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Review Article

To screen or not to screen for chronic thromboembolic pulmonary hypertension after acute pulmonary embolism

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ABSTRACT

Chronic thromboembolic pulmonary hypertension (CTEPH) is the most severe long term complication of acute pulmonary embolism (PE). Untreated, CTEPH is associated with a very poor prognosis and high risk of mortality, although curation can be achieved by surgical removal of the obstructive endothelialised thromboemboli from the pulmonary arteries. Early CTEPH diagnosis may improve surgical possibilities and patients outcome. Currently, early diagnosis of CTEPH is a major challenge as demonstrated by an unacceptable median diagnostic delay of over a year and as a result, surgery is impossible in 40% of patients. Most important reasons for this delay are the non-specific clinical presentation of CTEPH and lack of guideline recommendations with regard to the optimal follow-up of patients with acute PE. Despite compelling reasons to diagnose CTEPH earlier, acute PE is not classified among the conditions that warrant screening for pulmonary hypertension. Meaningful screening programs improve the patients' prognosis, and screening tools should be simple, widely available, non-invasive and acceptable to patients. In this review, we discuss current knowledge of available screening instruments for CTEPH, provide recommendations for clinical practice and expand on future developments of this particular subject.
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1. Introduction

The purpose of screening for a certain disease is to identify patients with preclinical or early stages of disease in order to prevent or delay progression of disease through early management. Medical screening has been increasingly implemented over the past half century and is widely recognized to be one of the 'success stories' of modern medicine. Pulmonary hypertension (PH) is a serious disease spectrum associated with a poor prognosis [1,2]. Screening programs play an important part in the detection of PH in certain at-risk populations to enable early identification and treatment. Specifically, screening for PH is recommended for patients with systemic sclerosis, scleroderma spectrum disorders, BMPR2-mutation carriers, first-degree relatives of patients with familial pulmonary artery hypertension (PAH), portal hypertension and for patients with sickle-cell disease [2–7]. This screening has been shown to result in earlier diagnosis [5,8,9] and earlier treatment initiation, which was demonstrated to lead to improved long-term survival [9,10].

Chronic thromboembolic pulmonary hypertension (CTEPH), a specific subclass of PH, is a life-threatening complication of acute pulmonary embolism (PE). CTEPH is caused by persistent obstruction of the pulmonary arteries and progressive vascular remodelling giving rise to PH and right ventricular failure. CTEPH may be cured by pulmonary endarterectomy (PEA) [2,11]. When surgery is not feasible or fails in significantly reducing the pulmonary artery pressure, the patient's prognosis is poor [1,2,12]. Operability of a patient depends among others on the presence of more advanced distal pulmonary artery remodelling, a feature that is less expected if CTEPH is diagnosed early. The duration between last PE and PEA was indeed found to be a risk factor for mortality in the European CTEPH Registry [13]. Hence, early diagnosis may be crucial for an optimal treatment and outcome [14–16].

Early diagnosis of CTEPH has however been shown to be a major clinical challenge as demonstrated by a median diagnostic delay of 14 months in the European CTEPH Registry [17]. Also, 81% of patients diagnosed with CTEPH presented in NYHA functional class III or IV, indicating an advanced stage of disease. Notably, international guidelines do not provide a clear recommendation on the frequency and duration of medical follow-up after acute PE or on specific screening programs for CTEPH [18]. Even more, the ESC guideline recommends against routine echocardiography in all patients who are treated for acute PE (Class 3, level C) [2,18,19].

In this review, we aimed to discuss arguments pro and contra CTEPH screening. To do so, we used the principles for screening proposed by Wilson and Jungner. These principles give guidance in the selection of conditions that would be suitable for screening, based on the diagnostic capacity to detect the condition at an early state and the availability of an acceptable treatment [20] (Table 1).

Table 1
Wilson and Jungner principles of early disease detection.

1	The condition sought should be an important health problem
2	There should be an accepted treatment for patients with recognized disease.
3	Facilities for diagnosis and treatment should be available.
4	There should be a recognizable latent or early symptomatic stage.
5	There should be a suitable test or examination.
6	The test should be acceptable to the population.
7	The natural history of the condition, including development from latent to declared disease, should be adequately understood.
8	There should be an agreed policy on whom to treat as patients.
9	The cost of case-finding (including diagnosis and treatment of patients diagnosed) should be economically balanced in relation to possible expenditure on medical care as a whole.
10	Case-finding should be a continuing process and not a "once and for all" project.

2. The condition sought should be an important health problem

A health problem is considered important if a certain disease has serious consequences for the patient and his or her family, or serious consequences for the community if not discovered and treated [20]. In a recent meta-analysis, CTEPH has been estimated to occur in 0.13–0.98% of all patients who are diagnosed with acute PE on a population level [21]. This incidence is mainly based on two cohort studies of patients with acute PE with very few exclusion criteria who were followed for the occurrence of CTEPH, reporting incidences of 0.57% and 1.3% respectively [19,22].

The estimated incidence of a first venous thromboembolic event in the general population is 1–2 per 1000 person-years [23–25]. Assuming 743 million inhabitants of Europe, each year an estimated 4000 to 8000 patients with a history of PE will develop CTEPH. Of note, the reported weighted pooled incidence of CTEPH in patients who survive the PE event and visit the outpatient clinic after an initial anticoagulant treatment period of 3 to 6 months is ~3%. This incidence reported in the so called survivors is higher than the reported incidence on population level [21].

Before the introduction of PEA the prognosis of these patients was very poor. In older series in patients who only were prescribed vitamin K antagonists, the 3-year survival was as low as 30% [26,27]. In addition to a shorter life expectancy compared to the general population, patients with CTEPH have a substantially reduced quality of life in terms of physical capability, psychological wellbeing and social relationships [28]. Considering the above, CTEPH should be considered an important health problem.

3. The natural history of the condition, including development from latent to declared disease, should be adequately understood. There should be a recognizable latent or early symptomatic stage

CTEPH, a distinct form of PH, is believed to arise from one or multiple endothelialized pulmonary thrombi that do not resolve but lead to chronic obstruction of the pulmonary artery tree, small-vessel arteriopathy, high pulmonary vascular resistance, PH and progressive right heart failure. The pathophysiological mechanisms that prevent complete resolution of the embolic material after acute PE are not fully elucidated yet but involve among others inflammation, abnormal fibrinogen variants and aberrations in angiogenesis [29].

The most common presenting symptom in patients with CTEPH is dyspnoea [17]. The acute embolic event in patients with CTEPH can typically be followed by a so-called 'honeymoon' period during which the patients gradually recover [30]. This period can last for several months and sometimes even years. Later on, patients develop progressive dyspnoea on exercise as initial symptom of CTEPH [30]. Signs of right heart failure only become evident in more advanced disease [17]. Importantly, CTEPH can be diagnosed accurately in symptomatic as well as non-symptomatic patients if the correct diagnostic tests are applied (see below).

Several circumstances complicate easy clinical recognition of patients with CTEPH in the clinical course of PE, contributing to the substantial diagnostic delay of CTEPH. First, 36–56% of patients who survive an episode of acute PE report exertional dyspnoea [31,32]. Only a small number of these patients actually develop CTEPH [32]. CTEPH seems to be the extreme manifestation of a much more common phenomenon of permanent changes in pulmonary artery flow, pulmonary gas exchange and/or cardiac function caused by acute PE in combination with deterioration of the clinical symptoms, functional status or quality of life. This is in analogy to post-thrombotic syndrome after deep vein thrombosis referred to as the post-PE syndrome. Taking the above described frequently occurring honeymoon period of no or very limited symptoms into account as well, it is a challenge to easily identify patients with CTEPH at early stage based on their clinical presentation [33].

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