Chronic Thromboembolic disease

By Dr. Deepa Gopalan

Introduction:

Chronic thromboembolic disease (CTEPH) is a dual vascular disorder related to incomplete resolution of pulmonary embolism (PE) and is placed under Group 4 of the revised clinical classification of pulmonary hypertension (PH) [1]. The current definition of CTEPH is a mean pulmonary artery pressure of ≥25 mmHg, a pulmonary capillary wedge pressure of ≤15mmHg and the presence of organised thrombi in the pulmonary artery after at least 3 months of anticoagulant treatment [2]. Although PE and CTEPH are presented as a continuum, in about 25% of CTEPH cases, there is no prior history of symptomatic PE [3]. Hence, the true prevalence and incidence of CTEPH cannot be accurately predicted from acute PE follow-up studies. In addition, survivors of acute PE can develop post-PE syndrome characterised by chronic thrombotic remains in the pulmonary arteries, persistent right ventricular dysfunction, decreased quality of life and/or chronic functional limitations [4]. The definition of 'the post-PE syndrome' is evolving but CTEPH is thought to be its most extreme and uncommon manifestation whilst disturbances in pulmonary arterial flow and ventilation and impairment of cardiac function are relatively more frequent features. The cumulative CTEPH incidence varies between 0.1% and 9.1% [5]. The large margin of error is attributed to referral bias, non-specific clinical presentation, lack of uniformity in diagnostic algorithms between different institutions and the difficulty in differentiating acute PE from acute chronic thromboembolic disease.

Why is it important to diagnose CTEPH?

CTEPH is unique amongst other causes of PH as it is potentially possible to obtain a complete cure in selected patients with early intervention in the form of pulmonary endarterectomy. Conversely, if left untreated, it has a poor prognosis with 5-year survival rate of 10% in cases with mean pulmonary artery pressure (mPAP) of over 50 mmHg [6]. Data from cohort studies indicate that current practice patterns fail to achieve appropriate diagnosis at an opportune time. An International CTEPH Registry data has demonstrated a median time of 14 months between symptom onset and diagnosis in expert centers [7]. There are multifarious reasons for the referral delay including paucity of clinical symptoms in early stages with overt right heart failure developing only later in the disease course. Despite the availability of sophisticated imaging methodology, CTEPH can be under or mis-diagnosed due to the relative rarity of the disease and poor awareness among the imaging community contributing to lack of expertise in interpretation. Furthermore, economic constraints can restrict access to multimodality techniques.

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Pathophysiology of CTEPH:

Over the last few years, meaningful advances have been made in our understanding of the complex pathophysiology of CTEPH [8, 9]. Organisation of the persistent thrombotic material within the pulmonary arteries leads to fibrotic transformation and mechanical obstruction. These manifest as intravascular stenoses, webs, and occlusions, mainly in the large and medium-sized pulmonary arteries at the site of previous PE. This results in flow redistribution and progressive increase in pulmonary vascular resistance (PVR). Over time, there is secondary remodelling of the low resistance pulmonary microvasculature with the development of a peripheral arteriopathy similar to the small vessel disease of classic pulmonary arterial hypertension (PAH). Remodelling can be also be triggered by development of broncho-pulmonary collaterals forming anastomoses between the systemic vasculature and precapillary pulmonary arterioles well as pulmonary veins. The small vessel vaculopathy can result in discrepancies between the demonstrable macro-vascular disease on imaging and the pulmonary hemodynamics on right heart catheterisation.

Treatment of CTEPH:

The concept of multi therapeutic approach for CTEPH is constantly evolving. Pulmonary endarterectomy (PEA) remains the current Standard of Care and there have been tremendous improvements in existing surgical techniques with periprocedural mortality <2% to 5% in experienced centers [10]. Balloon pulmonary angioplasty (BPA) is emerging as an attractive alternative, with promising results, particularly for patients with inoperable disease. Riociguat, a new class of oral drug and stimulator of soluble guanylate cyclase, has been approved as the first medical treatment following successful demonstration of its efficacy in a multicenter randomised study of patients with non-operable CTEPH or persistent/recurrent PH after PEA [11]. Given the positive impact of these therapies, it is imperative to make the correct diagnosis of CTEPH so that appropriate treatment can be instituted.

Diagnosis of CTEPH:

Routine screening for CTEPH is not routinely advocated following acute PE but any patient with unexplained PH or persistent breathlessness following previous VTE should undergo evaluation for CTEPH.

Echocardiography is the initial test of choice in the diagnostic algorithm and is an indispensable screening tool for the assessment of PH. There are detailed guidelines describing the echocardiographic assessment of the right heart [12, 13]. Whilst it is non-invasive, does not involve radiation and is readily available, limitations of echocardiography include operator dependency

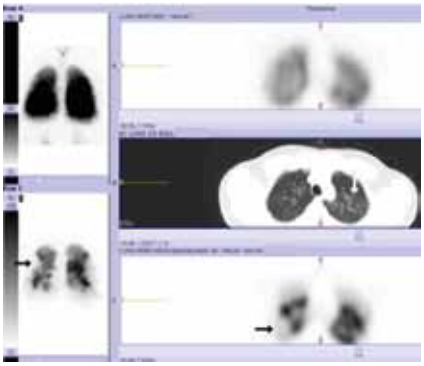

Fig 1. SPECT-VQ/CT in a 50 year old male with CTEPH. There are multiple segmental perfusion defects (black arrows) with normal ventilation. Mosaic attenuation (white arrow) is demonstrated on the low dose CT lung window reconstruction in the mid panel.

and poor acoustic window in patients with large body habitus or those with significant obstructive airways disease. In addition, in the early stages of the disease, echocardiography can miss PH in as many as 10–31% of cases [14]; doppler pressure estimates alone are not reliable to exclude PH. Also, some patients with chronic thromboembolic disease (CTED) may have normal resting pulmonary haemodynamics. This group may benefit from cardio-pulmonary exercise test (CPET), as it provides insight into the vascular reserve. In a retrospective study, CPET was able to detect chronic thromboembolic disease despite normal echocardiography [15]. CPET has the potential to differentiate thromboembolic disease from other causes of PH and although multicentre prospective validation is lacking, CPET is emerging as a promising complementary diagnostic tool for functional evaluation of pulmonary vascular disease.

VQ scintigraphy is the most sensitive test in the diagnostic algorithm for excluding CTEPH. Normal perfusion has a negative predictive value approaching 100% and hence VQ is an effective screening tool [16]. Although the most typical finding in CTEPH is the presence of segmental wedge shaped perfusion defects with corresponding normal ventilation, any mismatched perfusion defect is abnormal and requires downstream testing. Mismatched perfusion defects can be present in a variety of conditions such as large vessel vasculitis, pulmonary arterial malignancies such as sarcoma, fibrosing mediastinitis and extrinsic compression of the pulmonary artery. Perfusion abnormalities can also be seen in idiopathic pulmonary arterial hypertension (IPAH) as well as pulmonary venoocclusive disease (PVOD and capillary haemangiomatosis (PCH). These tend to be mostly heterogenous reduction of perfusion in a non-anatomical distribution but occasionally can also be segmental defects. Another important consideration is that injected technetium labelled macro-aggregatesd albumin particles can pass through partially recanalysed vessels in CTEPH resulting in potential underestimation of the disease severity [17].

Single Photon Emission Computed Tomography-Ventilation-Perfusion (SPECT-VQ) is a 3-dimensional technique with higher sensitivity than planar VQ in detection of CTEPH [18] The radiation profile of SPECT VQ is better than CT, particularly with reference to the female breast as it delivers only 4 % of the CT dose [19]. However, there is an emerging trend to actually add low-dose CT to SPECT-VQ [Fig 1] as this has been shown to improve the specificity of the technique by identifying concomitant parenchymal lung disease in patients with perfusion defects [20] It is possible to do perfusion quantitation with SPECT-VQ in CTEPH and this can provide a measure of disease severity as was shown in a recent publication [21] A case study from Japan has also shown the possibility of using SPECT/CT as an adjunct to balloon pulmonary angioplasty as the 3D fusion images can be rotated to different angles and the culprit lesion in the pulmonary artery causing the regional hypoperfusion can be easily identified on the image overlay [22]. Although these are single centre experiences, the utility of SPECT-VQ in CTEPH is beginning to be apparent.

The vascular abnormalities of CTEPH have been extensively described in the literature and can be delineated by a variety of techniques [Fig. 2a-e] Of these, **catheter pulmonary angiography** is deemed to be the historic gold-standard and has the best temporal resolution that allows for excellent anatomical characterisation of both proximal and distal pulmonary vasculature. In addition, important information can also be gained from the capillary phase of pulmonary angiography as reduced subpleural perfusion is associated with poor surgical outcome of CTEPH, with increased

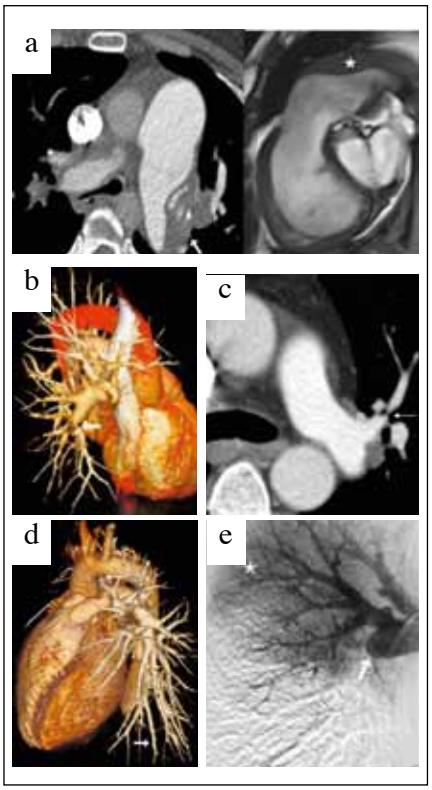

Fig. 2. CTEPH pulmonary vascular abnormalities on multi-modality techniques in different patients.
2a. Axial CT (left) with calcified eccentric thrombus (arrow) and sagittal MR SSFP sequence (right) with eccentric non-calcified thrombus (star)
2b. CT volume rendered technique (VRT) showing a significant lower lobe trifurcation web (arrow)
2c. Axial CT with tight stenosis followed by post-stenotic dilatation in the left upper lobe (arrow)
2d. Abrupt truncation of diseased upper lobe vasculature (thin arrow) compared to a more normal transition of vessel calibre in the lower lobe (block arrow)
2e. A large pouch defect in the right lower lobe (black arrow). Note the preserved perfusion (white star) in the upper lobe in comparison to the absent perfusion in the occluded middle and lower lobes.

mortality and higher postoperative PVR [23]. In spite of the sophisticated non-invasive alternative modalities, there is renewed interest in catheter angiography due to the advent of BPA for CTEPH patients who are not suitable for surgery. It is important to keep in mind that catheter angiography can be performed at the same sitting as right heart catheterisation which is an integral part of the CTEPH diagnostic algorithm, thereby saving the need for an additional puncture.

Computed Tomography pulmonary angiography (CTPA) is a widely available non-invasive technique that can provide exquisite images of the pulmonary

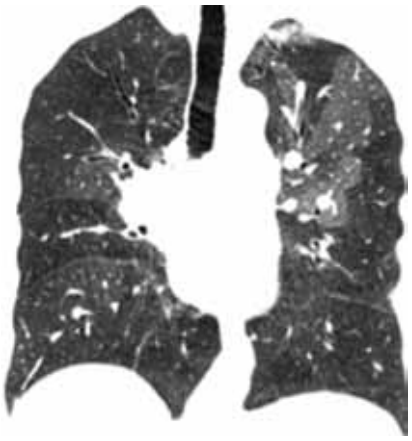

Fig 3. Coronal CT, lung window reconstruction in a 65 year old male with CTEPH. The black areas represent abnormal perfusion with reduced vessel count whilst the grey zones represent preserved perfusion.

circulation. Multidetector CT is now acknowledged to the reference standard for acute PE. However, while acknowledging the advantages, most existing guidelines and consensus documents are more guarded in their recommendation for its use in CTEPH. This is not only due to the difficulty in excluding distal disease where the morphological changes are difficult to visualise in the macro-circulation but also due to the variability in CT interpretation in non-CTEPH expert centres. However, in high-volume institutions, CT has been shown to outperform MR angiography and catheter angiography by having the best image quality and the highest level of sensitivities and specificities at the main/lobar and segmental levels [24]. CT has several advantages over other modalities. It can distinguish acute PE from CTEPH as they have very dissimilar appearances. This is of immense clinical importance as these conditions need different therapeutic options. It

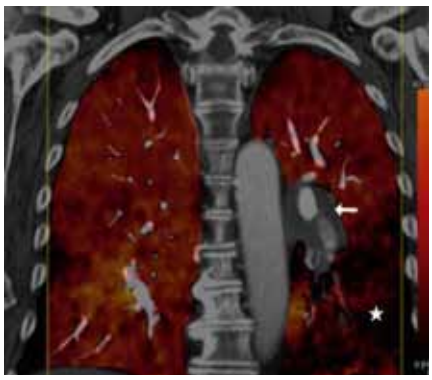

Fig 4. DECT, coronal windows in a 45 year old female with CTEPH. There is eccentric thrombus in the left pulmonary artery (block white arrow) with a corresponding large perfusion defect in the left lower lobe (white star)

has also been shown that a substantial number of patients diagnosed with acute PE might already have underlying chronic disease with previously unidentified PH [25]. This is particularly relevant in the clinical setting where patients present acutely and are being considered for thrombolysis. CT also has the potential to differentiate other conditions that mimic CTEPH such as Takayasu's vasculitis, pulmonary artery sarcoma conditions that cause extrinsic vascular compression like sarcoidosis, congenital abnormalities of the pulmonary artery and *in situ* thrombosis [26]. It is also possible to use CT for precise depiction of the bronchial and non-bronchial collateral vessels that develop during the course of CTEPH but this requires simultaneous opacification of the pulmonary and systemic circulations. CT is excellent for evaluating the underlying lung abnormalities that can be evident in CTEPH such as mosaic attenuation, characterised by geographical heterogeneity of lung parenchymal perfusion [Fig. 3]. This is a useful discriminator for chronicity in patients with suspected acute-on-chronic disease. Its presence in the absence of visually demonstrable abnormalities in the pulmonary arteries should raise the suspicion of distal thromboembolic disease. Complications such as pulmonary infarction and parenchymal scarring can be easily depicted by CT and kept under surveillance if necessary. A paramount unmet need in PH imaging is the ability to adequately delineate distal pulmonary vasculature.

Dual energy CT (DECT) is an innovative off-shoot of CT technology that allows for the concomitant visualisation of the morphological changes in the pulmonary artery as well as the lung perfusion abnormalities by simultaneous acquisition of two datasets at different tube voltages [Fig. 4]. Based on material decomposition of iodine, it is possible to portray relative regional blood volume in the pulmonary parenchyma but iodine is only measured at a single time point. Hence, DECT is only a surrogate measure of microvascular circulation. Qualitative and quantitative perfusion blood volume [PBV] maps have shown good correlation with mosaic attenuation and pulmonary haemodynamics measured on right heart catheterisation respectively and thus have the potential to diagnose distal vasculopathy as well as measure disease severity.[27, 28].

Pioneering flat-panel techniques such as **cone-beam CT** are principally useful as an intra-procedural adjunct whilst performing BPA rather than for CTEPH diagnosis.

The role of **cardiac magnetic resonance imaging (CMR)** is two-fold. Evaluation of the pulmonary circulation is a multi-step process with a 3D contrast enhanced dynamic time-resolved perfusion sequence to assess the microcirculation followed by a high spatial resolution contrast-enhanced angiography (CE-MRA) for visualisation of the macro-circulation [Fig. 5] The diagnostic accuracy is improved with the combination technique [29] Overall, MR is comparable to CTPA and catheter angiography for disease detection in main, lobar and segmental vessels but is inferior for the subsegmental vasculature [30]. In a recent publication from a single centre comparing the efficacy of perfusion MR and SPECT VQ, MR demonstrated 100% sensitivity for CTEPH screening [31]. It is possible to render a 3D roadmap of the pulmonary vascular abnormalities by creating rotating maximum-intensity projections. This can be used for operability assessment in high volume centres with concentrated expertise. CMR is also the reference standard for assessment of right ventricular (RV) morphology and function. Semi-quantitative analysis of balanced Steady-state free precession (SSFP) cine sequence provides an accurate and consistent estimation of biventricular function. The RV adapts to the gradual increase in pulmonary pressures initially by hypertrophy and subsequently by progressive dilatation with global impairment of systolic function. Worsening pressure overload results in interventricular septal flattening followed by end-systolic bowing toward the left ventricle (LV). The reversal of the septal curvature leads to LV under-filling with decreased stroke volume even in the presence of normal LV systolic function. Late gadolinium enhancement (LGE) at the right ventricular insertion points is non-specific but is deemed to be a marker of adverse prognosis in CTEPH [32]. Aortic and pulmonary artery flows and distensibility can be measured using phase-contrast sequence (PC-MRI) allowing for estimation of cardiac output as well as the extent of broncho-pulmonary shunting. The shunt severity has been demonstrated to decrease in proportion to the success of the surgical revascularisation.

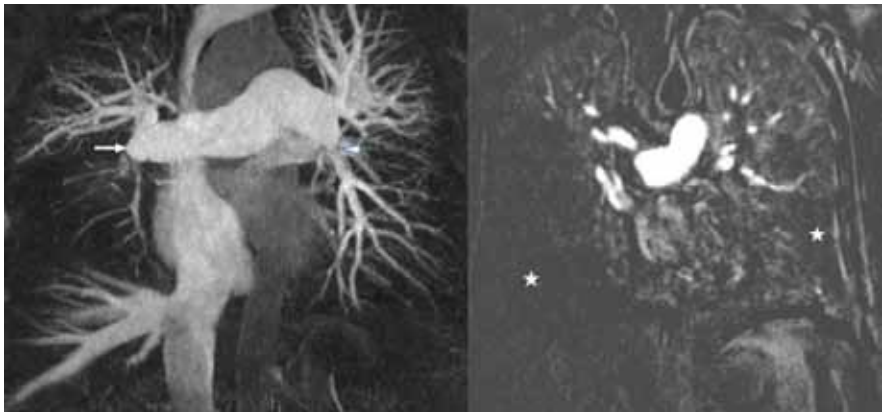

Fig 5. Coronal view of MRPA (left) and MR perfusion (right) in a 57 year old male with proximal CTEPH. There is a pouch defect (block white arrow) in the right lower lobe with occlusion of right middle and lower lobe vessels and a tight trifurcation stenosis in the left lower lobe (arrowhead). with corresponding perfusion defects.

There is a growing body of evidence for using **multi-parametric MR** techniques for characterisation of RV structure and physiology but their clinical utility in CTEPH is yet to be proven. **Multidirectional 4D phase-contrast MR** is a compelling tool for evaluation of the flow patterns within the RV and pulmonary circulation. Whilst it has the potential to provide unique insights into pulmonary arterial physiology, its role in CTEPH remains to be explored.

Based on current evidence, non-invasive measures of haemodynamic parameters show only modest success. Right heart catheterisation is mandatory as accurate estimation of PVR is integral to decisions regarding appropriate treatment. If the PVR is not commensurate with the extent of demonstrable disease on imaging, there is likely to be a signifiant small vessel component and surgery may not be the most appropriate treatment.

Need for multidisciplinary team (MDT) discussion:

Given the disease complexity, all CTEPH cases should be referred to an expert centre for further management. It is imperative from the start to involve radiologists with specialist interest in PH imaging, anaesthesiologists and intensive care physicians in addition to the pulmonologists, cardiologists and cardiothoracic surgeons as each member of the multidisciplinary team has a defined role in determining the success of the CTEPH programme. It is critical to remember that whilst technical feasibility is an important consideration, surgical appropriateness is governed by other factors such as co-morbidities and patient choice.

Conclusion:

Multimodality CTEPH imaging allows for comprehensive evaluation of the right ventricle and pulmonary circulation in terms of anatomical delineation, functional quantification and tissue characterisation. Emerging techniques such as hybrid SPECT-CT, dual energy CT, 4D phase contrast MR have enormous potential but need prospective trials to establish their applicability in a wider clinical setting.

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