Pulmonary embolism : diagnostic management and prognosis

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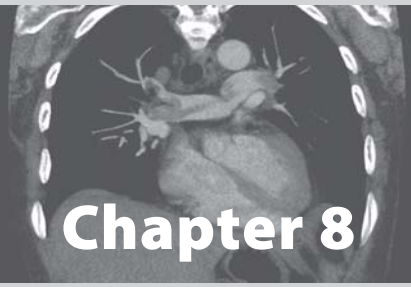

Chapter 8

Prospective cardiopulmonary screening program to detect chronic thromboembolic pulmonary hypertension in patients after acute pulmonary embolism

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Haematologica 2009; in press

ABSTRACT

Rationale

Chronic thromboembolic pulmonary hypertension (CTEPH) after pulmonary embolism (PE) is associated with high morbidity and mortality. Understanding the incidence of CTEPH after PE is important for evaluating the need for screening but also debated as a result of different inclusion criteria among previous studies. We determined the incidence of CTEPH after acute PE in an unselected patient cohort, and the utility of a screening program for this disease.

Methods

A cohort screening study in an unselected series of consecutive patients (n=866) diagnosed with acute PE between January 2001 and July 2007 was conducted. All patients who were not previously diagnosed with pulmonary hypertension (PH) and had survived until study inclusion were invited for echocardiography. Patients with echocardiographic suspicion of PH underwent complete work-up for CTEPH, including ventilation-perfusion scintigraphy and right heart catheterization.

Results

After an average follow-up of 34 months and from all 866 patients, PH was diagnosed in 19 patients by routine clinical care and in 10 by our screening program; 4 patients had CTEPH, who were all diagnosed by routine clinical care. The cumulative incidence of CTEPH after all cause PE was 0.57% (95% confidence interval [CI] 0.02-1.2%) and after unprovoked PE 1.5% (95% CI 0.08-3.1%).

Conclusion

The incidence of CTEPH after PE in our large and unselected patient cohort was 0.57%. Because of this low incidence and the very low yield of the echocardiography based screening program, wide scale implementation of prolonged follow-up including echocardiography of all patients with PE to detect CTEPH seems not warranted.

INTRODUCTION

Chronic thromboembolic pulmonary hypertension (CTEPH) is a life-threatening condition characterized by intraluminal thrombus organization and fibrous stenosis or complete obliteration of the pulmonary arteries.[1] CTEPH has commonly been associated with acute pulmonary embolism (PE), although the pathogenesis of impaired clearance of acute thrombi and the resulting vascular remodeling is unknown, and a history of symptomatic venous thromboembolism (VTE) is lacking in 31–42% of the patients diagnosed with CTEPH.[1-3]

The incidence of CTEPH has been reported to be between 0.1% and 8.8% in patients after acute PE.[1,4-7] This wide range can be explained by important differences in the inclusion and diagnostic criteria between these previous studies: selection of patients was often based on the etiology of the acute PE, patients with other comorbid conditions associated with pulmonary hypertension were frequently excluded and the diagnosis of CTEPH was not always confirmed by right heart catheterization.[1,4-7]

Since CTEPH is a very serious but potentially treatable disease, the exact incidence of CTEPH in the clinical course of acute PE is of particular interest. High frequencies of 3.8 to 8.8%[4,6] would suggest the need for prolonged follow-up after discontinuation of anticoagulant therapy including specific screening programs for CTEPH by echocardiography, whereas lower frequencies would not.

The purpose of this study was to evaluate the efficacy of a screening program for CTEPH in patients after acute PE. This evaluation was based on the overall incidence of CTEPH and the additional utility of this screening program on top of standard clinical care. Accordingly, we performed a prospective cohort screening study evaluating the occurrence of CTEPH in an unselected large series of patients diagnosed with acute PE.

METHODS

Patients

Consecutive patients diagnosed with a first or recurrent episode of acute PE in the period between January 1st 2001 and July 1st 2007 of an academic (Leiden University Medical Center, Leiden, the Netherlands) and affiliated teaching hospital (Medical Center Haaglanden, The Hague, the Netherlands) were eligible for study inclusion, irrespective of age, medical history or comorbid conditions. Neither of these 2 hospitals serves as a tertiary referral center for CTEPH. All patients diagnosed and treated for acute PE are registered in a database by physicians of all clinical specialties of both hospitals. For the purpose of this study, we have crosschecked this database with data from the radiology department to ensure no patients were missing. The diagnosis of acute PE was verified for all registered patients according to predefined criteria which were intraluminal filling defects on pulmonary angiography or computed tomography

pulmonary angiography (CTPA), high probability ventilation perfusion scintigraphy (VQ-scan) or intermediate probability VQ-scan in combination with objectively diagnosed deep venous thrombosis (DVT).[8] All patients fulfilling these criteria were included in this analysis. Unprovoked PE was defined as PE occurring in the absence of the following risk factors: active malignancy, immobility more than 3 days or recent long flight, recent surgery or fracture of extremity, pregnancy or peri-partum period, hormone replacement therapy and use of oral contraception. Patients were initially treated with at least 5 days of either unfractioned heparin aiming at a 1.5 to 2.5 prolongation of the activated partial thromboplastin time, or weight based therapeutic doses of LMWH, followed by vitamin K antagonists for a period of at least 6 months with a target international normalized ratio (INR) of 2.0 to 3.0.[9] In patients with severe acute PE, anticoagulant treatment was preceded by administration of thrombolytic drugs, thrombosuction or surgical embolectomy according to the judgment of the attending clinician. Clinical follow-up and treatment monitoring after hospital discharge were performed in the local pulmonary, internal or vascular medicine outpatient clinic as well as in the anticoagulation clinic.

Outcome

Primary outcomes of this study were the incidence of CTEPH and the effectiveness of our screening program. Criteria for the diagnosis of CTEPH were mean pulmonary artery pressures assessed by right heart catheterization exceeding 25 mmHg and normal pulmonary capillary wedge pressure in combination with an abnormal perfusion scintigram and signs for distal or central CTEPH on conventional pulmonary angiography.[10,11] CTEPH was considered excluded in case of a normal perfusion scintigram.[10,11]

Procedures

The original admission and outpatient medical charts of all patients diagnosed with acute PE in the registration period were systematically reviewed using predefined criteria. Only patients with geographical inaccessibility (living outside the Netherlands) precluding follow-up were excluded from study participation. Data regarding diagnostic management, etiology, treatment and documented clinical course of the acute PE at registration as well as recurrent episodes, and established diagnosis of pulmonary hypertension were assembled. For all eligible patients who had died before study inclusion (July 2007), time and cause of death were extracted from the autopsy report or verified with the treating physician or general practitioner. All surviving patients not identified as having pulmonary hypertension were interviewed by telephone to obtain a detailed medical history, presence of clinical symptoms suggestive of pulmonary hypertension and if applicable, results of recent echocardiography. In addition, information on known risk factors for venous thromboembolism (VTE) and CTEPH were noted down. The latter includes large central emboli, unprovoked VTE, splenectomy, presence of lupus anticoagulant or antiphospholipid antibodies, chronic inflammatory conditions and ventriculo-atrial shunts.[12] Furthermore, all these latter patients were invited for a single visit to our vascular medicine

outpatient clinic for a pulmonary hypertension screening by echocardiography. This visit was scheduled between July 1st 2007 and January 1st 2009 and planned at least one year after the index event, or one year after a recurrent thromboembolic episode, to rule out the initial effect of acute PE. All patients who responded to our invitation underwent physical examination and standardized transthoracic echocardiography performed by an experienced technician. This echocardiography was reviewed by an independent expert cardiologist, without knowledge of the patient's medical condition. Echocardiographic criteria for suspected pulmonary hypertension were one or more of the following: 1) maximal tricuspid regurgitation velocity >2.8 m/s, 2) estimated systolic pulmonary artery pressure ≥35 mmHg (maximal pressure gradient across the tricuspid valve calculated by the modified Bernoulli equation plus the estimated right atrium pressure), 3) estimated mean pulmonary artery pressure ≥25 mmHg (estimated systolic pressure plus 2 times enddiastolic pressure as estimated by pulmonary regurgitation enddiastolic velocity divided by 3), 4) borderline value of criterion 1 or 2 in combination with a right ventricular TEI index >0.36 (isovolumic contraction time plus isovolumic relaxation time divided by ejection time), 5) secondary changes associated with pulmonary hypertension, e.g. systolic septal flattening, right ventricular hypertrophy or W-pattern in the right ventricular outflow curve, 6) AcT (acceleration time) <120 or AcT/RVET (right ventricular ejection time) <0.40.[11,13,14] All patients who met one or more of these 6 criteria were suspected of having pulmonary hypertension and underwent further standardized work-up including perfusion lung scintigraphy and right heart catheterization for pressure measurements. The final diagnosis was assessed by an independent expert panel according to our predefined criteria. This study was approved by the Institutional Review Board of both participating hospitals and all patients provided written informed consent.

Statistical analysis

Patients were categorized in 4 sub-groups according to their medical history of single or recurrent and provoked or unprovoked PE. The cumulative incidence of CTEPH after acute PE for all 4 study groups was calculated by the Kaplan-Meier life table method. In addition, we calculated the incidence rates of CTEPH. The number of patient years (py) for both analyses was calculated from the date of the index event until diagnosis of CTEPH was established or ruled out or else until death had occurred, whichever came first. SPSS version 14.02 (SPSS Inc, Chicago, IL) was used for all analysis.

RESULTS

Patients

In 877 patients the diagnosis of acute PE had been established between January 1st 2001 and July 1st 2007. Eleven patients were excluded because of geographical inaccessibility, leaving

866 patients for study inclusion. General characteristics of these patients are shown in Table 1: mean age at registration was 56 years, 410 (47%) were males and 308 patients (36%) had suffered an unprovoked episode of PE. More than 90% of the patients were initially treated with either unfractionated heparin or LMWH alone. A small number of patients additionally received thrombolytic therapy, had a vena cava filter inserted or had surgical embolectomy performed (Table 1). The average follow-up period was 2.8 years.

Table 1. Characteristics of included patients.

	Study patients (n=866)
Age at registration event (years ±SD)	56 ±19
Male sex (n, %)	410 (47)
Unprovoked PE (n, %)	308 (36)
Initial treatment first PE	
Low molecular/unfractioned heparin (n, %)	808 (93)
Thrombolysis (n, %)	38 (4.4)
Surgery, VCF or both (n, %)	20 (2.3)
COPD (n, %)	83 (9.6)
Left sided heart failure (n, %)	42 (4.8)
Overall mortality[§] (n, %)	259 (30)
PE related mortality (n, %)	67 (7.7)
Malignancy related mortality (n, %)	110 (13)
Other (n, %)	82 (9.4)
Number of patient years[‡]	2427

[‡]Number of years from registration date until diagnosis of CTEPH was established or ruled out, or until death had occurred; [§]mortality between registration date and July 1st 2007. PE=Pulmonary embolism, SD=standard deviation, n=number, VCF=vena cava filter, COPD=chronic obstructive pulmonary disease.

Chart review

After reviewing the medical charts of all patients, 19 cases of previously diagnosed pulmonary hypertension were identified (Figure 1) of whom 4 had CTEPH. During the study period 259 patients died, 67 (7.7%) as a direct result of acute (recurrent) PE, 110 (13%) of malignant disease and 82 (9.4%) by other conditions. Of these 259 patients, 185 (71%) had died within the first year after the acute PE, 216 (83%) within 2 years, 238 (92%) within 3 years and 247 (95%) within 4 years. In 69 patients, autopsy reports or echocardiography performed before the patients' death ruled out the presence of pulmonary hypertension. Further, pulmonary hypertension was not adjudicated as cause of death in any of these patients. Therefore, and in accordance with criteria from previous studies[4-7], we assumed that none of these patients had developed CTEPH.

The remaining 588 patients were invited for our screening program. We were able to complete this program in 402 (68%) of them. None of these patients had clinically suspected acute PE at the moment of echocardiography. Echocardiographic criteria for suspected pulmonary

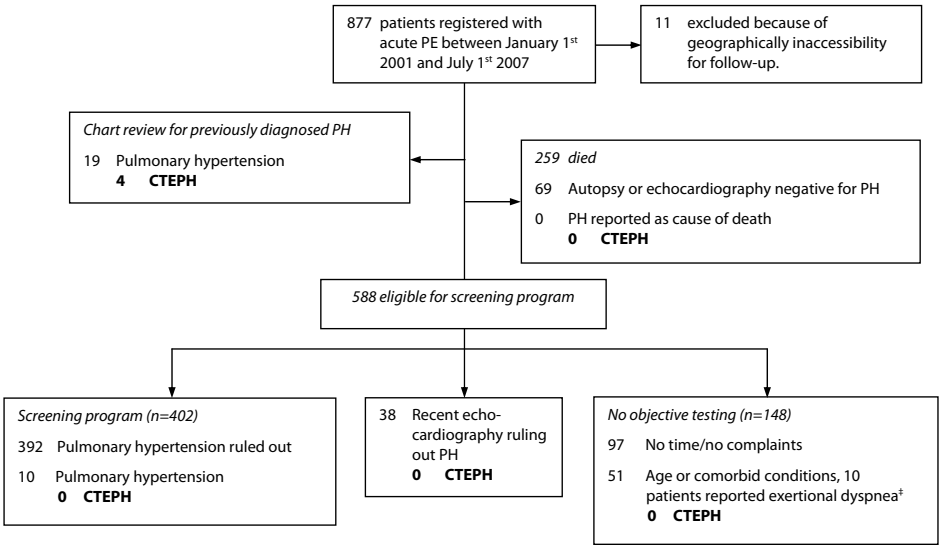

Figure 1. Flowchart of the cohort study. ‡In all 10 patients (100%) with dyspnea, previously diagnosed cardiopulmonary disease reasonably explaining the dyspnea was reported. PE=pulmonary hypertension, PH=pulmonary hypertension, CTEPH=chronic thromboembolic pulmonary hypertension.

hypertension were met by 25 patients. After further clinical work-up and right heart catheterization, pulmonary hypertension was diagnosed in 10 of these patients.

From the 186 patients who did not respond to our invitation, 38 had undergone echocardiography for clinical reasons other than our screening study. None of these patients was diagnosed with pulmonary hypertension. Objective testing for pulmonary hypertension was not performed in the remaining 148 surviving patients. Of these, 97 declared to be in excellent health without any physical complaints and to have no time to be involved in any clinical trials. The final 51 patients were unable to visit our hospital due to old age or comorbid conditions. Most of these patients were over the age of 80 years and suffered from severe cancer. Of these latter 51 patients, 10 reported exertional dyspnea that was reasonably explained by previously diagnosed cardiopulmonary diseases, i.e. chronic obstructive pulmonary disease (COPD), systolic left-sided heart failure, pulmonary cancer, severe anemia or a combination of these conditions. Since none of these patients had unexplained dyspnea[4-6] we assumed that CTEPH was not present in these patients for the purpose of the incidence calculation.

Incidence of CTEPH

Upon study inclusion, 19 patients with a history of PE were already diagnosed with pulmonary hypertension of various causes. Among these, 4 had been diagnosed with CTEPH by routine clinical care, and CTEPH was ruled out by perfusion scintigraphy or pulmonary angiography in the remaining 15 patients. Our screening program identified an additional 10 patients with pulmonary hypertension, but distal or central CTEPH was ruled out in all of these patients after

Table 2. Characteristics of patients with CTEPH.

CTEPH	Sex	Age at first PE (years)	Recurrent PE	Risk factor first PE	Localisation first PE	Thrombolysis, VCF or surgery for first PE	Additional risk factors for CTEPH[§]	Time from first PE to diagnosis CTEPH (days)	Mean PAP at diagnosis CTEPH (mmHg)	NYHA classification at diagnosis CTEPH
1	female	70	Yes	unprovoked	segmental	No	none	118	48	II
2	male	68	No	unprovoked	central	No	none	298	50	III
3	female	59	No	unprovoked	central	No	none	466	48	III
4	female	65	No	unprovoked	segmental	No	none	157	49	III

[§]Additional risk factors for CTEPH to central PE and unprovoked PE, i.e. splenectomy, lupus anticoagulant or antiphospholipid antibodies, chronic inflammatory conditions and ventriculo-atrial shunts.[12] CTEPH=chronic thromboembolic pulmonary hypertension, PE=pulmonary embolism, NYHA=New York Heart Association, PAP=pulmonary artery pressure.

Table 3. Cumulative incidence by the Kaplan-Meier life table method and incidence rates of CTEPH in the study population.

	Number	Cumulative incidence		Incidence rate	
	n CTEPH/n overall	%	95% CI	n/100 py	95% CI
Overall population	4/866	0.57	0.02-1.2	0.16	0.04-0.42
Single event	3/671	0.59	0.02-1.3	0.16	0.03-0.48
Recurrent events	1/195	0.53	0.01-1.6	0.17	0.004-0.93
Unprovoked PE	4/308	1.5	0.08-3.1	0.44	0.12-1.1
Single event	3/220	1.7	0.05-3.7	0.47	0.10-1.4
Recurrent events	1/88	1.2	0.01-3.6	0.37	0.01-2.1
Provoked PE	0/558	0.0	-	0.0	0.0-0.24
Single event	0/451	0.0	-	0.0	0.0-0.31
Recurrent events	0/107	0.0	-	0.0	0.0-1.1

CTEPH=chronic thromboembolic pulmonary hypertension, n=number, CI=confidence interval, PE=pulmonary embolism, py=patient years.

normal perfusion scintigraphy or pulmonary angiography. All 4 patients with CTEPH returned to their physician within 2 years after their first acute PE because of typical symptoms of CTEPH, including exertional dyspnea (Table 2). None of them was found to have additional risk factors for CTEPH or other comorbidity causing pulmonary hypertension. The diagnoses were confirmed by right heart catheterization and measurement of pulmonary artery pressure. Mean time to diagnosis was 260 days. The cumulative incidence of CTEPH in our cohort was 0.57% (4/866, 95% CI 0.02-1.2%) in the overall population, 1.5% (4/308, 95% CI 0.08-3.1%) in the patients with unprovoked PE and 0.0% (0/558) in the patients with provoked PE (Table 3, Figure 2). Incidence rate of CTEPH was 0.16/100 py (95% CI 0.04-0.42/100 py) for the overall population, 0.44/100 py (95% CI 0.12-1.1/100 py) for patients with unprovoked PE and 0.0/100 py (95% CI 0.0-0.24/100 py) for patients with provoked PE (Table 3). Incidences following a single event or recurrent disease were not different between the study groups (Table 3).

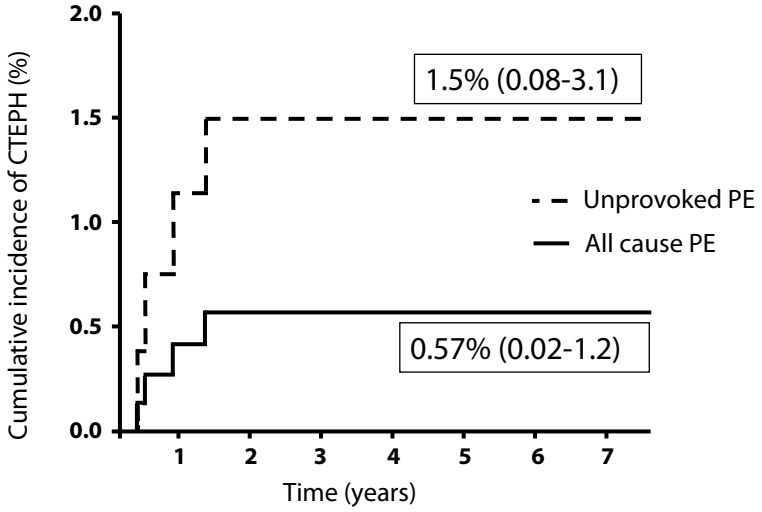

Figure 2. Cumulative incidence of chronic thromboembolic pulmonary hypertension.

Follow-up of patients with CTEPH

Because of distal pulmonary artery involvement, only 1 of the 4 patients with CTEPH was considered suitable for pulmonary endarterectomy. However, this patient refused surgery for personal reasons and was treated with the oral dual endothelin receptor antagonist bosentan.[15] Two additional patients were treated with bosentan of whom one developed severe elevation of transaminases. As a consequence, this treatment was stopped in the latter patient. The final patient did not receive treatment because of the benign clinical presentation of CTEPH (NYHA Class II, satisfactory exercise tolerance without severe desaturation during maximal exercise). At the moment of drafting this paper (April 1st 2009) and after a mean follow-up of 43 months after diagnosis of CTEPH, the clinical condition of all 4 patients was stable.

Efficacy of the screening program

Ten patients with pulmonary hypertension were identified by the screening program in the 402 patients with a history of acute PE but without established pulmonary hypertension, with a mean of 2.8 years after the index thromboembolic event. Pulmonary angiography did not reveal CTEPH in these 10 patients: the pulmonary hypertension was caused by left sided heart disease in 5 patients and by COPD in the remaining 5 patients. All patients with CTEPH from our total study population were previously diagnosed by routine clinical practice.

DISCUSSION

This study has two main findings. First, we observed a 0.57% incidence of CTEPH after acute PE in an unselected large patient series. Second, the yield of a standard screening program to detect CTEPH in patients after acute PE is low, since additional cases of CTEPH to cases identified by routine clinical care, were not detected in our study population.

Understanding of the CTEPH incidence is important to guide the screening and diagnostic strategy in patients after acute PE. The incidence of CTEPH we observed challenges other studies reporting higher incidences ranging from 3.8 to 8.8%.[4-7] There are several reasons for these discrepancies. These previous studies included selected patient cohorts, e.g. excluding patients with transient or permanent risk factors for PE[5] and excluding patients with other conditions associated with pulmonary hypertension.[4-6] In addition, the diagnosis of CTEPH was partly based on results from echocardiography alone without confirmation by right heart catheterization.[6] An incidence of 3.8% was reported in the widely quoted study by Pengo et al, which is considerably higher than the incidence observed in our population.[4] That study and our study mainly differed in inclusion criteria: whereas we only excluded patients who were geographically inaccessible, Pengo additionally excluded all patients with other diseases that could have caused non-thromboembolic pulmonary hypertension (e.g. COPD) or had preexisting exertional dyspnea. Although by design of our study, we are unable to precisely estimate the prevalence of those latter patients in our cohort, they provide a considerable contribution to our sample size. The selection criteria applied by Pengo may have influenced his results, leading to a higher incidence of CTEPH. The duration to diagnosis (within 2 years after diagnosis of PE) on the other hand was well comparable between the 2 studies.

We consider our results to be representative for several reasons. First, we included all patients that presented to the participating hospitals, independently on etiology or severity of the acute PE or presence of comorbid conditions. Our study comprised about 3 times the number of previous reports. All patients received up-to-date anticoagulant treatment regimes with a duration of at least 6 months. Our study involved well over 2400 patient years and only 11 patients (1.3%) were excluded for geographical reasons. Second, we studied all patients with PE, irrespective of persistent symptoms at follow-up and used very sensitive echocardiographic

criteria for establishing the suspicion of pulmonary hypertension.[11,13,14] Third, all cases of CTEPH were diagnosed after invasive hemodynamic measurements and pulmonary artery angiography. Fourth, all patients with CTEPH presented with typical symptoms of pulmonary hypertension and were diagnosed with CTEPH within the first 2 years after their first acute PE. These observations are consistent with the results of earlier studies.[4-7] Finally, the incidence of CTEPH in patients with unprovoked PE in our study was 1.5%. This is in accordance with or within the lower limit of the confidence interval of the incidences described in studies focusing solely on patients with unprovoked PE.[4,5]

It could be reasoned that our estimation of 0.57% represents an underestimation of the incidence of CTEPH since objective testing to confirm or reject this diagnosis was not performed in the complete study population. However, this same issue can be applied to all previous reports on this subject. The vast majority of the non-survivors in our study died within one year after the PE was diagnosed, and a reasonable alternative cause of death was reported in all of them. Furthermore, all cases of CTEPH presented with symptoms of cardiopulmonary impairment. Hence, it is unlikely that we missed cases of CTEPH in the asymptomatic patients who were not able to visit our outpatient clinic or in the patients that had died. Also, plausible alternative diagnoses for dyspnea were confirmed in all 10 patients who reported exertional dyspnea but did not visit our outpatient clinic. Importantly, our estimated incidence of 0.57% is only applicable to patients with a history of acute PE, and not to a more general population.

In this study, a cardiopulmonary screening program to detect CTEPH was evaluated. Although completed by 402 patients, this screening program did not result in any additional patients being detected with a diagnosis of CTEPH beside those patients that were identified by routine clinical practice. In combination with the low frequency of CTEPH, this leads to the conclusion that wide scale implementation of screening programs for CTEPH after acute PE is not warranted and echocardiography to rule out or establish CTEPH should be restricted to patients presenting with characteristic symptoms.

We conclude that CTEPH is a rare complication of acute PE (incidence 0.57%) and that this diagnosis is more frequent in patients with unprovoked acute PE (incidence 1.5%). CTEPH becomes clinically apparent and is diagnosed within the first 2 years following acute PE. Wide scale screening for CTEPH after acute PE results in a very low yield. Although CTEPH occurs infrequently in the clinical course of acute PE, physicians should be aware of this potentially lethal but treatable disease, especially in those patients with unprovoked disease and persistent dyspnea. The direct clinical consequence of our study is that because of the very low incidence of CTEPH after PE, the implementation of extensive follow-up programs for the detection of CTEPH after acute PE seems to be unnecessary.

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