Chronic thromboembolic pulmonary hypertension in patients with persistent chest symptoms after acute pulmonary embolism

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Abstract

Objective: This study aimed to analyze the role of chronic thromboembolic pulmonary hypertension (CTEPH) in patients with persistent chest symptoms after acute PE.

Methods: Patients aged between 18 and 80 years who were followed up for acute PE were screened for chest symptoms which persisted after the anticoagulation treatment. Patients suffering other types of pulmonary hypertension (PH) or metastatic malignancies were excluded in this study. Demographic and functional data of patients included this study were collected. The patients underwent transthoracic echocardiography and ventilation/perfusion (VQ) scans. Also, invasive hemodynamic studies were done to patients with intermediate/high probability of VQ scans.

Results: Of the 140 patients screen for this study, 29 patients (Female/Male=16/13) with mean age of 56.1±11.2 years and follow-up time of 35.1±17.7 months met the inclusion criteria. The mean systolic pulmonary artery blood pressure (sPAP) on transthoracic echocardiography was 28.9±4.9 mm Hg (range=20–40 mm Hg). Furthermore, intermediate or high probability of VQ scans was detected in 2 patients, who were subsequently diagnosed with CTEPH (6.9%) via right heart catheterization.

Conclusion: CTEPH was diagnosed at a low rate in patients with persistent chest symptoms after the anticoagulation treatment for PE. CTEPH is still an elusive entity, which requires a multidisciplinary and invasive approach.

Keywords: pulmonary embolism; chronic thromboembolic pulmonary hypertension; ventilation-perfusion scan; right heart catheterization

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Introduction

Chronic thromboembolic pulmonary hypertension (CTEPH), though previously thought to be a scarce clinical entity that may occur after venous thromboembolism (VTE), has recently been detected more frequently as a result of detailed investigation. The epidemiological studies of CTEPH are not somewhat inconclusive. This is because the incidence of CTEPH after pulmonary embolism (PE) has been reported to vary between the range of 0.1%–14% (1). Intriguingly, there are several studies where CTEPH was frequently diagnosed in patients without any previous clinical episode of acute PE or deep venous thrombosis (up to 50% in some series) (2-5). Therefore, it is difficult to determine the overall incidence and prevalence of CTEPH because not all the patients have a history of acute PE. Moreover, it is still an elusive diagnosis.

Evidence abound on the rarity of complete anatomic and hemodynamic recovery after pulmonary embolism. However, majority of the patients remain asymptomatic with partial recovery, and a smaller fraction of the patients may show a progressive disease which can result to CTEPH (6). In spite of the fact that CTEPH is now treatable, it is still associated with high morbidity and mortality. Reasons for this may include insufficient knowledge/awareness regarding the early stages and variable course of CTEPH (which leads late clinical presentation with advanced stages of right heart failure), underdiagnosis due to silent VTEs, performance of pulmonary thromboendarterectomy (PTEA) to few patients with the correct diagnosis, high mortality rate of

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PTEA in centers with less experience, and lack of effective medical treatment for patients who were either ineligible or refused surgical treatment (7).

Some patients may lay complains of persistent dyspnoea that impairs their quality of life and capacity to exercise after PE, even though they ostensibly have no pulmonary hypertension (PH). Recent studies on this scenerio suggest that the underlying cause may be dead-space ventilation and lack of right ventricular compliance with exercise, and chronic thromboembolic pulmonary disease (CTED) is the proposed name. Since the outcomes of PTEA in these patients are more promising, diagnosis at early stages is be critical for the treatment and prognosis (8-13). Herein, we aimed to investigate patients with persistent chest symptoms after completion of anticoagulation treatment for PE.

Methods

Medical records of PE patients diagnosed and treated for Chest Diseases at Yedikule Hospital with Surgery between January 01, 2010 and January 01, 2014 were screened. All PE patients within the age range of 18–80 years were screened. Asymptomatic patients, patients with metastatic malignancy, PH due to groups 1, 2, 3 or 5, as well as patients without follow-up data were excluded (14). Symptomatic (dyspnea, exercise intolerance and chest pain) patients were further studied in details. Echocardiographic investigation was done at Cerrrahpaşa School of Medicine. All study subjects were screened and examined by the investigators to determine their final status. Demographic, laboratory, and imaging data were obtained and reviewed by an experienced team of pulmonologist, radiologist, and cardiologist.

Age, gender, comorbidity, chest symptoms, physical examination findings (blood pressure, pulse rate, oxygen saturation, edema, rales, rhonchi), and risk factors for PE were recorded.

The presence of COPD, asthma, hypertension, diabetes mellitus, congestive heart failure, ischemic heart disease, chronic kidney disease, panic disorder, depression, psychosis, non-metastatic malignancy were reviewed as the comorbid diseases. The patients were grouped according to their number of comorbidities (no comorbidity, 1 comorbidity, and ≥2 comorbidities).

The risk factors of PE were grouped as surgery, immobility, thrombophilia, and malignancy, while protein C, S, and antithrombin III deficiency, factor V Leiden mutation, hyperhomocysteinemia, Lupus anticoagulant (LAC), antiphospholipid antibodies (APA) were recorded as thrombophilic factors.

The final investigations include 6 minutes walk test (6MWT), spirometry (with DLCO) (MIR Spirolab), transthoracic echocardiography, and VQ scan (PIOPED criteria) (15). Patients with either intermediate to high probability VQ scans or supporting findings of PH on echocardiography were referred for right heart catheterization. The diagnosis of CTEPH was based on the following criteria: patients with (1) at least three months of effective anticoagulation treatment, (2) PH symptoms, (3) mean pulmonary artery pressure (mPAP) ≥25 mm Hg with pulmonary capillary wedge pressure (PCWP) ≤15 mm Hg or non-measurable PCWP, (4) and chronic/organized thrombi/emboli in the elastic pulmonary arteries (main, lobar, segmental, or subsegmental level) (2, 4).

The study was approved by the Ethics Committee, and informed consent was obtained from all participants. The study was conducted according to the Declaration of Helsinki.

Statistical analysis

Data were presented as mean±standard deviation. Yates correction χ^2 test was used for the comparison of categorical variables, while Mann Whitney U test was used for the comparison of continuous variables. $P<0.05$ was considered significant. All statistical analysis was done using SPSS version 20.0 for Windows (SPSS Inc, Chicago, IL, USA).

Results

General characteristics

Of the 140 patients with the diagnosis of PE screened within the time frame of the study, 29 patients with persistent chest symptoms (M/F=13/16) met the inclusion criteria and were eligible for the final analysis (Fig. 1). Mean age and follow-up time were 56.1±11.2 years and 35.1±17.7 months, respectively. The most common persistent symptoms after completion of anticoagulation treatment were dyspnoea and exercise intolerance, with about 90% and 82% observed in the subjects, respectively. The average number of risk factors for PE was 0.59±0.82, with 25% of the patients having deep vein thrombosis (DVT) at the time of diagnosis of PE (Tables 1 and 2).

VQ scintigraphy

The results of VQ scans at last visits of the patients were normal (41%), low-probability (51%), intermediate-probability (3.4%), and high-probability (3.4%) (Table 2). There was no statistically significant difference between patients with normal/low-probability and intermediate/high-probability VQ scans in terms of the demographic and follow-up data, apart from the longer duration of anticoagulation treatment for the intermediate/high probability VQ scan group (18±8.4 vs. 6.9±4.2 months, p=0.031) (Table 3).

Echocardiography

The mean ejection fraction and systolic pulmonary artery pressure (sPAP) on transthoracic echocardiography were 58.6%±4.4 and 28.9±4.9 mm Hg, respectively. Minimal and mild tricuspid regurgitations were observed in 76% and 24% of the patients, respectively (Table 2).

Spirometry and 6MWT

The mean findings on spirometry were as follows: FEV1 (2.2±0.8 Lt); FVC (2.7±1.0 Lt); FEV1/FVC (80.1±8); DLCO (24.5±7.8

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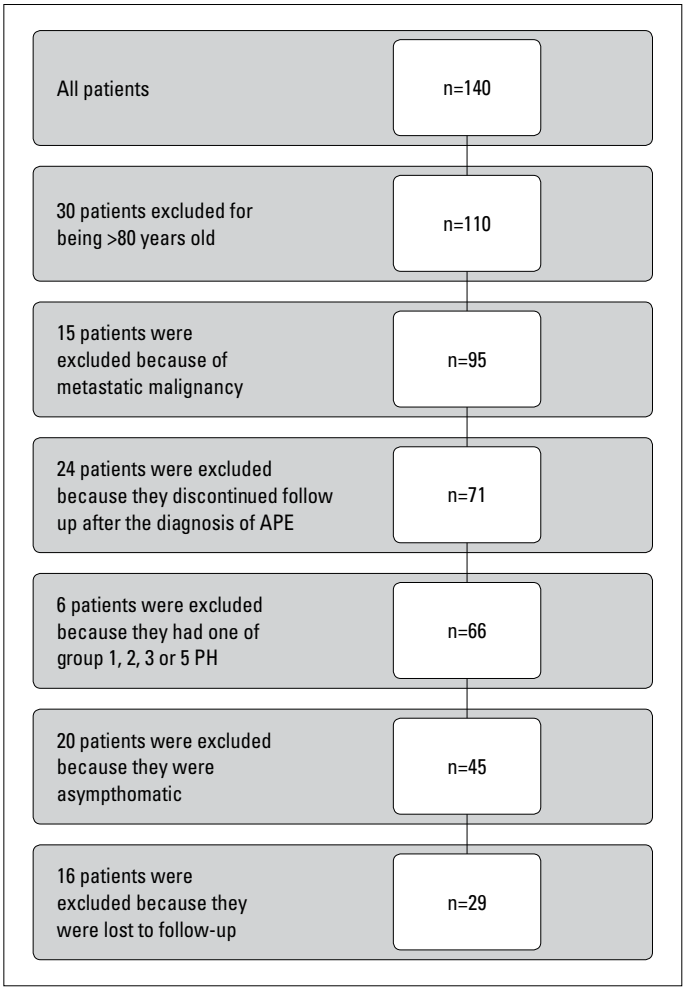

Figure 1. Patient flow chart
APE - acute pulmonary embolism; PH - pulmonary hypertension

mmol CO per min per kPa); DLCO/VA (5.0±1.2). Mean six minutes walk distance, oxygen saturation at finish, and pulse rate recovery time on 6MWT were 420.5±92 meters, 96%±2.5% and 209.4±122 seconds, respectively (Table 2).

Anticoagulation

All patients were administered low molecular weight heparin (LMWH) at the acute phase of PE. Outpatient anticoagulation treatment was administered with warfarin in 86%, LMWH in 10%, and non-vitamin K oral anticoagulants in 3.4% of the patients. The mean duration of anticoagulation treatment was 7.7±5.2 months (Table 1).

Right heart catheterization

Invasive hemodynamic studies were conducted on the 2 patients with intermediate or high VQ scans at their last visit. Both patients (6.9%) were diagnosed with CTEPH based on the aforementioned criteria. One patient (age=66, gender=female) had PE 21 months prior to enrolment in this study, with a medical history including positive Lupus anticoagulant test, hypertension, COPD, ischemic heart disease, and panic disorder. Her

Table 1. Baseline characteristics of the included patients

	All patients (n=29)
Age (year)	56.1±11.2
Gender (Female/Male)	16/13
Number of comorbidities (n, %)	
None	11/29
1 comorbidity	4/29
≥2 comorbidities	14/29
Risk factors for VTE (n, %)	
Surgery	4/29
Immobility	6/29
Malignancy	1/29
Hypercoagulability	6/29
Deep vein thrombosis (n, %)	6/24
Treatment for PE	
Warfarin	25/29
LMWH	3/29
NOAC	1/29
Duration of anticoagulation treatment (month)	7.7±5.2

VTE - venous thromboembolis; PE - pulmonary embolism; LMWH - low molecular weight heparin; NOAC -non-vitamin K oral anticoagulant

Table 2. Assessment of the symptoms, cardiac and pulmonary status of patients (n=29) at last visit

Symptoms	
Dyspnoea (n)	26/29
Chest pain (n)	15/29
Exercise intolerance (n)	24/29
Echocardiography	
sPAP (mm Hg)	28.9±4.9
TAPSE (mm)	22.2±4.0
Tricuspid regurgitation	
Minimal	22/29
Mild	7/29
LV-EF (%)	58.6±4.4
V/Q scintigraphy	
Normal	12/29
Low probability	15/29
Intermediate probability	1/29
High probability	1/29
6-MWT	
Walked distance (m)	420.5±92
Pulse rate at start (per minute)	81.3±14.1
Pulse rate at the end (per minute)	103.9±18
D-Dimer above cut-off (n)	2/26

sPAP - systolic pulmonary artery pressure; TAPSE - tricuspid annular plane systolic excursion; LV-EF - left ventricular ejection fraction; VQ - ventilation perfusion scan; 6-MWT - 6 minutes walking test

Table 3. Comparison of the patients with normal/low-probability and intermediate/high-probability VQ scans

	Normal/Low-probability VQ scan (n=27)	Intermediate/High-probability VQ scan (n=2)	*P*
Age (year)	56.1±11.2	55.5±14.8	0.931
Gender (Female/Male)	14/13	2/0	0.186
Comorbidities			
0 comorbidity	11/27	0/2	0.181
1 comorbidity	4/27	0/2	
2 ≥ comorbidities	12/27	2/2	
Number of comorbidities	1.33±1.4	3.5±2.1	0.107
Risk factors of PE			
Surgery	4/27	0/2	0.558
Immobility	6/27	0/2	0.454
Malignancy	1/27	0/2	0.782
Thrombophilia	5/27	1/2	0.289
Deep vein thrombosis (n)	6/22	0/2	0.394
Symptoms			
Dyspnoea	24/27	2/2	0.619
Chest pain	14/27	1/2	0.960
Exercise intolerance	22/27	2/2	0.504
Echocardiography			
sPAP (mm Hg)	28.3±4.5	36±5.6	0.073
TAPSE (mm)	22.5±4.0	18.5±0.7	0.084
Tricuspid failure			
Minimal	20/27	2/2	0.408
Mild	7/27	0/2	
PA diameter (mm)	24.4±3.6	26.0±0	0.341
LV-EF %	58.8±4.4	55±0	0.148
6-minutes walking test			
Walk distance (m)	426±94	356±21.9	0.086
Initial pulse rate (/minute)	80.7±14	87±15.5	0.170
Finale pulse rate (/minute)	102±16	120±28	0.453
Anticoagulation			
Warfarin	23/27	2/2	0.952
LMWH	3/27	0/2	
NOAC	1/27	0/2	
Duration of anticoagulation treatment (months)	6.9±4.2	18±8.4	0.031
Duration of follow up (months)	36.3±17.7	19.0±11.0	0.123

VQ - ventilation perfusion scan; PE - pulmonary embolism; sPAP - systolic pulmonary artery pressure; TPASE -tricuspid annular plane systolic excursion; PA - pulmonary artery; LV-EF - left ventricular ejection fraction; LMWH - low molecular weight heparin; NOAC - non-vitamin K oral anticoagulant

left ventricular ejection fraction and sPAP on transthoracic echocardiography were 55% and 40 mm Hg, respectively, while the right pulmonary artery diameter was 20.3 mm. VQ scan revealed an intermediate probability for PE. The invasive hemodynamic study revealed calcific stenoses in the upper lobe branches of the right pulmonary artery, and irregularity in the segmenter artery walls in upper lobe branches of the left pulmonary artery, with sPAP, mPAP, PCWP, and transpulmonary gradient (TPG) of 54 mm Hg, 31 mm Hg, 17 mm Hg, and 14 mm Hg, respectively. Thrombosis was not seen in the main branches of the pulmonary artery.

The other patient (age=45, gender=female) had PE 36 months prior to enrolment in this study, with medical history including diabetes mellitus and hypertension. The left ventricular ejection fraction and sPAP on transthoracic echocardiography were 55% and 32 mm Hg, respectively, while the right pulmonary artery diameter was 13.5 mm. VQ scan revealed a high probability of PE. The invasive hemodynamic study revealed

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web-like structures within the proximal segments of right A1-A2 branches, as well as total thrombosis in the A7, A9, and A10 branches of the pulmonary artery, with sPAP, mPAP, PCWP, and TPG of 45 mm Hg, 29 mm Hg, 12 mm Hg, and 17 mm Hg, respectively.

Discussion

In this study, we have found CTEPH in 2 out of the 29 PE patients who were symptomatic despite the minimum 3 months of anticoagulation treatment. Demographic and functional parameters were not different between patients with normal/low probability and intermediate/high probability VQ scans, apart from duration of the anticoagulation treatment.

In a prospective study by Pengo et al. (2), 223 patients had a mean follow-up of 94.3 months after their initial episodes of PE. Patients with persistent and/or new onset of pulmonary symptoms were screened with a sPAP of ≥40 mm Hg on echocardiography and perfusion defects on VQ scan, and the eligible patients underwent right heart catheterization. The authors found that the 3.8% incidence of CTEPH within the first 2 years, and no additional cases occurred subsequently. Recently, Yang at al. (16) reported a larger cohort of 614 PE patients in which both symptomatic and asymptomatic patients were prospectively screened via echocardiography, right heart catheterization (pulmonary angiography), pulmonary CT angiography or VQ scan. Patients who did not give their consent for an invasive hemodynamic study were diagnosed with CTEPH provided they had a sPAP of at least 50 mm Hg with additional supporting findings from computed tomographic pulmonary angiography and VQ scans (16). The incidence of CTEPH was found 1.3% within 2 years and 1.7% within 3 years following the initial PE event, and no new cases of CTEPH were observed beyond the third year of follow-up (16). A higher cut-off value for sPAP, as well as the inclusion of asymptomatic patients may have diluted the incidence, unlike that of the preceding study (16). The number of patients in this study was much lesser than the number of patients in the two aforementioned studies, and the methods employed in these studies were somewhat different, thus making one-to-one comparison difficult even though the incidence of CTEPH was higher (6.9%) in the present study, which may be possibly due to low power of the study and the fact that only clinically symptomatic patients were included. In the present study, the two patients were diagnosed of CTEPH within 2 years of follow-up after their initial episodes of PE, which was similarly observed in previous series.

The risk factors for the development of CTEPH are not well-studied. Younger age, large perfusion defects, history of VTE, and idiopathic PE were the significant risk factors in the study by Pengo et al. (2) The study by Yang et al. (16) reports that varices in the lower extremities (HR 4.7), sPAP of >50 mm Hg at acute PE (HR 37.9), ratio of right to left ventricular diameter of >1 (HR 4.3), higher CT obstruction index 3 months after acute PE (HR 42.5), and an intermediate-risk score of pulmonary embolism severity index at diagnosis of PE (HR 1.2) were significant predictors of CTEPH. The present study included a limited number of subjects, among which, there were only two CTEPH patients. In that regard, analysis for the risk factors could not be conducted. However, positive Lupus anticoagulant test in one of our patients may be an important finding because, in a retrospective study by Auger et al. which included 216 CTEPH patients referred for surgical treatment in 1995, 10.6% of the patients had positive test results for Lupus anticoagulant (2, 17).

PTEA is recommended as the definitive treatment for CTEPH patients with symptoms at rest as well as moderate to severe hemodynamic impairment. There are also case reports in patients who develop symptoms only with exercise (CTED) due to benefits from PTEA (13). The preoperative mortality of PTEA in experienced centers is around 5%, and comorbidities and age are not considered as contraindications since patients over 80 years of age had undergone successful PTEA (12, 18). Pulmonary angiography is recommended for patients considered for PTEA due to the fact that the surgery can only be performed for those who have accessible thrombi in the main, lobar, or segmental pulmonary arteries. Medical treatment may be conducted as a bridge to surgery, as well as for those either ineligible for surgery or with insufficient improvement after PTEA. In addition, Transcatheter pulmonary angioplasty has also been performed in selected cases (10, 12, 19, 20). In the cases of the present study, pulmonary angiography did not reveal a surgically accessible thrombi within the main pulmonary branches, thus making medical treatment the only feasible option.

CTED is a recently defined condition characterized by persistent pulmonary thromboembolic occlusions without pulmonary hypertension, and it is suspected as an earlier form of CTEPH (13). It is recommended that patients presenting symptoms at exercise after completion of an effective anticoagulation treatment should be further investigated for CTED. The main difference from CTEPH is that the patients have normal sPAP at rest despite the presence of residual thrombus on angiography, and that the definitive diagnosis requires right heart catheterization (11, 12). In this regard, invasive hemodynamic evaluation was offered to the 2 patients with intermediate or high probability risk on VQ scans in our study, which revealed PH in both patients despite the sPAP not being high on transthoracic echocardiography. As a result, there was no CTED patient in this study. However, adopting VQ scan as indirect evidence for the residual pulmonary artery obstruction may have underestimated the incidence, whereas if invasive hemodynamic studies were done to all patients, some elusive CTED cases could have beeen revealed. However, performing invasive studies to patients with normal echocardiogram and normal/low risk VQ scan was considered an unjustified high risk. As a result, the relationship between persistent symptoms and history of PE remains largely unknown.

Study limitations

One of the limitations of this study is that it is a retrospective analysis with limited number of patients. The other limitations are that echocardiography during exercise and pulmonary angiographies were not performed in all patients.

Conclusion

Few patients (6.9%) with persistent symptoms after an episode of PE show findings that fulfill the criteria for CTEPH. VQ scan may serve as screening method for symptomatic patients with history of PE. However, diagnosis of CTEPH entails multidisciplinary, hazardous, and invasive procedures. Further studies are needed for simple and practical screening/diagnostic methods.

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