Prediction of long-term complications of venous thromboembolism

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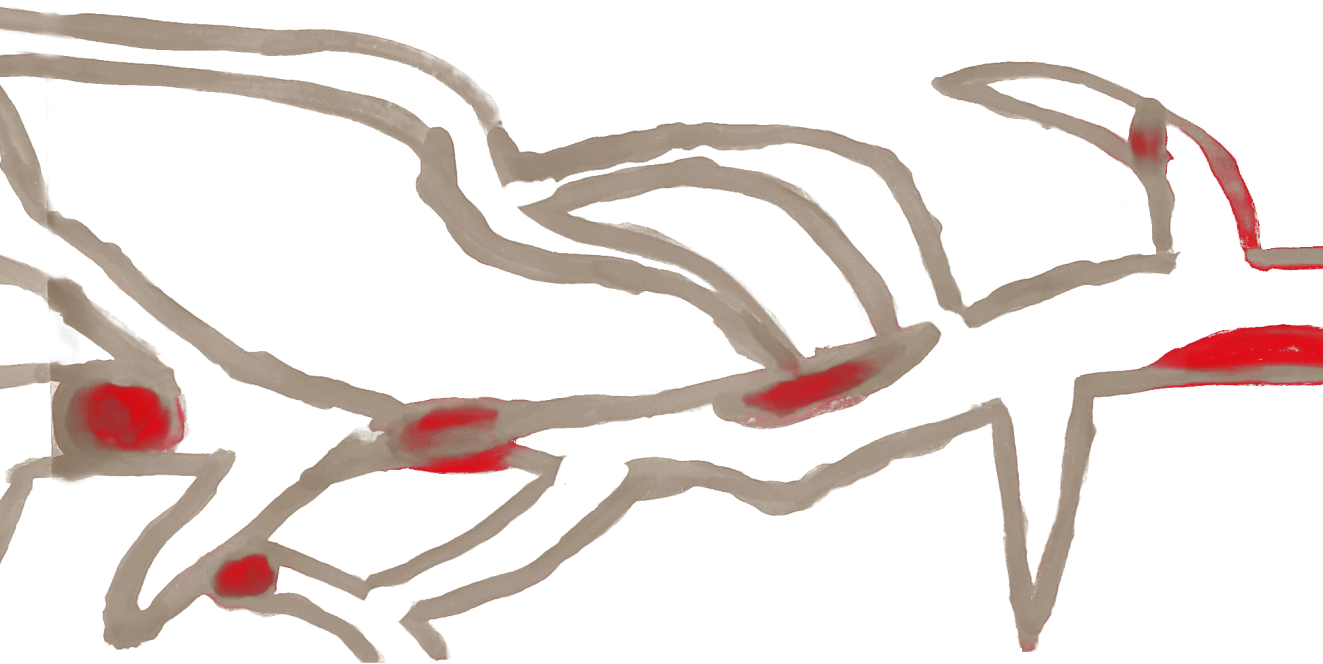**Issue Date**: 2019-11-07

Chapter 2

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.

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.

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.

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].

Second, CTEPH should be distinguished from chronic thromboembolic disease (CTED). CTED is defined as persistent pulmonary vascular obstruction and exercise intolerance without PH at rest [34]. CTED is one of the manifestations of the post-PE syndrome, as is CTEPH. It has however been suggested that some of these patients may have exercise induced PH [35]. PH on exercise may be an intermediate pathophysiological stage of PH although limited data exist on the natural history of PH on exercise and it is currently not recognized as disease entity in current guidelines. The prognosis of patients with

CTED is favourable without treatment, although PEA has been suggested to result in significant improvement in symptoms and quality of life in this patient category too [36]. Finally, growing evidence supports the hypothesis that CTEPH is often misclassified as acute PE [2, 37-39]. The clinical course of symptom relief after initiation of anticoagulant treatment in such patients is likely different from patients with true acute PE. Of note, early screening programs for CTEPH after acute PE would be suitable to identify this specific patient category as well.

FACILITIES FOR DIAGNOSIS AND TREATMENT SHOULD BE AVAILABLE

According to the current guidelines, patients with a history of venous thromboembolism who present with signs or symptoms suggestive for right sided heart failure should be subjected to a diagnostic evaluation for CTEPH. A CTEPH diagnosis is based on findings obtained after at least three months of effective anticoagulation in order to discriminate CTEPH from acute PE. The recommended diagnostic work-up starts with transthoracic echocardiography, during which an estimate of pulmonary artery pressure can be made by Doppler evaluation. A tricuspid regurgitation velocity of >2.8m/s indicates an intermediate to high probability of PH. Other signs suggesting PH are right ventricle/left ventricle basal diameter ratio >1.0, flattening of the interventricular septum (left ventricular eccentricity index >1.1 in systole and/or diastole), right ventricular outflow Doppler acceleration time <105 msec and/or midsystolic notching, early diastolic pulmonary regurgitation velocity >2.2 m/sec, inferior cava diameter >21 mm with decreased inspiratory collapse (<50% with a sniff or <20% with quiet inspiration), right atrial area (end-systole) >18 cm^2 and lastly PA diameter >25 mm [2].

When echocardiographic findings are indicative for PH, the next diagnostic step is ventilation/perfusion (V/Q) lung scintigraphy carrying a 96%-100% sensitivity and 86%-95% specificity for CTEPH [2, 40-42]. The gold standard test to diagnose CTEPH is right heart catheterisation (RHC) with digital subtraction pulmonary artery angiography, the latter being crucial for the assessment of surgical treatment as well. A pulmonary arterial pressure ≥25mmHg and pulmonary artery wedge pressure ≤15mmHg, in combination with multiple chronically organized occlusive thrombi in the pulmonary arteries is diagnostic for CTEPH [2, 18, 43]. Initial steps of this recommended diagnostic algorithm, i.e. echocardiography and V/Q lung scintigraphy, are widely available, while the final diagnosis should be confirmed in a PH/CTEPH expert centre.

THERE SHOULD BE AN ACCEPTED TREATMENT FOR PATIENTS WITH RECOGNIZED DISEASE AND AN AGREED POLICY ON WHOM TO TREAT AS PATIENTS

PEA is the only curative treatment option for patients with CTEPH and treatment of choice according to the guidelines [2]. This surgery is performed through a median sternotomy incision, followed by a cardiopulmonary bypass enabling hypothermia to 20°C and intermittent deep hypothermic circulatory arrest. During the circulatory arrest, all obstructive thromboembolic material of the affected parts of the lung will be removed with dissection of the intima and part of the media [44]. Most patients experience immediate improvement in symptoms and near normalization of pulmonary hemodynamics [13, 17, 45], even in patients with limited segmental-level disease [46]. Recent large cohort studies show in-hospital mortality rates between 2.2% and 6.5% [13, 17, 45, 46], 1-year survival rates of 91-93% [1, 13, 45] and 3-5 year survival rates of 82-90% [1, 46, 47].

At time of diagnosis, up to 40% of patients are not suitable for surgery in some centers for reasons including surgical inaccessibility of the thrombotic lesions, the degree of impairment of pulmonary hemodynamics or the presence of severe comorbidities [1, 13]. Notably, the threshold for surgery is shifting throughout recent years to more and more peripheral disease. For patients who are deemed inoperable, pharmacological therapy may be considered. Long term clinical outcome studies have however shown that patients who underwent PEA had lower 3-year mortality rate compared with non-operated, medically treated patients (11-13% compared to 30-35%) [1, 48]. The five-year survival rate was 86.3% compared to 64.9% respectively [12]. PEA is thus the only curable treatment option and should be considered in every patient with CTEPH. Since the natural course of disease includes progressive involvement of distal pulmonary arteries, implicating that diagnostic delay may possibly be associated with a lower chance of operability, it can by hypothesised that early diagnosis is essential for the patients' prognosis [11]. Importantly it has never been indisputably shown that earlier diagnosis is associated with better operability and improved prognosis.

To date, only two large randomized controlled trials have assessed the efficacy and safety of pharmacological treatment in inoperable CTEPH patients. Riociguat, a soluble guanylate cyclase stimulator stimulates and increases the sensitivity of the guanylate cyclase receptor to the vasodilatator nitric oxide, is the only therapeutic agent approved for pharmacological treatment of CTEPH [49, 50]. Compared with placebo, riociguat was associated with an increased 6-min walking distance and reduced pulmonary vascular resistance in inoperable CTEPH patients after 16 weeks of treatment [50]. With continued treatment (CHEST-2 study), these improvements maintained for up to 2 years with an estimated survival rate at 1 year of 93% [51]. Bosentan, a dual endothelin receptor antagonist, reduces the endothelin levels and the endothelin receptor expression, a

process involved in the vascular remodelling in CTEPH [52]. It was shown to significantly reduce pulmonary vascular resistance after 16 weeks of treatment, but without improvement of the 6-minute walking distance compared to placebo [52]. New pharmacological treatment options being studied are macitentan, a dual endothelin receptor antagonist (phase 2 MERIT-2 trial; NCT02060721) and ambrisentan, a selective endothelin receptor antagonist trial (phase3 AMBER II; NCT01894022).

Balloon pulmonary angioplasty (BPA) is a novel treatment for patients with inoperable, persistent or recurrent pulmonary hypertension after PEA. BPA is a catheter-based invasive procedure to open stenotic or obstructed lesions in the pulmonary artery with a balloon catheter. Several studies have shown that BPA can lead to haemodynamic improvements that are compatible to those typically seen following PEA, although further evaluation of BPA as first or second line treatment of CTEPH is needed [53-57].

THERE SHOULD BE A SUITABLE SCREENING TEST OR EXAMINATION AND THIS TEST SHOULD BE ACCEPTABLE TO THE POPULATION

Candidate screening instruments for CTEPH in the clinical course of acute PE include echocardiography, V/Q lung scintigraphy, CT pulmonary angiography (CTPA), electrocardiography (ECG), measurement of biomarkers and clinical pre-test probability assessment. For obvious reasons RHC, while being the diagnostic standard, is not a suitable first line screening test.

Echocardiography

Echocardiography is widely accepted by the medical community as the first-line non-invasive diagnostic tool for PH and CTEPH specifically. Transthoracic echocardiography is a non-invasive, simple test and can be used to image structural and functional effects of PH on the heart as well as to estimate the pulmonary artery pressure from continuous Doppler measurements. However and especially in patients with mild disease, both false positive and false negative estimates may occur due to the lack of precision in estimating the pulmonary artery pressure (reported range -19 mmHg to 18 mmHg) [58]. Six cohort studies including 1045 patients after an episode of acute PE reported the incidence of CTEPH using echocardiography as the first diagnostic test. For every correct diagnosis of CTEPH, echocardiography appeared to be false positive in three patients, who were consequently incorrectly referred for further invasive diagnostic tests (**Table 2**) [19, 37, 59-62]. Also, performing echocardiography in all patients with a history of acute PE has been shown to be cost-ineffective due to the low diagnostic yield of less than 1% [19]. Lastly, in patients with severe tricuspid regurgitation, transthoracic echocardiography cannot be used to exclude CTEPH [2]. For all above reasons, the ESC

Table 2. Post PE patients screened for CTEPH with echocardiography.

Article	Number of patients screened with echocardiography	Number of patients with an abnormal echocardiography result	Number of patients diagnosed with CTEPH (n, %)
Giuliani *et al* 2014[59]	111	15	5 (33)
Guerin *et al* 2014[37]	146	8	7 (88)
Kayaalp *et al* 2014[61]	85	31	5 (6)
Klok *et al* 2015[60]	134	25	4 (16)
Klok *et al* 2010[19]	459	44	6 (14)
Marti *et al* 2010[62]	110	23	10 (44)
Total	1045	146	37 (25)

Note: PE: pulmonary embolism. CTEPH: chronic thromboembolic pulmonary hypertension.

guideline recommend against routine application of all patients who are treated for acute PE to transthoracic echocardiography during follow-up [2].

V/Q lung scintigraphy

Multiple wedge-shaped perfusion defects with normal ventilation scan is typical for CTEPH while a normal scan results virtually rules out CTEPH. Previous studies have reported that in patients suspected of having PH, V/Q lung scintigraphy has a sensitivity of 96%-100% and a specificity of 86%-95% for detection of CTEPH using RHC as diagnostic standard [40-42]. However it has been estimated that 10-30% of PE patients have persistent perfusion defects despite adequate anticoagulant treatment, contributing to an average specificity of V/Q scintigraphy for CTEPH in unselected PE survivors [22, 63]. Taking the costs and associated radiation exposure [64] into account, this imaging modality cannot be recommended as a first-line routine screening tool for CTEPH in all PE survivors.

CT pulmonary angiography

CTPA is considered suggestive of CTEPH if it shows intravascular webs, recanalized thrombi, perfusion abnormalities or vascular strictures. In general, CTPA detects less residual PE than V/Q lung scintigraphy [65] and CTPA is more widely available and less costly. Even so, the sensitivity of CTPA is lower than that of V/Q lung scintigraphy, i.e. 51-92% using RHC as diagnostic standard [40, 41]. Consequently, a normal CTPA cannot rule out CTEPH. Also, the subtle characteristics of CTEPH are quite different from those of acute PE and may be misinterpreted by physicians lacking experience in the imaging of CTEPH. Moreover, the radiation exposure of CTPA exceeds that of V/Q lung scintigraphy. In conclusion, CTPA is not the optimal screening instrument for CTEPH after acute PE and guidelines recommend against routine CTPA in the clinical course of acute PE [66].

ECG

Several ECG abnormalities suggestive of the presence of PH include right axis derivation, right ventricular hypertrophy, right ventricular strain, right bundle branch block and QTc prolongation [2]. Conventional ECG assessment however lacks sufficient sensitivity and is not recommended as a screening tool for the detection of PH or CTEPH according to current guidelines [2, 67]. Interestingly, both the combination of several ECG variables as well as three-dimensional electrocardiography, i.e. electrocardiogram-derived ventricular gradient, have been suggested to be sensitive to early changes in right ventricular afterload as well as to clinically overt PH (sensitivity 89% and 97% respectively) [67, 68]. Confirmation of this high sensitivity for PH of both in large studies is however lacking.

Biomarkers

A wide variety of biomarkers have been explored for their potential to diagnose or screen for PH and CTEPH [2, 69]. No valid biomarker for CTEPH or vascular remodelling has however been identified. N-Terminal pro-Brain Natriuretic Peptide (NT-proBNP) is the only biomarker that is being widely used in diagnostic and therapeutic work-up of suspected PH, although it has been shown that it lacks sensitivity as well as specificity to function as stand-alone test for PH or CTEPH screening [2].

Combination of ECG and biomarkers

The combination of ECG and biomarker assessment as diagnostic test for PH has been evaluated in several settings. In one study, none of the 251 patients referred for suspicion of pre-capillary PH was diagnosed with PH in the absence of both a right ventricular strain pattern on ECG and elevated NT-proBNP [70]. In another study, it was shown that ECG assessment (right axis) and NT-proBNP measurement (threshold 100 pg/ml) are major components of a non-invasive algorithm that accurately excludes precapillary PH in patients with systemic sclerosis [5].

The combination of ECG and biomarker assessment has also been studied for its ability to rule out CTEPH. In a case control study, several combinations of ECG characteristics and biomarkers were evaluated to distinguish patients with the post-PE syndrome without CTEPH from patients with confirmed CTEPH [69]. The so called 'CTEPH rule out criteria' consisting of a normal NT-proBNP test result in combination with the absence of three specific electrocardiographic characteristics of right ventricular overload (rSR' or RSr' pattern in lead V1; R:S >1in lead V1 with R >0.5mV and QRS axis >90°; **Figure 1**) were found to be the optimal combination for this purpose, with a sensitivity of 94% (95% confidence interval (CI) 86-98%) and a specificity of 65% (95%CI 56-72%). The area under the receiver-operator-characteristic curve was 0.80 (95%CI 0.74-0.85%) for the diagnosis of CTEPH. Even with high CTEPH prevalences of up to 10%, the negative predictive value of the 'CTEPH rule out criteria' were very high (99%, 95%CI 97-100%).
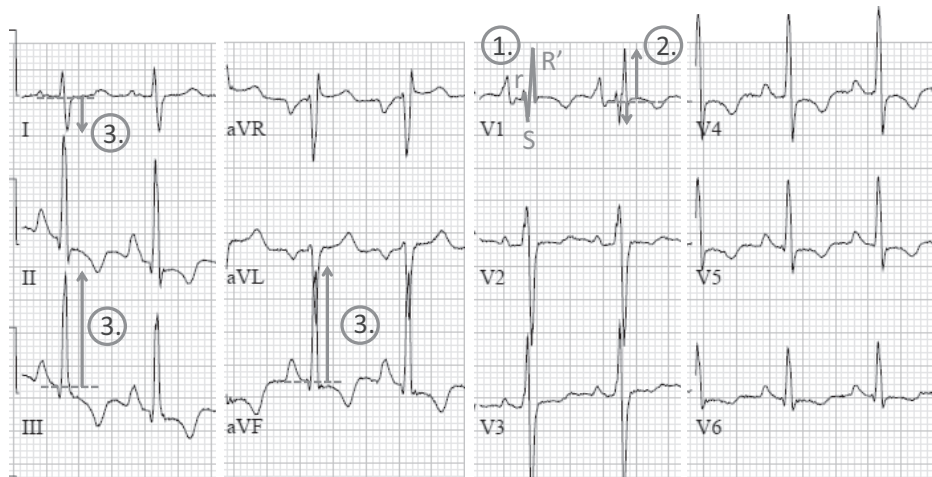
Figure 1. ECG demonstrating the three specific electrocardiographic characteristics of right ventricular overload, the 'CTEPH rule out criteria' .1) Right bundle branch block: rSR' or RSr' pattern in lead V1 with a QRS duration ≥ 120ms; 2) R:S >1 in lead V1 with R>0.5mV and 3) Right QRS axis deviation QRS axis >90°. Note: CTEPH: chronic thromboembolic pulmonary hypertension. ECG: electrocardiography.

The diagnostic accuracy as well as the reproducibility of the 'CTEPH rule out criteria' were recently subjected to external validation in a real-world cohort of PE patients: inter-observer agreement for the adjudication of the ECG characteristics was found to be excellent (kappa-statistic 0.97) and the sensitivity for CTEPH was 100% [60]. A total of 47% of all patients with a recent PE scored none of the 'CTEPH-rule out criteria' positive, of whom none were diagnosed with CTEPH. The high sensitivity of the 'rule-out criteria' comes however at cost of an average specificity and thus false positive results in up to 40% if all patients with one or more 'CTEPH-rule out criteria' criteria present are referred for echocardiography.

Clinical prediction score

In a recent patient-level meta-analysis including 772 PE-survivors without major cardiopulmonary comorbidities, a clinical prediction score for diagnosis of CTEPH after PE was developed, the so called 'CTEPH prediction score' [71]. Factors associated with the development of CTEPH were unprovoked PE, known hypothyroidism, symptom onset >2 weeks before PE diagnosis, right ventricular dysfunction on CT or echocardiography, known diabetes mellitus and thrombolytic therapy or embolectomy (**Table 3**), all scored at the moment of PE diagnosis. The CTEPH prediction score has a 2-level outcome, with 6 points or less indicating low-risk (73% of patients, 0.38% CTEPH incidence) and more than 6 points indicating high risk (27% of patients, 10% CTEPH incidence). The area under the receiver operating characteristic curve of this score was 0.89. The score still awaits external validation [71].

Table 3. CTEPH prediction score.

Unprovoked PE	+6 points
Known hypothyroidism	+3 points
Symptom onset > 2 weeks before PE diagnosis	+3 points
Right ventricular dysfunction on computed tomography or echocardiography	+2 points
Known diabetes mellitus	-3 points
Thrombolytic therapy or embolectomy for the acute PE event	-3 points

Note: Cut-off points: low risk (-6 to 6 points), high risk (>6 points).
CTEPH: chronic thromboembolic pulmonary hypertension. PE: pulmonary embolism.

Combining the 'CTEPH prediction score' with the 'rule-out criteria' might constitute a feasible and cost-effective strategy for standardized follow-up after acute PE. At present, this screening algorithm is being evaluated in an international multicentre prospective management study (Clinical Trials.gov identifier NCT02555137). This study will likely answer the question whether the implementation of screening will lead to an earlier CTEPH diagnosis.

THE COSTS OF CASE-FINDING SHOULD BE ECONOMICALLY BALANCED IN RELATION TO POSSIBLE EXPENDITURE ON MEDICAL CARE AS A WHOLE AND CASE-FINDING SHOULD BE A CONTINUING PROCESS AND NOT A "ONCE AND FOR ALL" PROJECT.

As outlined above, studies focussing on the cost-effectiveness of any screening strategy are currently unavailable. Even so, especially screening algorithms that apply inexpensive non-invasive tests such as clinical probability assessment, ECG and/or NT-proBNP measurement, and if indeed associated with an earlier CTEPH diagnosis and increased likelihood of operability, may very well be associated with an overall reduction in costs and a beneficial incremental cost-effectiveness ratio. Considering the high incidence of acute PE, it will not be appropriate to actively recall every single patient with a history of PE to be screened for CTEPH in a single effort, but -if a screening strategy is proven accurate and cost-effective- it should become incorporated in routine care for all future PE patients.

CONCLUSION

Despite several compelling reasons for early identification of CTEPH and the current undesirable long diagnostic delay, firm conclusions to answer the question whether 'we

should screen for CTEPH after acute PE or not' cannot be drawn yet due to lack of conclusive evidence. Even so, bearing in mind the principles of Wilson and Jungner, screening for CTEPH fulfils the basic criteria with regard to magnitude and frequency of the health problem, the ability to recognize early and advanced disease stages, and the availability of diagnostic tests as well as effective treatment. The main questions that still need to be answered are 1) whether the implementation of one of the candidate screening tests indeed leads to an earlier CTEPH diagnosis, 2) whether earlier CTEPH diagnosis by screening is associated with better operability and improved prognosis and 3) whether CTEPH screening algorithms prove to be cost-effective. For now, we recommend not to screen unselected PE patients for CTEPH with echocardiography, CTPA or VQ lung scintigraphy in accordance with current European guidelines [2]. Clinicians should nonetheless maintain a low threshold of suspicion for CTEPH after acute PE and pursue targeted diagnostic tests in patients who report new or persistent dyspnoea after three months of anticoagulant treatment or symptoms of right heart failure. We speculate that in a few years from now, routine assessment of the presence of CTEPH with subsequent application of non-invasive tests in all patients with a recent PE diagnosis will become the standard of care.

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