Full Length Article

Modern diagnosis of chronic thromboembolic pulmonary hypertension

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A B S T R A C T

Chronic thromboembolic pulmonary hypertension (CTEPH) should be suspected in patients presenting persistent dyspnea three months after a pulmonary embolism or in patients presenting with acute pulmonary embolism and suggestive images on the CT-scan. For these patients, a specific diagnostic work-up should be performed.

First step consists of the ventilation/perfusion (V/Q) scan which is a good screening test due to its high sensitivity and high negative predictive value. Pulmonary angiography remains the gold standard approach for the confirmation of the diagnosis and pre-surgical evaluation of CTEPH. New emerging technologies such as Dual-Energy Computed Tomography angiography (DECT) and Computed Tomography angiography (CTA) are developing and broadly available. These non invasive methods provide diagnostic information similar to conventional pulmonary angiography and surgical operability information. They are to be considered as an alternative in the diagnostic approach of patients with CTEPH as presented in the ESC/ERS guidelines.

Haemodynamic measurement whiles exercising during right heart catheterization may improve diagnostic sensitivity of CTEPH and could therefore be used as a diagnostic test in patient with normal haemodynamic at rest.

1. Introduction

Chronic thromboembolic pulmonary hypertension (CTEPH) is a form of pulmonary hypertension (PH), secondary to the obstruction of pulmonary arteries by an organized tissue [1,2,3]. The consequence is an increase in pulmonary vascular resistance (PVR) leading to a right heart failure. CTEPH is classified in group IV, subgroup 4.1 according to the WHO classification of pulmonary hypertension [2,4]. There is currently no clear guideline recommending systematic screening for CTEPH in patient presenting with acute pulmonary embolism (PE). Nevertheless, one should suspect CTEPH in patients presenting persistent respiratory symptoms 3 months after an acute PE and receiving effective anticoagulation therapy [2]. CTEPH suspicion should also be raised in patients with the diagnosis of acute PE and suggestive context like disproportional PH or evocative CT-scan images.

The current diagnostic criteria for CTEPH includes a pre-capillary pulmonary hypertension confirmed by right heart catheterization (RHC) performed at rest, mismatched perfusion defects on ventilation/perfusion (V/Q) scan, and vascular signs of thromboembolic disease on conventional pulmonary angiography [1]. When a CTEPH is suspected, patients should be referred to an expert PH centre for comprehensive diagnosis workup. As in all suspicion of PH, an initial evaluation of level of diagnosis probability, including PH screening by trans-thoracic echocardiography (TTE) is warranted. In the recent years, new techniques and better knowledge of haemodynamic characteristics of CTEPH have emerged. This article reviews the modern techniques available in the diagnostic approach with the new imaging findings, haemodynamic features and surgical feasibility evaluation in chronic thromboembolic pulmonary hypertension.

2. Definition and risk factors

CTEPH results of the persistent or recurrent obstruction of pulmonary arteries associated with pre-capillary pulmonary hypertension [5], defined as a mean pulmonary artery pressure (mPAP) $\geq$ 25 mm Hg with a pulmonary artery wedge pressure (PAWP) $\leq$ 15 mm Hg. It is the second most frequent type of pre-capillary pulmonary hypertension reported, corresponding to 25% of patients in Switzerland according the Swiss Pulmonary Hypertension Registry [6]. Patients usually complaint of non specific symptoms such as shortness of breath, exercise intolerance, tiredness and can present with right heart failure signs. As a consequence, the mean time to diagnosis often exceed 1 year [7].

Some risk factors are identified with higher risks of developing CTEPH [8]: thrombophilia, non-O-type blood groups, splenectomy, inflammatory bowel disease and local vascular devices as implanted pacemaker, where the hypothesis is a chronic plasmatic inflammation [9]. In 20% of patients with CTEPH a high plasmatic level of antiphospholipid antibodies is found [10]. Alterations of the fibrinogen pathway or platelet function were also suggested to be potentially associated with increased risk of CTEPH.

3. Epidemiology

CTEPH is a condition often under-diagnosed making it difficult to determine its precise incidence [11]. Current estimation of its incidence is 3–5 per million per year [2,11,12]. The highest risk of developing CTEPH is considered during the first 24 months after an acute PE. Here, cumulative incidence has been described as of 1%, 3.1% and 3.8% at 6, 12, 24 months respectively [13]. CTEPH is associated to a significant mortality if not treated with a median survival rate of 10–20% at 2–3 years [5] reinforcing the importance of an early diagnosis. An estimated pulmonary artery systolic pressure higher than 60 mmHg during an episode of PE is suggestive of a chronic obstruction of the pulmonary output and should therefore lead to more investigations as for the presence of CTEPH [7].

4. Pathophysiology

The natural history of CTEPH is defined by progressive rise of the pulmonary pressure due to increase pulmonary vascular resistance. Progressive right heart failure suggests the potential role of progressive lesions in small pulmonary arteries and the presence of organized micro-thrombi. The consecutive flux perturbation leads to pulmonary hypertension. In < 0.5% of patients with acute PE, the resolution of the thrombus is disturbed; the clot becomes organized and occludes the pulmonary vascular bed, described as a "dead tree" on the pulmonary angiography [14]. Both proximal and distal pulmonary arteries are involved. In distal pulmonary arteries, vasculopathy involving occluded and non-occluded vessels are described [9,15]. This involvement of small non-occluded vessels may be due to shear stress and pressure inflammation, making CTEPH a disease that shares some patho-physiological features of pulmonary arterial hypertension, a disease characterized by an intense remodelling of the pulmonary arteries of small calibre, due to the proliferation of endothelial and smooth muscle cells and a medial hypertrophy. Consequently, > 50% of the pulmonary vascular bed is compromised in CTEPH patients [14]. Interestingly, there is no clear correlation between the extension of visible perfusion defects found in the V/Q scans and CTEPH severity [16]. This is consistent with the fact that at least two effects co-exists: a direct effect of vascular obstruction and lesions in smaller arteries not detected on V/Q scans.

5. Diagnosis algorithms

When probability of PH is considered intermediate or high by initial observation (Fig. 1) including TTE assessment which is an important screening tool, patient enter a comprehensive diagnostic algorithm for CTEPH. Despite being a non-invasive and valuable method for several indirect cardiac parameters, TTE depends on the operator's skills and shows important limitations including imprecision of systolic pulmonary artery pressure (sPAP) estimation [17]. Moreover, differentiation of pre and post-capillary PH and determination of cardiac output may be difficult. Therefore PH confirmation is formally not excluded or confirmed by TTE alone. Once CTEPH is suspected, a V/Q scan should be performed as normal V/Q scan may exclude the diagnosis [5], with a high sensitivity > 96% [17]. If a mismatch is revealed by V/Q scan, a confirmation test is mandatory [1]. At this stage, the current guidelines [2] recommend referral to an expert PH/CTEPH centre, where,
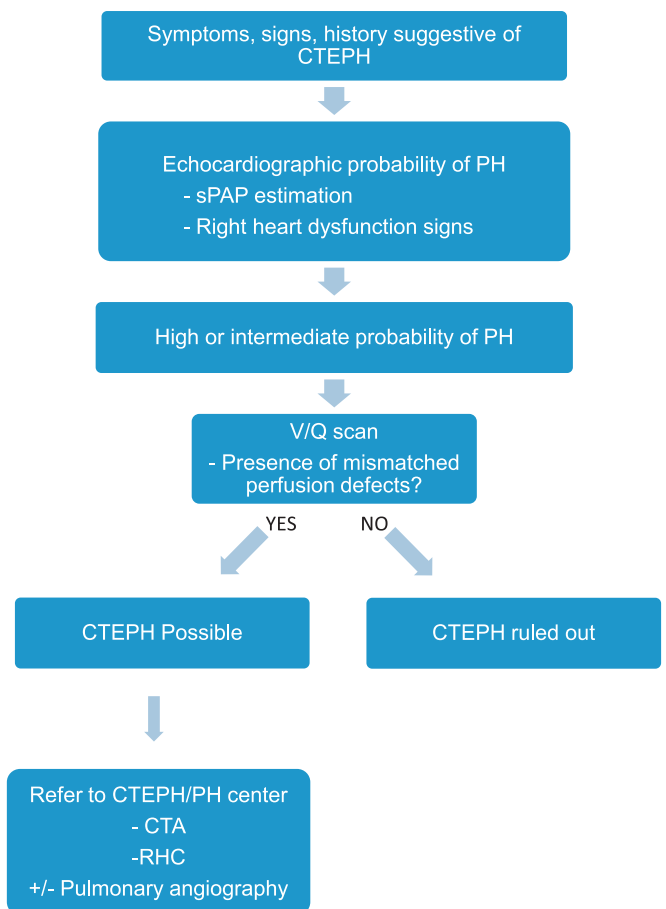

Fig. 1. Diagnostic algorithm of CTEPH.
sPAP = Pulmonary artery systolic pressure; CT = computed thomography; CTEPH = chronic thromboembolic pulmonary hypertension; PH = pulmonary hypertension; V/Q = ventilation/perfusion; RHC = Right heart catheterization; CTA = CT Angiography.
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conventional pulmonary angiography (CPA), right heart catheterization and pulmonary angiography can be performed to confirm diagnosis.

6. Conventional imaging

6.1. Ventilation-perfusion scanning (V/Q scan)

Ventilation/perfusion (V/Q) scan remains the cornerstone test for CTEPH diagnosis. A normal perfusion scan can exclude a CTEPH, whereas overall sensitivity of standard computed tomography angiography (CTA) is insufficient to exclude it [18]. Mismatched segmental defects, unmatched by ventilation are suggestive of CTEPH [19] (Fig. 2) and more definitive diagnostic tests are recommended. V/Q scan can distinguish between large-vessel occlusive and small-vessel disease in case of multiple small sub segmental defects but it may underestimate the burden of vascular obstruction [20] and the severity of haemodynamic compromission.

6.2. Conventional pulmonary angiography (CPA)

CPA has been historically and remains the gold standard for the diagnosis of CTEPH with dilatation of main pulmonary artery, and stenosis, web, or occlusion of pulmonary arteries, and segmental defects of perfusion [21] (Fig. 3). With the development of CTA, this invasive