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REVIEW

Diagnostic testing to guide the management of chronic thromboembolic pulmonary hypertension: state of the art

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ABSTRACT: Chronic thromboembolic pulmonary hypertension (CTEPH) is a life-threatening and debilitating disease affecting up to 5% of survivors of pulmonary embolism. Diagnostic testing is important to distinguish it from other forms of pulmonary hypertension and to assess the feasibility of pulmonary endarterectomy.

This review provides an up-to-date perspective on the diagnosis and assessment of the disease. Patients with CTEPH often have a history of pulmonary embolism, deep-vein thrombosis, thrombophilia, splenectomy, ventriculo-atrial shunt, inflammatory bowel disease or malignancy. Chest radiography may reveal pulmonary infarcts. CTEPH is often diagnosed as a wedge-shaped perfusion defect with normal ventilation scan during ventilation–perfusion scintigraphy, but multi-slice computed tomography angiography may be needed for differential diagnosis.

Right heart catheterisation is required for diagnostic confirmation. Suitability for surgery is assessed by evaluating the number of obstructed vessels which could be disobliterated in the context of the pulmonary vascular resistance. Pulmonary vascular resistance that is out of proportion to evident obstructions is indicative of distal disease. Conventional pulmonary angiography, multi-slice computed tomography angiography and, potentially, magnetic resonance imaging can aid the decision to operate, but risk stratification systems are needed.

In conclusion, CTEPH can be cured surgically, providing that patients are diagnosed and assessed using the appropriate techniques.

KEYWORDS: Angiography, catheterisation, diagnosis, endarterectomy, hypertension, pulmonary

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Chronic thromboembolic pulmonary hypertension (CTEPH) is a result of the obstruction of the pulmonary vascular bed by nonresolving thromboemboli [1, 2]. While evidence is accumulating that CTEPH may be initiated by a range of thrombotic or inflammatory lesions in the pulmonary vasculature, pulmonary embolism remains the most common cause of CTEPH. Whereas thromboemboli resolve in most patients within 30 days [3], with concomitant normalisation of haemodynamics and gas exchange, up to 25% of patients show persistent pulmonary hypertension or abnormal perfusion lasting several months or more [4, 5].

The cumulative incidence of CTEPH following pulmonary embolism has been reported to be between 1.3% [6] and 5.1% [7] after 1 yr, and between 0.8% [8] and 3.8% [9] after 2 yrs. Although these studies detected no cases of CTEPH >2 yrs after pulmonary embolism [8, 9], their relatively short duration may have led to an underestimation of the overall occurrence of CTEPH. Furthermore, many patients who develop CTEPH (62% of those with proximal and 49% with distal disease) have no history of pulmonary embolism [10]. Data from the only population-based CTEPH registry suggest that the incidence of CTEPH in the UK was 1.75 per million in 2005 [10]. However, this estimate only takes into account patients who were diagnosed at a specialist centre for the management of pulmonary hypertension.

Pulmonary endarterectomy (PEA) remains the treatment of choice for CTEPH and is performed successfully in a small number of specialist centres [11, 12]. Targeted therapies for pulmonary arterial hypertension have been studied in patients with inoperable CTEPH,

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but no therapies have been associated with functional improvements in randomised clinical studies [1, 13]. Diagnostic testing is important to distinguish CTEPH from other forms of pulmonary hypertension and to assess operability. Updated guidance on the management of pulmonary hypertension has recently been provided by the Fourth World Symposium on Pulmonary Hypertension [1] and the European Society of Cardiology and the European Respiratory Society Task Force for the diagnosis and treatment of pulmonary hypertension [14, 15]. The aim of this review is to provide an up-to-date perspective on the diagnosis and pre-operative assessment of CTEPH.

DIAGNOSIS OF CTEPH

CTEPH should be considered in all patients with unexplained pulmonary hypertension, with the diagnostic process beginning with the patient history. Data from three European specialist centres have shed light on risk factors for CTEPH by comparing patients with CTEPH and those with pulmonary arterial hypertension [16]. In addition to previously established risk factors, such as a history of pulmonary embolism, deep-vein thrombosis, ventriculo-atrial shunt, infected pacemakers and splenectomy [16, 17], the study identified novel factors associated with CTEPH, such as thyroid replacement therapy and a history of malignancy. Other established risk factors include myeloproliferative disorders and inflammatory bowel disease [2]. CTEPH registries in the UK and the prospective European CTEPH Registry have the potential to characterise CTEPH patients further [18, 19]. Additional epidemiological studies in patients surviving a pulmonary embolism are also required.

Routine haematological and biochemical tests are usually unremarkable in patients with CTEPH, although lupus anticoagulant/anti-cardiolipin antibodies have been identified in 10–20% of CTEPH patients [16, 20]. There is also some indication of an increased thrombophilic tendency [21, 22]. Pulmonary function tests in patients with CTEPH are generally within the normal range or show only a mild restrictive pattern resulting from parenchymal scarring [23]. The diffusing capacity for carbon monoxide may be normal or reduced. Chest radiography may reveal focal areas of hypovascularity or wedge-shaped peripheral infiltrates consistent with pulmonary infarcts, but is often unremarkable [1]. Echocardiography may be useful for the follow-up of survivors of acute pulmonary embolism who showed signs of pulmonary hypertension or right ventricular dysfunction during their hospital stay to determine whether or not pulmonary hypertension has resolved 3–6 months after discharge [14].

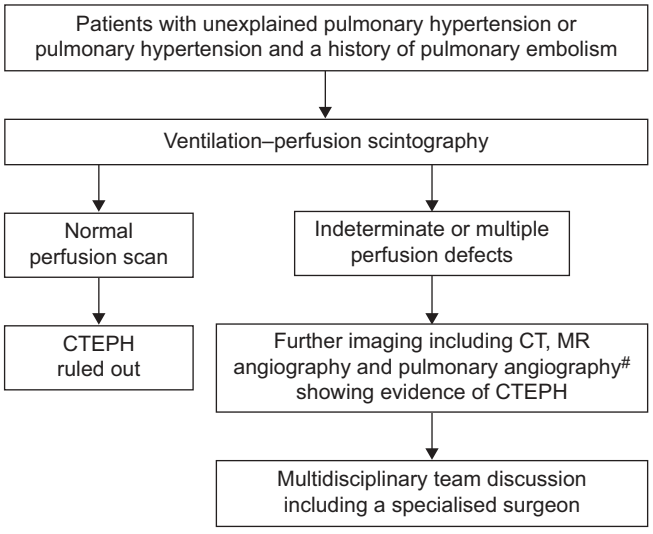

FIGURE 1. Diagnostic imaging algorithm for chronic thromboembolic pulmonary hypertension (CTEPH). CT: computed tomography; MR: magnetic resonance. #: pulmonary angiography is usually performed in conjunction with right heart catheterisation and should be performed at centres experienced with CTEPH and pulmonary endarterectomy. Reproduced from [1] with permission from the publisher.

Ventilation–perfusion scintigraphy is the examination of choice for ruling out CTEPH (fig. 1) [1]. The complete absence of perfusion to one lung raises the suspicion of other disease processes, such as malignancy, mediastinal fibrosis or vasculitis. A wedge-shaped perfusion defect with normal ventilation scan is a clear indication of CTEPH (fig. 2), but additional imaging techniques may be required to differentiate from idiopathic pulmonary arterial hypertension [24]. For instance, multi-row computed tomography angiography reveals vascular obstructions and a mosaic perfusion pattern in patients with CTEPH. In contrast, vascular pruning may be seen in idiopathic pulmonary arterial hypertension on pulmonary angiography. A nodular ground-glass pattern and mediastinal adenopathy are also sometimes visible *via* computed tomography in patients with pulmonary arterial hypertension. While these features are not necessarily specific to pulmonary arterial hypertension, they can help to differentiate between small-vessel pulmonary hypertension and CTEPH. Haemodynamic evaluation of CTEPH using right heart catheterisation is essential; either at rest or in patients with mild symptoms during exercise. The presence of pre-capillary pulmonary hypertension (mean pulmonary arterial pressure $\geqslant$25 mmHg, pulmonary capillary wedge pressure $\leqslant$15 mmHg and pulmonary vascular resistance $>$2 Wood units) confirms the diagnosis of CTEPH in patients with chronic/organised thromboembolic obstructions (table 1) [14]. In addition to its role in the diagnosis of CTEPH, right heart catheterisation can provide additional information regarding disease severity, right heart function and mixed venous oxygen saturation [1]. Exercise testing at the time of right heart catheterisation can also contribute to the assessment of disease severity.

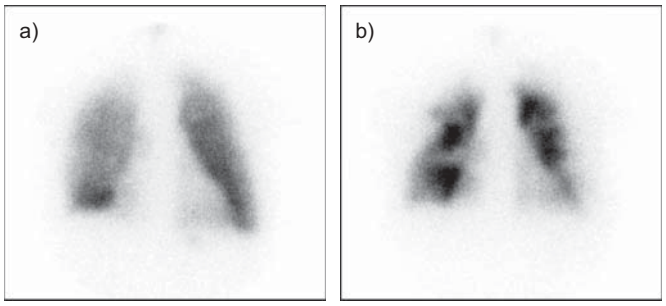

FIGURE 2. a) Ventilation and b) perfusion scintigraphy of the lungs of a patient with chronic thromboembolic pulmonary hypertension. The dark areas indicate regions of the lung with good ventilation or perfusion, respectively.

TABLE 1 Recommendations for the diagnosis and pre-operative assessment of chronic thromboembolic pulmonary hypertension (CTEPH)

Statement	Class[#]	Level[¶]
The diagnosis of CTEPH is based on the presence of pre-capillary PH ($\bar{P}_{pa}$ ⩾25 mmHg, PWP ⩽15 mmHg, PVR >2 Wood units) in patients with multiple chronic/organised occlusive thrombi/emboli in the elastic pulmonary arteries (main, lobar, segmental, subsegmental)	I	C
Once perfusion scanning and/or CT angiography show signs compatible with CTEPH, the patient should be referred to a centre with expertise in surgical pulmonary endarterectomy	IIa	C
The selection of patients for surgery should be based on the extent and location of the organised thrombi, on the degree of PH and on the presence of comorbidities	IIa	C

PH: pulmonary hypertension; $\bar{P}_{pa}$: mean pulmonary arterial pressure; PWP: pulmonary wedge pressure; PVR: pulmonary vascular resistance; CT, computed tomography. [#]: I: evidence and/or general agreement that a given treatment or procedure is beneficial, useful or effective; II: conflicting evidence and/or a divergence of opinion about the usefulness/efficacy of the given treatment or procedure (IIa, weight of evidence/opinion is in favour of usefulness/efficacy); [¶]: C: consensus of opinion of the experts and/or small studies, retrospective studies or registries. Modified from [14].

PRE-OPERATIVE ASSESSMENT OF CTEPH

Whether a patient with CTEPH can be treated surgically with PEA depends, to a large extent, on the distribution of obstructions in the pulmonary vasculature. The dual-compartment pulmonary vascular bed hypothesis proposes that there are two types of pulmonary vascular lesion in CTEPH: 1) proximal nonresolving thromboemboli; and 2) distal obstructions with concomitant small vessel arteriopathy and remodelling [25]. However, the two cannot be distinguished on the basis of pulmonary haemodynamics alone [26]. Consequently, angiography is required to visualise the distribution of the vascular changes.

Conventional pulmonary angiography is the gold standard technique for the work-up of CTEPH prior to surgery, and can reveal dilation of the pulmonary artery, vascular obstructions, webs, post-obstructive dilatations and poorly perfused areas of the lung (fig. 3) [24]. However, the invasive nature of conventional angiography limits its use in clinical practice. Multi-slice computed tomography angiography has the advantage of being noninvasive, while having a resolution approaching that of conventional pulmonary angiography. Additionally, it shows a characteristic mosaic pattern of lung attenuation once air trapping has been excluded (fig. 4) [24].

Magnetic resonance imaging is another noninvasive technique with great potential, albeit with limited availability. It can be used for morphological, anatomical and functional assessment of both the heart (*e.g.* cardiac chamber dimensions, ventricular muscle mass and wall motion) and pulmonary circulation (*e.g.* webs, vascular obstructions and pulmonary arterial flow, allowing for estimation of blood volume and cardiac output).

It is mandatory to relate haemodynamic values from right heart catheterisation to vascular obstructions seen by imaging. This is to distinguish inoperable disease from surgically amenable disease: pulmonary vascular resistance that is excessively elevated when compared with the degree of visible obstruction is a typical sign of inoperable disease.

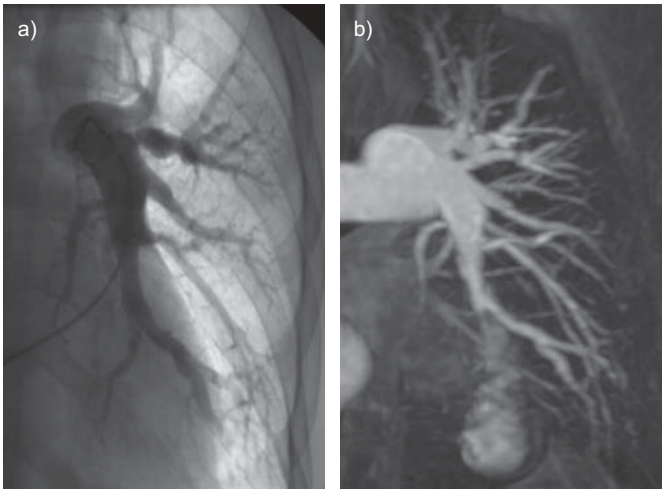

FIGURE 3. a) Conventional angiography and b) magnetic resonance angiography of the lungs of a patient with chronic thromboembolic pulmonary hypertension, showing webs and occlusions.

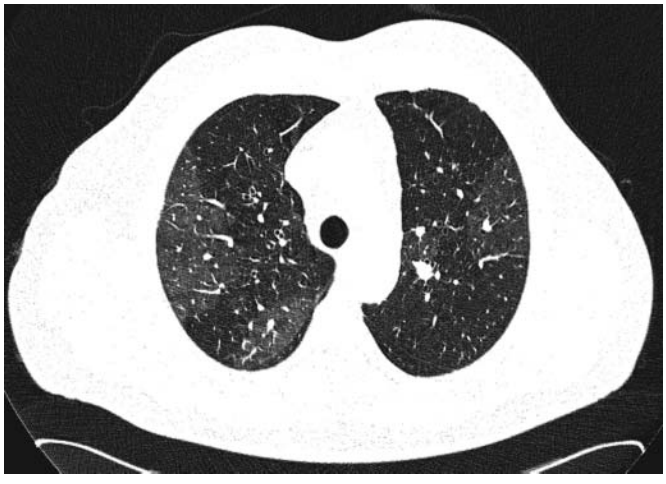

FIGURE 4. Multi-scan computed tomography showing mosaic perfusion in the lungs of a patient with chronic thromboembolic pulmonary hypertension. The darker areas indicate regions of poor perfusion.

Three-dimensional imaging can support the decision to operate, but a number of difficulties remain. For instance, there is no risk stratification or scoring system to aid the selection of patients for surgery and no method of assessing the dissection plane before the operation. The most important task in assessing patients for surgical management is to select those who will benefit from PEA with minimal risk of residual post-operative hypertension. The complexity of the decision-making process means that investigations to assess whether CTEPH is operable should be performed at specialist centres which collaborate closely with surgical centres performing PEA. The final decision on operability should be taken by a multi-disciplinary team and involve the surgeon performing PEA.

CONCLUSION

CTEPH is a life-threatening and debilitating disease that is potentially curable by PEA. It can be identified by following up patients with risk factors, such as a history of pulmonary embolism, and should be considered in all patients with unexplained pulmonary hypertension. PEA is the treatment of choice for CTEPH. The suitability of particular patients for surgery should be considered on a case by case basis by an experienced multidisciplinary team, including the surgeon responsible.

STATEMENT OF INTEREST

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