Chronic thromboembolic pulmonary hypertension after the first episode of pulmonary embolism? How often?

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Background. Surviving pulmonary embolism (PE) brings a risk of thromboembolic disease chronicity. Chronic thromboembolic pulmonary hypertension (CTEPH) develops as a result of one or multiple pulmonary embolic events. It is an incapacitating long-term complication of thromboembolic disease with a negative impact on the patient's quality of life and prognosis. Contemporary pharmacological and especially surgical treatment possibilities offer hope for the patient's full recovery, but an early diagnosis is crucial for success.
Methods. In a prospective study cohort of 97 consecutive patients with a proven diagnosis of PE as the first documented thromboembolic event we tried to estimate the incidence of CTEPH during a 2-year follow-up.
Results. Four individuals from our study population developed CTEPH, which represents an incidence of 4.2%.
Conclusion. Chronic thromboembolic pulmonary hypertension in pulmonary embolism survivors is a not uncommon complication deserving the attention of clinicians. Patients at risk of CTEPH can be identified for effective follow-up according to echocardiographic finding of elevated pulmonary artery systolic pressure and NT-proBNP levels at the time of hospital discharge.

Key words: chronic thromboembolic pulmonary hypertension, incidence, pulmonary embolism

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INTRODUCTION

We have been witnessing an increasing interest in pulmonary vasculature diseases during the past two decades. Pulmonary hypertension (PH) has become a widely discussed theme, especially because of the emerging field of treatment modalities. Since 1973 the clinical classification of pulmonary hypertension has undergone evolution up to the last version established in 2008 at Dana Point, California[1], and which was updated at the 5th World Symposium on Pulmonary Hypertension held in March 2013 in Nice, France[2]. Chronic thromboembolic pulmonary hypertension (CTEPH) constitutes class 4 of the current clinical PH classification. It is believed to arise from one or multiple pulmonary thromboembolic events, which probably trigger a series of functional and structural changes in the pulmonary artery (PA) vascular bed. They include organized residua of unresolved thrombi adhering to the vessel wall, endothelial dysfunction, vascular smooth muscle hypertrophy, intimal thickening, in-situ thrombosis, and plexiform lesion formation[3].

The CTEPH incidence data in the literature vary between 0.5% and 9.1% (ref.[4-10]), but CTEPH is believed to develop in about 3.8% of patients surviving the first episode of pulmonary embolism. To contribute to a more accurate estimation of CTEPH incidence we created a project in our tertiary cardiology department for systematic follow-up of all patients with a proven diagnosis of pulmonary embolism.

PATIENTS AND METHODS

Between July 2007 and March 2010 163 patients with a proven diagnosis of PE were hospitalized in our specialized tertiary center. The diagnosis of PE was made by CT pulmonary angiography (CTA), except in one case in which the diagnosis was based on perfusion lung scan and in another case where there was a matching combination of history, clinical presentation, duplex lower limb ultrasonography and echocardiography. Two patients died early (on the second and fourth hospitalization day respectively). We excluded 11 patients with a previous history of venous thromboembolism as well as patients with left heart disease, lung disorders and systemic connective tissue disease. Also excluded from follow-up were non-consenting patients and patients who were apparently non-compliant or in the terminal stage of concomitant disease. The remaining 120 consecutive patients signed an informed consent for 2-year follow up (for the dispensary protocol see Table 1). The informed consent and study design were approved by the local Ethics Committee of our institution. The control pulmonary CTA was not performed to exclude/verify a diagnosis of CTEPH, but only to assess pulmonary embolism residua.

For pulmonary CTA we used a Siemens Somatom Emotion 6 (multidetector CT) with 6x1 mm collimation, pitch 1.8, 130 kV, 110-150 mA, and 0.8 s scanning time. Contrast agent (Iomerone 400, Bracco U.K. Ltd) was injected (Stellant CT Injection Systems, MEDRAD

Table 1. Study dispensary protocol.

On admission	Pulmonary CTA, echocardiography, troponin-T, NT-proBNP and D-dimer assessment
Discharge (7 to 10 days after acute PE)	Echocardiography, troponin-T, NT-proBNP, and D-dimer assessment if elevated initially
6-months after PE	Pulmonary CTA, echocardiography, D-dimer assessment
12-months after acute PE	Echocardiography
24-months after acute PE	Echocardiography

CTA - computed tomography angiography; NT-proBNP - N-terminal fragment of brain natriuretic peptide; PE - pulmonary embolism

Inc. U.S.A) at a rate of 3 mL/s to a total volume of 60-85 ml into a 20-gauge peripheral venous catheter placed in the antecubital fossa. Scanning was performed during the patient's suspended inspiration in the caudo-cranial direction within the space between the diaphragm and a level 2 mm above the aortic arch. Images were evaluated at settings for pulmonary vasculature (window width 700, level 80 HU) and lung parenchyma (window width 1500, level -500 HU). CT scans were evaluated by 2 independent experienced radiologists, blinded from clinical and echocardiographic data. Echocardiography was performed by an experienced sonographer, using PHILIPS SONOS 5500 or GE Vivid 7 according to standard protocol, with an emphasis on pulmonary artery systolic pressure estimation, RV diameter, and RV systolic function. Right ventricle diameter was measured in the parasternal long axis. Signs of RV systolic dysfunction included tricuspid annular plane systolic excursions (TAPSE), peak velocity of this movement in tissue doppler paging mode (Sa_{Tri}), and evaluation of right ventricle free wall hypokinesis. Pulmonary artery systolic pressure estimation was based on peak tricuspid regurgitation jet velocity, and right atrium pressure was estimated according to the diameter and respiratory variations of the inferior vena cava.

On admission blood samples were assessed to determine levels of troponin-T and N-terminal fragments of brain natriuretic peptide precursor (NT-proBNP) (electrochemiluminescence method on Elexis device (Roche Company)).

Data exploration and statistical analysis were performed using Statistica 1O CZ (StatSoft, Tulsa, U.S.A.). Continuous data with normal data distribution were assessed by Student's t-test. Discrete data were assessed by Mann-Whitney U-test. Significance of hazard ratios was assessed by Fisher's exact test.

All patients were treated according to recent guidelines[11,12]. Altogether 107 patients (89.2%) were treated with unfractionated heparin or low-molecular weight heparin, which were administered until therapeutic and stable levels of international normalized ratio (INR) were achieved by vitamin K antagonist (warfarin). In 13 cases (10.8%) systemic thrombolysis (alteplase) was administered with concurrent parenteral administration of unfractionated heparin, followed by the above-mentioned anticoagulant treatment. All patients were discharged with therapeutic doses of anticoagulant therapy.

RESULTS

The study population baseline characteristics are summarized in Table 2.

Unfortunately there was a decline in the number of patients during follow-up for several reasons: death (oncological disease (8), stroke (2), pneumonia (2), unknown cause not due to RV failure (1)), immobility, change of residence, non-compliance (10). For these reasons only 103, 101 and 97 patients respectively attended the 6-, 12- and 24-month visits. Anticoagulant treatment duration was based on recent guidelines and international normalized ratio was controlled by general practitioners in most cases or by our outpatient department. There was one patient with a recurrence of venous thromboembolism during follow-up after discontinuation of anticoagulation therapy. The cause was a large aneurysm of the popliteal

Table 2. Baseline characteristics of study population.

Number of patients	120
Age (years)	57.9 ± 16.2
Women, n (%)	60 (50)
Men, n (%)	60 (50)
BMI (kg/m^2)	29.2 ± 5.48
Systolic blood pressure (mm Hg)	135 ± 23.7
Diastolic blood pressure (mm Hg)	80.6 ± 14.1
Smokers, n (%)	21 (17.5)
Steroid hormone users, n (%)	24 (20)
History of trauma/surgery/ immobilization, n (%)	13 (10.8)/13 (10.8)/ 15 (12.5)
Oncological disease, n (%)	17 (14.2)
Thrombophilia (known or newly detected), n (%)	15 (12.5)
On admission NT-proBNP (pmol/L)	246 ± 490
Discharge NT-proBNP (pmol/L)	51 ± 173
Troponin-T (μg/L)	0.031 ± 0.0462
On admission echocardiography	
RV diameter (mm)	31.4 ± 4.51
PAsP (mm Hg)	50.8 ±17.7
TAPSE (mm)	20.5 ± 4.64
Sa_{Tri} (cm/s)	12.3 ± 2.65

(BMI - body mass index; NT-proBNP - N-terminal fragment of brain natriuretic peptide; PAsP - pulmonary artery systolic pressure; RV - right ventricle; Sa_{Tri} - velocity of tricuspid annular systolic plane excursions in tissue doppler imaging mode; TAPSE - tricuspid annular plane systolic excursion)

vein diagnosed at the time of recurrence, and was indicated for resection. A ventilation/perfusion (V/Q) lung scan was performed whenever patients developed symptoms during the follow-up and there were echocardiographic signs of pulmonary hypertension; it was also performed in asymptomatic patients with echocardiographic signs of pulmonary hypertension of unknown cause as described below. In addition, a further assessment including right heart catheterisation was offered to all those patients with perfusion defects. Two symptomatic patients agreed and CTEPH was verified. However in one of them it was coincident with ischemic heart disease found during the invasive assessment, and symptoms completely resolved after percutaneous coronary revascularization.

Three additional patients with echocardiographic signs of pulmonary hypertension underwent a V/Q lung scan. One of them was symptomatic with an estimated PAsP 57 mm Hg. V/Q lung scan revealed ventilation/perfusion mismatch, but there was no other known cause of pulmonary hypertension; however this patient refused further invasive assessment. Another patient who was also symptomatic developed moderate to severe mitral insufficiency and mild left ventricle systolic dysfunction, but had no ventilation/perfusion mismatch, and the pulmonary hypertension according to echocardiography was not out of proportion (estimated PAsP 43 mmHg). The third patient with echocardiographic signs of pulmonary hypertension (estimated PAsP 39 mm Hg) was completely asymptomatic up to the end of follow-up; he underwent only lung perfusion scan showing ventilation/perfusion mismatch, and was not investigated invasively (Table 3). CTEPH was diagnosed in 4 patients from our study cohort, which represents an incidence of 4.2%.

15 patients in the study had proven thrombophilia, although not all patients had been tested: older patients were not screened routinely. The most common reason was another possible provoking/risk factor for venous thromboembolism (e.g. smoking, contraceptives, trauma, immobilisation, surgery, cancer). Identified thrombophiliac cases were – methylenetetrahydrofolate reductase (MTHFR) mutation homozygous carrier (n=1); factor II mutation 20210A heterozygous carriers (n=3); high level of factor VIII (n=5); mutation of factor V Leiden homozygous carrier (n=1); mutation of factor V Leiden heterozygous carriers (n=4); antithrombin III deficiency (n=1). Among the patients diagnosed with CTEPH one was a homozygous MTHFR mutation carrier, and one a heterozygous mutation carrier of factor V Leiden. The other 2 CTEPH patients had no evidence of thrombophilia.

Patients with a diagnosis of CTEPH did not differ significantly from patients without CTEPH in anamnestic, laboratory (incl. thrombophilia), electrocardiographic, or echocardiographic parameters. Neither was there any statistical difference related to the initial extent of PE on CTA, or in the treatment strategy (thrombolysis x anticoagulant therapy alone). The study population size is probably too small, but we were not able to identify any specific CTEPH risk factor. None of the CTEPH patients had ventriculo-atrial shunt, history of splenectomy, central venous catheter, pacemaker or chronic inflammatory process. The D-dimer assessment after 6 months added no important information and showed no correlation with any of the tested variables. The only interesting fact concerning D-dimers was that they were negative at the time of acute PE diagnosis in 2 patients in our study cohort (1.67%).

DISCUSSION

There is no doubt that a clinician's suspicion and an early diagnosis of CTEPH are crucial for the patient's destiny. Pulmonary endarterectomy (as the treatment of choice for CTEPH patients) and modern specific pharmacotherapy might help us to break a vicious circle of pathophysiological changes leading to right ventricle failure and death.

As we presented formerly[13] 50.8% of patients have echocardiographic signs of persisting pulmonary hypertension at the time of hospital discharge, and these findings correlate with NT-proBNP elevation on admission. We found 4 patients of the 97 surviving probands with

Table 3. CTEPH patient characteristics.

Patient	1	2	3	4
On admision NT-proBNP (pmol/L)	1359	448.2	58	3770
Discharge NT-proBNP (pmol/L)	172.6	169	0	1513
PAsP baseline (mm Hg)	85	90	47	73
PE to CTEPH diagnosis (months)	15	7	24	6
Symptoms to CTEPH diagnosis time (months)	15	7	NA	7
Functional class (NYHA)	I	II-III	I	II
PAsP at the time of CTEPH diagnosis (mm Hg)	37	80	39	57
PAmP at the time of CTEPH diagnosis (mm Hg)	25	47	NA	NA
PVR (Wood units)	2.28	14	NA	NA
CI	2.72	2.1	NA	NA

CI - cardiac index; CTEPH - chronic thromboembolic pulmonary hypertension; NT-proBNP - N-terminal fragment of brain natriuretic peptide; NYHA - New York Heart Association; PAsP - pulmonary artery systolic pressure; PAmP - pulmonary artery mean pressure, PVR - pulmonary vascular resistance

proven CTEPH at the end of our study. All of them had elevated NT-proBNP also at the time of hospital discharge. Although it can be said that this is a small-numbers game and that this finding has no statistical significance, the selection of patients for effective follow-up for CTEPH can be even more specific by using the above-mentioned parameters.

It is necessary to point out the rather high values of on-admission PAsP in some of our study patients, resulting in a high average PAsP on admission (Table 3). This suggests the possibility of preexisting elevation of PAsP due to previous asymptomatic and thus untreated thromboembolic event(s). Nevertheless these patients still met our study inclusion criterion of having a first symptomatic thromboembolic event. These patients should receive anticoagulant therapy for at least 3 months before CTEPH assessement.

We can also address the question of CTEPH screening in PE survivors. There is indeed a consensus to follow-up symptomatic patients with signs of right ventricle overload at the time of PE diagnosis. Our data also support this experts' advice. A screening algorithm for CTEPH has been published, based on ECG criteria of right ventricle hypertrophy and overload, and estimation of NT-proBNP levels. This algorithm is able to identify patients without CTEPH with a very high negative predictive value[14]. However, although the costs of NT-proBNP level estimation and echocardiography are similar, the latter is able to offer more clinically relevant information about the patient's heart. Hence we do not reject echocardiography as a CTEPH screening tool, especially if there is sufficient echolab personnel capacity.

Study limitations

The major limitation of our study is the cohort size, together with the limitation of study monocentricity. Additional limitations include the decrease in study population during follow-up, and the use of echocardiography for estimation of pulmonary hypertension (albeit routine invasive investigation of all study patients would have given rise to some indefensible ethical and economic barriers – for this reason only symptomatic and consenting patients were assessed invasively). Another limitation of our study is also the fact that in not all patients considered as having CTEPH was the diagnosis confirmed in a standard way (right heart catheterization and pulmonary angiography). We were also unable to guarantee adequate anticoagulant treatment throughout the period of the study in all patients.

All blood samples were obtained immediately at the time of admission to hospital – at this time the cardiomarker levels could be negative in some patients due to the kinetics, as we observe in acute coronary syndromes. It might also be better to freeze all blood samples and to assess them all at once to minimize laboratory error. However, we tried to conduct the study in a way as close to common clinical practice as possible; laboratory results and echocardiography were also used for individual treatment decisions.

ABBREVIATIONS

BMI, Body mass index; CT, Computer tomography; CTA, Computer tomography angiography; CTEPH, Chronic thromboembolic pulmonary hypertension; INR, International normalized ratio; NT-proBNP, N-terminal fragment of brain natriuretic peptide; PAsP, Pulmonary artery systolic pressure; PAmP, Pulmonary artery mean pressure; PE, Pulmonary embolism; PH, Pulmonary hypertension; RV, Right ventricle; Sa_{Tri}, Velocity of tricuspid annular systolic plane excursions in tissue Doppler imaging mode; TAPSE, Tricuspid annular plane systolic excursion; V/Q, Ventilation/perfusion.

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REFERENCES

1. Simonneau G, Robbins IM, Beghetti M, Channick RN, Delcroix M, Denton CP, Elliott CG, Gaine SP, Gladwin MT, Jing ZC, Krowka MJ, Langleben D, Nakanishi N, Souza R. Updated clinical classification of pulmonary hypertension. J Am Coll Cardiol 2009;54(suppl S):S43-S54.
2. Simonneau G, Gatzoulis MA, Adatia I, Celermajer D, Denton C, Ghofrani A, Gomez Sanchez MA, Krishna Kumar R, Landzberg M, Machado RF, Olschewski H, Robbins IM, Souza R. Updated clinical classification of pulmonary hypertension. J Am Coll Cardiol 2013;62:D34-41.
3. Ogata T, Iijima T. Structure and pathogenesis of plexiform lesion in pulmonary hypertension. Chin Med J (Engl) 1993;106(1):45-8.
4. Pengo V, Lensing AW, Prins MH, Marchiori A, Davidson BL, Tiozzo F, Albanese P, Biasiolo A, Pegoraro C, Iliceto S, Prandoni P; Thromboembolic Pulmonary Hypertension Study Group. Incidence of chronic thromboembolic pulmonary hypertension after pulmonary embolism. N Eng J Med 2004;350:2257-64.
5. Fedullo PF, Auger WR, Kerr KM, Rubin LJ. Chronic thromboembolic pulmonary hypertension. N Engl J Med 2001;345(20):1465-72.
6. Becattini C, Angelli G, Pesavento R. Incidence of Chronic Thromboembolic Pulmonary Hypertension After a First Episode of Pulmonary Embolism. Chest 2006;130:172-5.
7. Miniati M, Monti S, Bottai M, Scoscia E, Bauleo C, Tonelli L, Dainelli A, Giuntini C. Survival and Restoration of Pulmonary Perfusion in a Long-Term Follow-Up of Patients After Acute Plmonary Embolism. Medicine 2006;85:253-62.

8. Ribeiro A, Lindmarker P, Johnsson H, Juhlin-Dannfelt A, Jorfeldt L. Pulmonary embolism: one-year follow-up with echocardiography doppler and five-year survival analysis. Circ 1999;99:1325-30.
9. Dentali F, Donadini M, Gianni M. Incidence of chronic pulmonary hypertension in patients with previous pulmonary embolism. Thromb Res 2009;124(3):256-8.
10. Martí D, Gómez V, Escobar C, Wagner C, Zamarro C, Sánchez D, Sam A, Briongos S, Gaudó J, Sueiro A, Jiménez D. Incidence of symptomatic and asymptomatic chronic thromboembolic pulmonary hypertension. Arch Bronconeumol 2010;46(12):628-33.
11. Torbicki A, Perrier A, Konstantinides S, Agnelli G, Galiè N, Pruszczyk P, Bengel F, Brady AJ, Ferreira D, Janssens U, Klepetko W, Mayer E, Remy-Jardin M, Bassand JP; ESC Committee for Practice Guidelines (CPG). Guidelines on the diagnosis and treatement of acute pulmonary embolism. European Heart Journal 2008;29:2276-315.
12. Widimský J, Malý J, Eliáš P, Lang O, Franc P, Roztočil K. Doporučení diagnostiky, léčby a prevence plicní embolie, verze 2007. Cor Vasa 2008;50(Suppl):1S25-1S72. In Czech.
13. Vavera Z, Vojacek J, Pudil R, Maly J, Elias P. NT-proBNP levels on admission predicts pulmonary hypertension persistence in patients with acute pulmonary embolism. Cor et Vasa 2012;54(1):e27-e31.
14. Klok FA, Surie S, Kempf T, Eikenboom J, van Straalen JP, van Kralingen KW, van Dijk AP, Vliegen HW, Bresser P, Wollert KC, Huisman MV. A simple non-invasive diagnostic algorithm for ruling out chronic thromboembolic pulmonary hypertension in patients after acute pulmonary embolism. Thromb Res 2011;128(1):21-6.