The aftermath of acute pulmonary embolism: approach to persistent functional limitations

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Why, whom, and how to screen for chronic thromboembolic pulmonary hypertension after acute pulmonary embolism

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ABSTRACT

Chronic thromboembolic pulmonary hypertension (CTEPH) is considered a long-term complication of acute pulmonary embolism (PE). Diagnosing CTEPH is challenging, as demonstrated by a considerable diagnostic delay exceeding 1 year, which has a negative impact on the patient's prognosis. Dedicated screening CTEPH strategies in PE survivors could potentially help diagnosing CTEPH earlier, although the optimal strategy is unknown. Recently published updated principles for screening in medicine outline the conditions that must be considered before implementation of a population-based screening program. Following these extensive principles, we discuss the pros and cons of CTEPH screening, touching on the epidemiology of CTEPH, the prognosis of CTEPH in the perspective of emerging treatment possibilities and potentially useful tests and test combinations for screening. This review provides a modern perspective on CTEPH screening including a novel approach using a simple non-invasive algorithm of sequential diagnostic tests applied to all PE survivors.

INTRODUCTION

Chronic thromboembolic pulmonary hypertension (CTEPH) is considered a potentially fatal long-term complication of acute pulmonary embolism (PE).[1,2] Early detection of CTEPH allows timely initiation of one of the available treatment options, preferably pulmonary endarterectomy (PEA).[3] Notably, current diagnostic delay is reported to range from 14 up to 24 months.[4,5] Although screening programs might be an important tool to reduce this unacceptable delay, those are currently not part of routine care for patients diagnosed with PE.[6]

Screening in medicine refers to application of tests, examinations or procedures in apparently healthy individuals to early detect unrecognized or early stage disease.[7] The target population itself would not have sought medical attention, but should be able to benefit from treatment or direct preventive action. The purpose of screening is to improve quality of life, prevent disability and reduce (premature) death.[8]

A recent review of our study group has elaborated on the effectiveness of screening for CTEPH based on principles of early disease detection by Wilson and Jungner.[9] Those ten criteria have been defined to simplify the evaluation of screening strategies and their implementation. While these criteria date back from 1968, they are still the most commonly used ones despite major scientific, technological and social developments over the past generation.[10]

Recently, a systematic review including Delphi consensus procedure was performed to define contemporary principles for screening.[11] Those extended principles provide a modern view on population-based screening and guide decisions including several components of screening programs. In this review, these more extensive principles are the basis of addressing an updated perspective on screening for CTEPH, in which we mainly focus on relevant considerations regarding disease and test principles.

1. DISEASE PRINCIPLES

Epidemiology of CTEPH (principle 1)

According to the first principle on screening as shown in **Table 1**, we here explain the epidemiology of CTEPH and the reasons why it concerns an important health problem. A recent meta-analysis summarized 16 studies on follow-up after acute PE, including a total of 4,047 consecutive patients who had been followed for mostly 2 years, ranging from 3 months to 8 years.[12] A weighted pooled incidence rate of CTEPH of 0.13-0.98% was found in all-comers diagnosed with acute PE. While this number likely estimates the prevalence of CTEPH on a population level, in this review we focus on PE survivors

Table 1: Refined set of consolidated screening principles

Domain	Consolidated screening principles (after systematic review and modified Delphi consensus process)
Disease/ condition principles	1. The epidemiology of the disease or condition: should be adequately understood, and the disease or condition should be an important health problem (e.g., high or increasing incidence or prevalence, or causes substantial morbidity or mortality).
	2. The natural history of the disease or condition: should be adequately understood, the disease or condition is well-defined, and there should be a detectable preclinical phase.
	3. The target population for screening: should be clearly defined (e.g., with an appropriate target age range), identifiable and able to be reached.
Test/ intervention principles	4. Screening test performance: should be appropriate for the purpose, with all key components specific to the test (rather than the screening program) being accurate (e.g., in terms of sensitivity, specificity and positive predictive value) and reliable or reproducible. The test should be acceptable to the target population and it should be possible to perform or administer it safely, affordably and efficiently.
	5. Interpretation of screening test results: test results should be clearly interpretable and determinate (e.g., with known distribution of test values and well-defined and agreed cut-off points) to allow identification of the screening participants who should (and should not) be offered diagnostic testing and other post-screening care.
	6. Post-screening test options: there should be an agreed course of action for screening participants with positive screening test results that involves diagnostic testing, treatment or intervention, and follow-up care that will modify the natural history and clinical pathway for the disease or condition; that is available, accessible and acceptable to those affected; and that results in improved outcomes (e.g., increased functioning or quality of life, decreased cause-specific mortality). The burden of testing on all participants should be understood and acceptable, and the effect of false-positive and false-negative tests should be minimal.

visiting the outpatient clinic after 3 to 6 months of anticoagulant treatment. The incidence in this latter population was found to be 2.0-4.4%.

The seriousness of this health problem is illustrated by several facts. In the International Prospective CTEPH Registry, the median age was 63 years with a New York Heart Association functional class III or IV in 81% of CTEPH patients at diagnosis.[13] Debilitating symptoms are most commonly exertional dyspnea, edema and fatigue, which give rise to substantial morbidity. Subsequent impaired quality of life, mostly affecting the domains physical capability, psychological wellbeing and social relationships, and impaired functional status illustrate the relevance of appropriate treatment.[14] Available treatment modalities have been shown to have a positive impact on prognosis of CTEPH patients if applied in time. However, the diagnostic delay of CTEPH in current daily practice is longer than 1 year, prohibiting early initiation of therapy.[4,5] Poor healthcare utilization in the diagnostic process was reported for 40 CTEPH patients who consulted a median of 4 different physicians for 13 consultations before the correct diagnosis was made.[4] Remarkably, this delay has been associated with higher pulmonary artery pressures at diagnosis and a higher risk of all-cause mortality, underlining the potential severity of progressive disease.[15]

Table 1: Refined set of consolidated screening principles *(continued)*

Domain	Consolidated screening principles (after systematic review and modified Delphi consensus process)
Program/ system principles	7. Screening program infrastructure: should be adequate and existing (e.g., financial resources, health human resources, information technology, facilities, equipment and test technology), or a clear plan to develop adequate infrastructure, that is appropriate to the setting to allow for timely access to all components of the screening program.*
	8. Screening program coordination and integration: all components of the screening program* should be coordinated and, where possible, integrated with the broader health care system (including a formal system to inform, counsel, refer and manage the treatment of screening participants) to optimize care continuity and ensure no screening participant is neglected.
	9. Screening program acceptability and ethics: all components of the screening program* should be clinically, socially and ethically acceptable to screening participants, health professionals and society, and there should be effective methods for providing screening participants with informed choice, promoting their autonomy and protecting their rights.
	10. Screening program benefits and harms: the expected range and magnitude of benefits (e.g., increased functioning or quality of life, decreased cause-specific mortality) and harms (e.g., overdiagnosis and overtreatment) for screening participants and society should be clearly defined and acceptable, and supported by existing high-quality scientific evidence (or addressed by ongoing studies) that indicates that the overall benefit of the screening program outweighs its potential harms.
	11. Economic evaluation of screening program: an economic evaluation (e.g., cost-effectiveness analysis, cost–benefit analysis and cost–utility analysis) of the screening program, using a health system or societal perspective, should be conducted (or a clear plan to conduct an economic evaluation) to assess the full costs and effects of implementing, operating and sustaining the screening program while clearly considering the opportunity costs and effect of allocating resources to other potential non-screening alternatives (e.g., primary prevention, improved treatments and other clinical services) for managing the disease or condition.
	12. Screening program quality and performance management: the screening program should have clear goals or objectives that are explicitly linked to program planning, monitoring, evaluating and reporting activities, with dedicated information systems and funding, to ensure ongoing quality control and achievement of performance targets.

Natural history and diagnosis of CTEPH (principle 2)

CTEPH is the only curable presentation of pulmonary hypertension. Chronic obstruction of proximal pulmonary arteries by persistent thrombi triggers small-vessel arteriopathy in both obstructed areas and downstream from occlusions. Whereas inflammation, impaired fibrinolysis and deficient angiogenesis have been associated with incomplete resolution of PE, the molecular process underlying microvasculopathy has not been fully elucidated yet.[16] Excessive blood supply from bronchial and systemic arteries presumably plays a role in the evolution of the disease.[17] The resulting increased pulmonary vascular resistance is associated with progressive right ventricular (RV) dysfunction, with ultimately RV failure.[18,19]

Both RV dysfunction and dead space ventilation may limit physical performance and cause symptoms.[1] Progressive dyspnea is the main symptom of CTEPH, although this may develop slowly, taking months to years after the acute event.[20] Notably, even after

an adequately treated acute PE, up to 50% of patients report persistent dyspnea and/or functional limitations, also referred to as the post-PE syndrome.[21-27] CTEPH is considered the extreme manifestation of this syndrome. In a considerable proportion of patients with post-PE syndrome, chronic thrombi are detected without causing increased pulmonary artery pressures, a condition also referred to as chronic thromboembolic disease (CTED). It has been argued that CTED is an early manifestation of CTEPH but this remains to be proven.[28]

CTEPH is a well-defined disease with strict diagnostic criteria. Those are traditionally obtained after ≥3 months of adequate therapeutic anticoagulation: 1) ≥1 mismatched segmental perfusion defect demonstrated by ventilation/perfusion scanning; 2) mean pulmonary artery pressure (mPAP) ≥ 25 mmHg at rest measured by invasive right heart catheterization; 3) pulmonary capillary wedge pressure ≤ 15 mmHg.[3] The evolving definition of PH set at the lower threshold of 20 mmHg is still a matter of debate in the specific setting of CTEPH, mostly because it has not been conclusively established whether endarterectomy of significant chronic vascular occlusions despite mPAP of 20-24 mmHg will result in improved outcomes.[1,29-31] The preclinical phase of CTEPH consists of a nonspecific presentation and a sometimes long honeymoon period.[5,32,33] In addition, poor awareness among treating physicians and highly variable PE follow-up procedures all contribute to the diagnostic delay.

The target population for screening (principle 3)

Three subgroups of PE patients should definitely be subjected to a diagnostic evaluation for CTEPH. The first group of patients consists of those with (progressive) signs or symptoms that may relate to CTEPH, particularly dyspnea and/or right heart failure. As argued above, this may involve up to half of all PE patients: symptoms such as persistent dyspnea do not allow easy differentiation between CTEPH and alternative explanations of the post-PE syndrome, while progressive right heart failure is more specific for underlying CTEPH.

The second subgroup of the target population consists of PE patients with a high pre-test probability for CTEPH. Several risk factors for or predisposing conditions of CTEPH have been identified, although clear causality has not yet been established for most of these conditions (**Table 2**).[6] Moreover, the absolute risk of CTEPH associated with these is unknown. A post-hoc analysis of 3 large observational studies in PE patients aimed to construct a CTEPH prediction score based on clinical and demographic predictors of CTEPH. A 6-variable CTEPH prediction score was derived, providing well-defined cut-off values with good interobserver agreement.[34,35] Although prospective validation has not been performed yet, to date, this CTEPH prediction score is the best studied tool for assessment of pre-test probability of CTEPH in PE patients.

Table 2: Risk factors or predisposing conditions for CTEPH

Findings obtained at the moment of acute PE diagnosis	Concomitant chronic diseases and conditions predisposing to CTEPH (documented at PE diagnosis or at 3-6 month follow-up)
CTPA findings suggestive of pre-existing chronic thromboembolic disease	Thrombophilic disorders, particularly antiphospholipid antibody syndrome and high coagulation factor VIII levels
Central thrombi in pulmonary arteries on CTPA	Non-O blood group
Echocardiographic signs of PH/RV dysfunction	Hypothyroidism treated with thyroid hormones
Previous episodes of PE or DVT	Myeloproliferative disorders
Unprovoked PE	History of cancer
	Infected chronic i.v. lines or pacemakers
	Ventriculo-atrial shunts
	Inflammatory bowel disease
	Chronic osteomyelitis
	History of splenectomy

Abbreviations: CTPA, computed tomographic pulmonary angiography; DVT, deep vein thrombosis; i.v., intravenous; LV, left ventricular; PH, pulmonary hypertension; RV, right ventricular.

Third, established radiological signs suggestive of CTEPH at the moment of acute PE diagnosis justify a dedicated work-up for CTEPH. Growing evidence supports the hypothesis that the clinical presentation as well as computed tomography of pulmonary arteries (CTPA) images of CTEPH often mimic acute PE, presumably resulting in diagnostic misclassification. Two studies have emphasized the benefit of close reading of the index CTPA performed to diagnose acute PE.[36-39] On these index scans of patients diagnosed with CTEPH during follow-up, typical radiological characteristics of CTEPH were often present, as judged by expert thorax radiologists. In one of these studies, 6 independent radiological predictors for CTEPH (in addition to RV/LV ratio >1; **Figure 1**) were derived.[37] The presence of ≥3 predictors had a sensitivity of 70% (95% confidence interval [CI] 55-82) and a specificity of 96% (95% CI 86-100) for a future CTEPH diagnosis. Prospective studies are needed to confirm the potential diagnostic yield of implementing a standardized CTPA evaluation for concomitant signs of CTEPH in (the follow-up of) patients with acute PE. In addition to closer CT reading, valuable information can be extracted from echocardiography at the moment of the PE diagnosis: an estimated mPAP of >60 mmHg is highly predictive of concurrent CTEPH.[3,36]

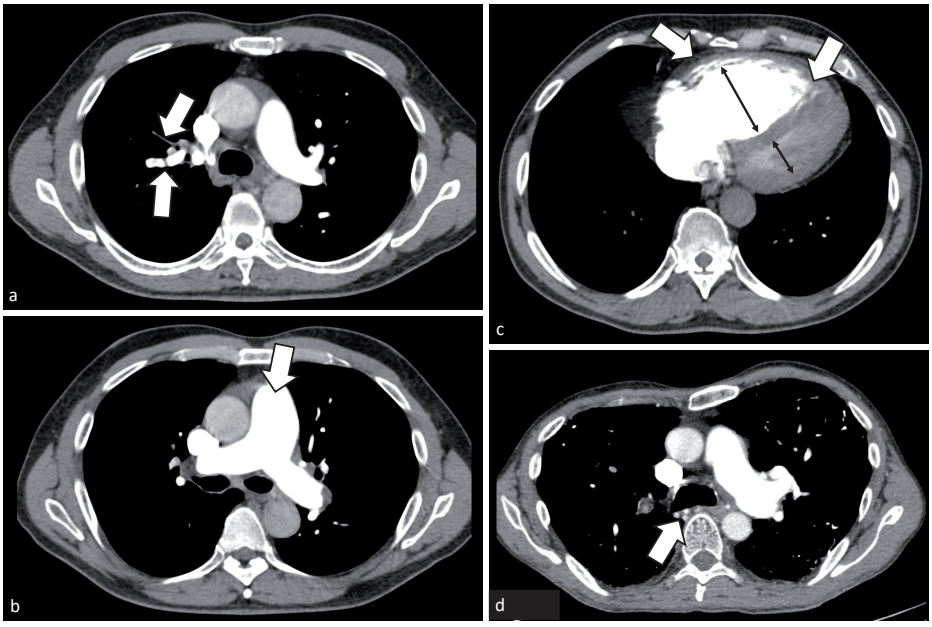

Figure 1: CTPA image showing the 6 radiological predictors of CTEPH, in addition to RV/LV diameter ratio of >1.0

Note: a) intravascular web and arterial retraction; b) dilated main pulmonary artery; c) flattening of the interventricular septum, RV hypertrophy and RV/LV diameter ratio >1.0; d) dilated bronchial arteries.

Abbreviations: CTPA, computed tomography pulmonary angiography; RV, right ventricle; LV, left ventricle.

2. TEST PRINCIPLES

Screening test performance and interpretation of its results (principles 4 & 5)

The initial step in the diagnostic process for CTEPH is a widely available transthoracic echocardiography. Echocardiographic probability of PH is based on both tricuspid regurgitation velocity and other signs of PH concerning the ventricles, pulmonary artery, inferior vena cava and right atrium (**Figure 2**). Those findings are used to differentiate between low, intermediate or high probability of PH. The next diagnostic step is a ventilation/perfusion (V/Q) scan in all individuals with echocardiographic intermediate or high suspicion of CTEPH. If abnormal, right heart catheterization (RHC) is the diagnostic standard for CTEPH, which should preferably be performed in a PH/CTEPH expert center. Furthermore, imaging techniques including CTPA, digital subtraction pulmonary artery angiography and/or magnetic resonance imaging contribute to the evaluation of surgical accessibility and alternative treatment options.[1,3,6]

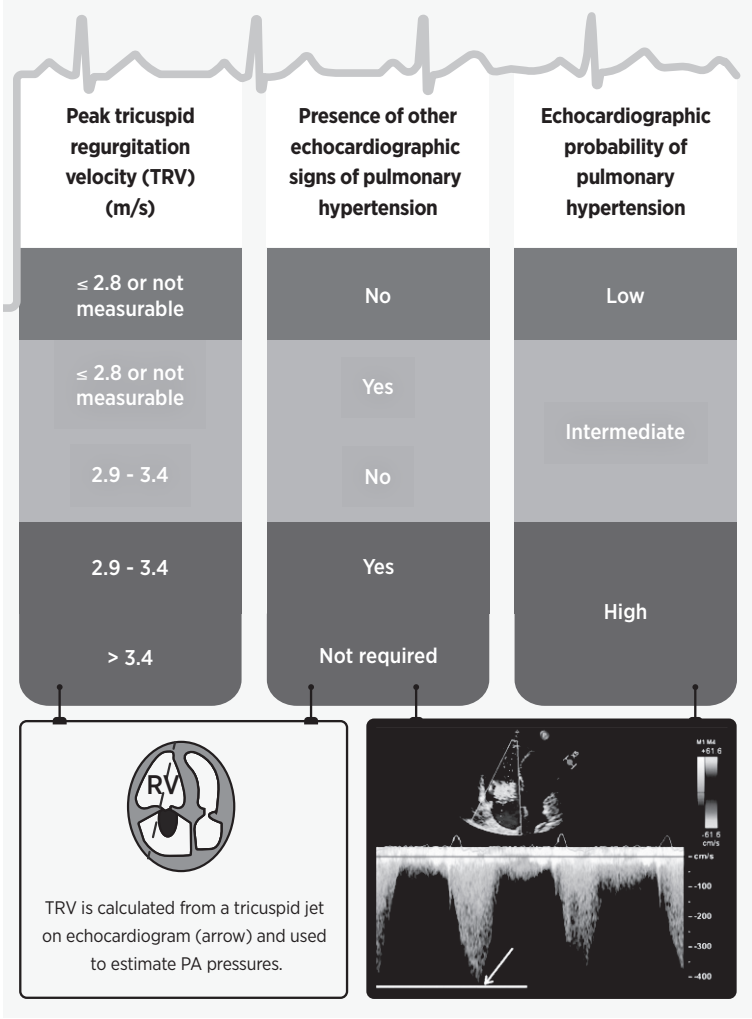

Figure 2: Echocardiography assessment probability of PH, initial test in diagnostic work-up for CTEPH performed after 3 to 6 months of adequate anticoagulant treatment

Note: Other echocardiographic signs suggesting PH used to assess the probability of PH in addition to TRV measurements in the '2015 ESC/ERS Guidelines for the diagnosis and treatment of PH' relate to: RV/LV basal diameter ratio >1.0, flattening of the interventricular septum (LV eccentricity index >1.1 in systole and/or diastole), RV outflow doppler acceleration time <105 msec and/or midsystolic notching, early diastolic pulmonary regurgitation velocity >2.2 m/sec, PA diameter >25 mm, 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.[3]

Abbreviations: PA, pulmonary artery; PH, pulmonary hypertension; RV, right ventricle; LV, left ventricle; TRV, tricuspid regurgitation velocity.

In search of a first-line screening test, RHC is unsuitable given its invasive nature. A V/Q scan is not an ideal test for routine screening either, given its suboptimal specificity, limited availability, radiation exposure and associated costs.[40,41] CTPA can also not be

recommended in standardized follow-up after PE, mainly because this test is unable to accurately exclude CTEPH. Echocardiography obviously has a central role in the work-up for PH since it is a non-invasive test which visualizes structural as well as functional changes of the heart due to PH. The (few) disadvantages relevant to consider are: 1) the need for specific expertise for performing and interpreting the results; 2) an estimation rather than a measurement of pulmonary artery pressures with a suboptimal sensitivity; 3) the high amount of false-positive test results; and 4) the established cost-ineffectiveness when performed as a stand-alone screening test in all PE patients.[23,42,43]

Another approach to screen for CTEPH is a simple algorithm of sequential diagnostic tests applied to all PE survivors, which provides more efficient use of health care resources compared to subjecting all patients to echocardiography. In the 2019 European Society of Cardiology/European Respiratory Society Guidelines for the diagnosis and management of acute PE, for the first time a dedicated follow-up strategy after acute PE was proposed.[6] This strategy recommends to perform echocardiography in specific PE patients with persistent (or new onset) dyspnea or functional limitations, and to consider it in those with risk factors or predisposing conditions for CTEPH. Following this strategy, echocardiography is not required in all but still in a considerable number of patients. Importantly, it has never been formally tested in a well-designed outcome study.

Alternatively, the InShape II algorithm aims at ruling out CTEPH early in the course of acute PE limiting the number of required echocardiograms. This algorithm starts at least three months after acute PE by determining a pre-test probability based on the CTEPH prediction score, the presence of symptoms suggestive of CTEPH and the CTEPH rule-out criteria.[34,44,45] Patients are subjected to the CTEPH rule-out criteria if they either have a CTEPH prediction score of more than 6 points or in case symptoms are present, allowing discrimination of those who should and should not be offered echocardiography. The CTEPH rule-out criteria consist of assessment of the presence of any of the 3 ECG criteria of RV pressure overload, or an abnormal age- and gender dependent NT-proBNP level. The InShape II study is currently evaluating this algorithm in a prospective, multicenter outcome study in consecutive acute PE patients (NCT02555137). Baseline results of the InShape II study showed that echocardiography was indicated in only 19% of patients, and the expected CTEPH incidence was found within 6 months following the index event (**Figure 3**).[46] Follow-up results will ultimately determine the sensitivity of the algorithm, and are expected by late 2020.

Course of action after screening strategy (principle 6)

A strict prerequisite for medical screening is one or more treatment options that result in improved outcomes. Indeed, 3 treatment options are available at PH/CTEPH expert centers.[3] CTEPH is potentially curable by PEA, comprising surgical removal of

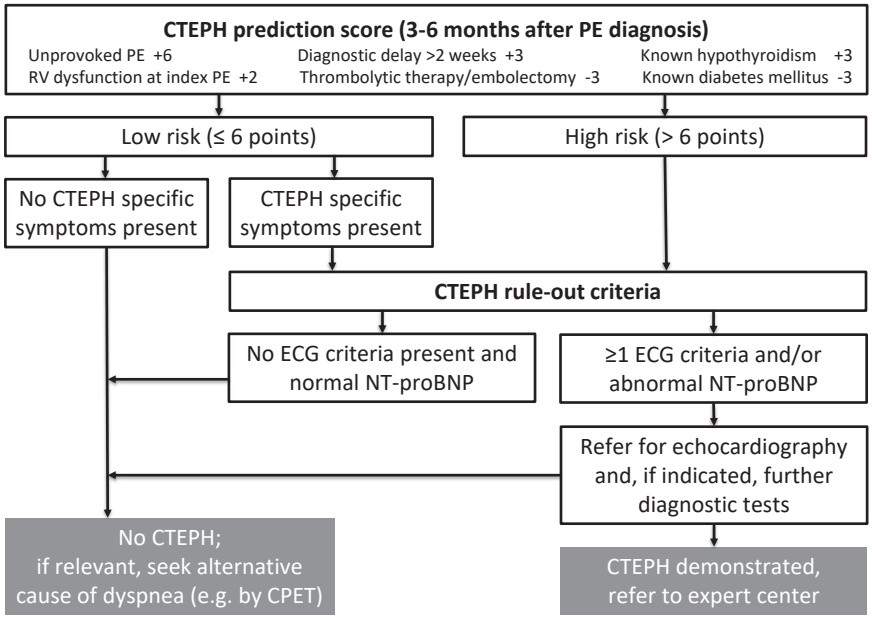

Figure 3: InShape II screening algorithm for early detection of CTEPH
Note: In case the 'CTEPH prediction score' indicates a high pre-test probability of CTEPH (>6 points), or if symptoms suggestive of CTEPH are present, ECG reading and an NT-proBNP assessment are performed as part of the 'CTEPH rule-out criteria'. Only if these criteria cannot rule out possible PH, patients are referred for echocardiography, and further diagnostic testing if necessary.
RV dysfunction is assessed on CTPA or echocardiography at the moment of index PE. The ECG criteria of RV pressure overload are: 1) rSR' or rSr' pattern in lead V1, 2) R:S >1 in lead V1 with R >0.5 mV and 3) QRS axis >90°.
Abbreviations: RV, right ventricular; ECG, electrocardiography; NT-proBNP, N-terminal pro-brain natriuretic peptide; PH, pulmonary hypertension.

all obstructive thromboembolic material.[47] This is the treatment of choice for those who have surgically accessible disease.[3,48] In the approximately 40% of CTEPH patients deemed inoperable, PH targeted medication is often initiated.[5] Riociguat, a soluble guanylate cyclase stimulator, is the only currently approved drug for this category of PH patients.[49,50] A significant reduction in pulmonary vascular resistance has been demonstrated in patients treated with riociguat, with concomitant improvement in World Health Organization functional class.

Balloon pulmonary angiography (BPA) is an emerging second option for inoperable CTEPH, or for those with persistent or recurrent pulmonary hypertension after PEA. BPA is an endovascular procedure aimed at widening stenotic or obstructed pulmonary arteries using a balloon catheter.[51-53] On average, 5 BPA sessions are required to improve RV function.[54] BPA treatment has been shown to lead to hemodynamic improvement shortly after the intervention, comparable to results after PEA.[52,55-57] These promising

results have not been confirmed by prospective long-term outcome studies comparing BPA to PEA or medical treatment so far, although studies are ongoing (NCT02634203).

A few decades ago, prognosis was considerably worse without the possibility of PEA as described by a survival rate of approximately 65% at 3 years after diagnosis.[19] Both PEA and BPA treatment have been shown to improve the prognosis. In the pre-BPA era, estimated 3-year survival after PEA was 89%, compared to 70% in non-operated patients despite PH targeted therapy in 61% in the latter group.[59] In a recent registry across non-operated patients, a better prognosis was demonstrated for patients treated with BPA than those who were not, i.e. 3-year survival of 93% versus 78%, respectively.[60]

In addition to prolonged survival, several studies have demonstrated improved health-related quality of life (QoL) following PEA or treatment with PH targeted medication, as measured by QoL questionnaires such as EQ-5D or SF-36.[49,61-65] To date, only one small study has described similar benefit of BPA on QoL.[56]

3. SCREENING PROGRAM PRINCIPLES

Infrastructure and timing (principles 7 & 8)

CTEPH screening is ideally organized by an already existing infrastructure allowing optimization of care continuity and timely access to the screening program for all PE patients. According to current guidelines, outpatient follow-up of acute PE patients is recommended 3-6 months after an acute PE.[6] This seems a useful time point for evaluation of CTEPH, because screening tests can be easily integrated to routine care, i.e. assessment of the presence of symptoms, risk factors or predisposing conditions for CTEPH, performing an electrocardiogram (ECG) and/or determining the N-terminal pro-brain natriuretic peptide level (NT-proBNP). Moreover, physical recovery of acute PE is expected to be achieved by this time. Lastly, a CTEPH diagnosis requires an adequate anticoagulant treatment of at least 3 months.[3,66]

Ethics and acceptability to screening participants (principles 9 & 10)

All the components of the screening methods outlined above are clinically, socially and ethically acceptable, mainly because of their non-invasive nature. Any patient should be clearly informed about the pros and cons of a particular test within a screening program. For optimal use of healthcare resources, we propose to perform echocardiography only in those patients with a high pre-test probability of CTEPH and in case biomarker or ECG results cannot rule out the possibility of RV pressure overload. If proven accurate, safe and affordable by ongoing studies, such a screening strategy should become incorporated in routine care for all future PE patients.

Economic evaluation (principle 11)

Large studies focusing on cost-effectiveness of CTEPH screening strategies in PE patients have not been performed so far. It has been reported that the reduction of diagnostic delay in CTEPH patients would yield a substantial increase in quality-adjusted life years (QALY), without considering costs of screening tests themselves.[67] Improved survival and quality of life were achieved at the expense of an incremental cost-utility ratio of maximally €25,000 per QALY, which is far below the deemed acceptable limit of €20,000 to 80,000 according to Dutch health-economic standards. Importantly, those gains against a beneficial price still must be confirmed by taking into account all costs accompanied by screening programs.

CONCLUSION

CTEPH is a rare disease that is potentially curable if treatment is initiated in time. CTEPH fulfils the criteria to consider screening because the diagnostic criteria of CTEPH are well-defined, it has a major impact on patients' lives, it is associated with high mortality, it is being diagnosed too late in current practice, treatment options have been shown to considerably improve the prognosis and the target population for screening is clear. A diagnostic evaluation of CTEPH is required in PE patients with signs or symptoms suggestive of CTEPH, in those with radiological signs matching CTEPH or in case of a high pre-test probability for CTEPH. In search of an accurate and reliable first-line screening method, several imaging tests have proven to be inappropriate as a stand-alone screening test. An alternative and promising approach to earlier diagnosis of CTEPH is a simple algorithm of sequential diagnostic tests applied to all PE survivors. Importantly and, needless to say, the accuracy, safety and cost-effectiveness of this (or comparable) screening program need to be proven before implementation in routine care is justified. Ongoing studies will provide sufficient evidence to allow for stricter recommendations in future guidelines, which is the ultimate road towards increasing awareness for CTEPH among PE caretakers.

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