with CTEPD/CTEPH, facilitating the decision-making process regarding PEA by an experienced multidisciplinary team. Efficiency and enhanced diagnostic precision can be attained by consolidating the spatial and temporal resolution from CTPA and perfusion imaging into a unified imaging modality by employing DECT or LSIM-CT. While the advantages of these imaging modalities have been acknowledged, their utilization is currently constrained by limited availability. V/Q scan remains a useful imaging modality in the early stages of the diagnostic algorithm for ruling out CTEPD in the presence of a normal or poor quality CTPA. However, alternatives including DECT, LSIM-CT, DCE-MRI offering similar sensitivities can be considered according to local experience and expertise. While PA-DSA performed concurrently with RHC may now be less essential for determining PEA candidacy, it remains critical and efficient in evaluating feasibility for BPA.

Advanced imaging modalities/techniques and innovative interpretation offers better insight into CTEPD management and has the potential to offer non-invasive holistic follow-up. However, utilization of these advances is limited due to perceived and genuine challenges including access, cost, lack of expertise and in some cases need for multicentre prospective trials. Leveraging AI/ML for automated segmentation and description of cardiopulmonary and vascular morphology have already shown potential to unlock the wealth of information provided by medical imaging. These automated quantification by harnessing ML models have the potential to revolutionize CTEPD diagnosis by reducing interobserver variation and streamline decision-making but requires robust prospective validation.

CRediT authorship contribution statement

Hakim Ghani: Writing – review & editing, Writing – original draft, Conceptualization. **Jonathan R. Weir-McCall:** Writing – review & editing. **Alessandro Ruggiero:** Writing – review & editing. **Joanna Pepke-Zaba:** Writing – review & editing, Supervision, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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