ORIGINAL INVESTIGATION

The Incidence and Related Risk Factors of Chronic Thromboembolic Pulmonary Hypertension after Acute Pulmonary Embolism

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Abstract

OBJECTIVES: More than half of (> 50%) the patients with chronic thromboembolic pulmonary hypertension (CTEPH) have no acute pulmonary embolism history with clinical signs, so determining the actual incidence and prevalence of CTEPH is difficult. This study aimed to investigate the incidence of CTEPH and the risk factors that may be associated with CTEPH in patients with acute pulmonary thromboembolism (PTE).

MATERIAL AND METHODS: Three hundred and eighteen patients with acute pulmonary embolism diagnosed by thorax CT or ventilation/perfusion scintigraphy in our clinic were included into this study. Patients with risk factors for pulmonary hypertension other than thromboembolic disease were excluded from the study. Patients with pulmonary hypertension (PHT) (systolic PAB > 35 mmHg) determined by echocardiography performed in the 6th month were enrolled into the study.

RESULTS: Fifty-seven of the 112 patients were female, and the mean age was 57.09 ± 17.30 (16-86) years. Presence of PHT was determined in the 6th month in 45 of the 112 patients (8 of them were symptomatic) and CTEPH incidence (symptomatic + asymptomatic) was identified as 40.16%. Symptomatic CTEPH incidence was calculated as 7.14%. When we searched about the risk factors that may have a role in the development of CTEPH; we determined that CTEPH risk was increased 4.59 times by only being male (95% CI 1.071-19.683, p= 0.040), 218 times by previous history of DVT (95% CI 1.235-38543.073, p= 0.041), and 56.903 times by PaO₂ < 80 mmHg (95% CI 2.656-1219.228, p= 0.010).

CONCLUSION: CTEPH development after PTE is a situation that can occur in many patients. If probable risk factors are known, patients can be closely monitored for CTEPH development.

KEYWORDS: Pulmonary thromboembolism, chronic thromboembolic pulmonary hypertension, incidence, risk factors

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INTRODUCTION

Pulmonary thromboembolism (PTE), which is defined as the travel of clots from systemic deep veins to the pulmonary vascular bed, is a commonly encountered but difficult to diagnose disease with high mortality [1]. Substances, such as serotonin, which is released when PTE develops, arachidonic acid metabolites, peptidoleukotriene, platelet activating factor (PAF), and platelet-derived growth factor (PDGF) are vasoconstrictive agents. These substances contribute to the increase in pulmonary vascular resistance (PVR) by creating stenosis in the pulmonary vascular bed and to the development of vasospasm through reflex by affecting the receptors in the vein wall [2]. Pulmonary artery pressure is elevated with the increase in PVR.

After an acute PTE attack, full resolution of the thrombus and restoration of the pulmonary vascular bed occur in 4 to 8 weeks [3]. However, full resolution has been reported only in 50-80% of the cases [4]. As a result of obliteration of the pulmonary vascular bed due to recurrent and organised PTE, chronic thromboembolic pulmonary hypertension (CTEPH) occurs. In order for a patient to receive CTEPH diagnosis, he/she should receive anticoagulant treatment for at least 3 months [5]. The incidence of CTEPH development after acute pulmonary embolism has been reported as 0.5-3.8% [6]. However, having no history of acute pulmonary embolism that gives clinical symptoms in more than 50% of the patients with CTEPH makes it difficult to specify the true incidence and prevalence of the disease. Diagnosis is usually made in the advanced stage since dyspnea, which is a primary symptom of the disease, is present in most patients. Diagnosis can be delayed if physical examination is normal in early stages. Patients can be asymptomatic even

when serious pulmonary hypertension develops. Therefore, CTEPH should be considered in patients undergoing a PTE attack and whose symptoms do not decrease despite anticoagulant treatment, and diagnosis should be confirmed with techniques like echocardiography and CT. In CTEPH etiology, the presence of thrombophilic factors is an unequivocal opinion, lupus anticoagulant and anticardiolipin anticores are positive only in 10-24% of the cases, and while factor V Leiden mutation is encountered in a 4-6.5% rate, protein C, protein S and antithrombin deficiencies are seen in a rate less than 0.5% [7,8].

The objective of this study was to investigate the frequency of CTEPH in patients with PTE and determine the risk factors associated with the development of CTEPH. It is our belief that CTEPH that could develop after a PTE attack can be foreseen with the detection of risk factors.

MATERIAL AND METHODS

Patients admitted to the Pulmonology Clinic of Firat University with a diagnosis of PTE between December 2010 and June 2013 were included into this study. The study was approved by the ethics committee of our university. Written consents were received from all patients who participated in the study. The study was planned to be prospective. The patients were followed for 6 months.

Patient Selection

Acute PTE diagnosis was made either by seeing hypodense filling defects in the vein lumen on thoracic CT angiography or by reporting ventilation/perfusion scintigraphy as 'high probability' in patients with a high clinical probability. Apart from thromboembolic diseases, patients with COPD, diffuse interstitial lung disease, sleep breathing disorders, systemic diseases (sarcoidosis, pulmonary Langerhans cell histiocytosis, lymphangioleiomyomatosis, neurofibromatosis, vasculitis), collagen tissue disease, congenital heart disease, left ventricle failure or valvular heart disease were excluded from the study.

Arterial blood gas (ABG), D-Dimer and troponin levels of the patients on admission were assessed, and lower extremity venous Doppler USG tests were carried out. Computed tomography pulmonary angiography (CTPA) and ECHO examinations were performed both upon admission and in the sixth month follow-up.

Computed tomography pulmonary angiography: CTPA was performed by using 64 multislice scanner (Toshiba). 100 m Iopromid was used during filming.

Echocardiography: Echocardiography was carried out by using 3.4 MHz transducer probe with two dimensional, classical and tissue Doppler. Patients, whose systolic pulmonary artery pressure was (sPAB) > 35 mmHg on the echocardiographic examination carried out in the sixth month, were considered as CTEPH [9,10]. Systolic pulmonary artery pressure was calculated by using Bernoulli equation and evaluating tricuspid regurgitation pressure gradient ($TIPG = 4 \times \text{tricuspid regurgitation velocity}^2$) in addition to right atrial pressure.

Arterial blood gas: ABG samples taken from the radial artery in room temperature were studied by blood gas analysis device (Rapidlab 348. Biobak. Bayer Diagnostic, UK).

D-dimer and troponin levels: 5cc venous blood was taken for D-dimer and troponin levels and its quantitative analysis was studied in autoanalyzer (Immolute 2000) with "chemiluminescent enzyme immunometric" method on Siemens kit.

Statistical Analysis

SPSS 16.0 computer program was used for the analysis of data. The results were presented as mean $\pm$ standard deviation. $p < 0.05$ values were considered statistically significant. When comparing the data of the patients with CTEPH and without CTEPH, student's t-test was used for the ones showing normal distribution and Mann-Whitney tests was used for the ones not showing normal distribution. Chi-square test was used in the evaluation of non-parametric data. Binary logistic regression analysis was performed in the determination of the risk factors in CTEPH development. Multivariable conditional logistic regression analysis of the prognostic factors with a < 1 significance in univariable analysis was carried out by using stepwise descending method.

RESULTS

Three-hundred and eighteen patients with a diagnosis of PTE were included into the study. Thirty-two patients were excluded from the study due to exitus (7 acute PTEs, 20 PTEs + Malignancy, 5 PTEs + comorbidity), 100 patients were excluded since they did not come to their sixth month follow-up and 74 patients were excluded due to the fact that they had additional diseases that could cause pulmonary hypertension (21 COPDs, 46 HYPs and/or CHDs, 3 COPDs + HF, 2 congenital heart diseases, one interstitial lung disease, one kyphoscoliosis). The remaining 112 patients were included into the study.

Mean age of the 112 patients included into the study was 57.09 ± 17.30 years (range, 16-86) and 57 were female. Fifty-four of the patients were started on unfractionated heparin (UFH) and 58 of them were started on low molecular weight heparin (LMWH) as first line treatment. As on-treatment, 81 patients were given oral anticoagulant (warfarin) and 31 patients were given DMARD. On-treatment of the patients was arranged to last 6 months in 69 of them, 3 months in 39 and lifetime in 4. CTEPH was detected in 52 of the 112 patients with PTE. Since 7 of these 52 patients with CTEPH had a previous history of PTE and DVT, these patients were excluded from the calculation of incidence. These patients were included into the study when other data were evaluated and risk factors were determined. PHT was detected by echocardiographic examination performed in the sixth month follow-up in 45 (8 symptomatics) of the 112 patients followed with a diagnosis of acute PTE. CTEPH incidence (symptomatic + asymptomatic) was determined as 40.16%. Only 8 of the CTEPH patients described symptoms, and hence, symptomatic CTEPH incidence was calculated as 7.14%. Thromboendarterectomy was performed on two of the eight patients with symptomatic

CTEPH, and six patients were started on medical therapy (iloprost for three patients, bosentan for 3 patients).

When patients with CTEPH and without CTEPH were compared, it was detected that the mean age was higher in patients with CTEPH ($p=0.02$); whereas, there was no significant difference between the two groups in terms of gender and the presence of risk factors ($p>0.05$ for all) (Table 1).

The presence of comorbidities was detected in 69 of the patients with CTEPH. The distribution of comorbidities in patients with and without CTEPH is presented in Table 2 and Table 3.

When the arterial blood gas findings of the patients during first admission were evaluated, PaO_2 and SaO_2 values in patients with CTEPH were significantly low when compared to the patients without CTEPH ($p=0.012$, $p=0.057$, respectively) (Table 4).

When the ECHO findings of the patients were assessed, it was determined that initial and 6th month PAB values of the patients with CTEPH were prominently higher than those of the patients without CTEPH ($p=0.001$, $p<0.001$, respectively). When the thoracic CT scans of all patients with PTE were evaluated as regards the location of thrombus, it was detected that the localization of the thrombus was similar in both groups. It was also detected that the routinely evaluated D-dimer and troponin levels of the patients with PTE did not show a statistically significant difference (Table 5).

When the cases included into the study were assessed with univariate logistic regression analysis in terms of risk factors that could play a role in the development of CTEPH, it was found that the male gender (OR; 4.59, 95% CI; 1.071-19.683, $p=0.040$), previous DVT existence (OR; 218, 95% CI; 1.235-38543.073, $p=0.041$) and PaO_2 value < 80 mmHg (OR; 56.903, 95% CI; 2.656-1219.228, $p=0.010$) were independent risk factors of CTEPH development (Table 6).

DISCUSSION

In this study where we investigated the developmental incidence of CTEPH in patients with acute pulmonary thromboembolism, we designated the number of patients, whose sPAB value was > 35 mmHg on the 6th month ECHO, as 45 (40.16%). We also detected that the male gender, previous DVT history and hypoxemia presence during diagnosis were independent risk factors.

Table 1. Demographic characteristics of the patients and risk factors

	CTEPH (+) (n= 52)	CTEPH (-) (n= 60)	p value
Age	62.46 $\pm$ 15.66	52.45 $\pm$ 17.44	0.02*
Gender (M/F)	30/22	25/35	> 0.05
Idiopathic	34	35	> 0.05
Acquired risk factor	15	24	> 0.05
Congenital risk factor	3	1	> 0.05
Previous DVT history	3	5	> 0.05
Previous PTE history	5	1	> 0.05
Presence of Accompanying DVT	20	18	> 0.05

CTEPH: Chronic thromboembolic pulmonary hypertension. DVT: Deep vein thrombosis, PTE: Pulmonary thromboembolism.

* Statistically significant.

Table 2. Detected comorbidities in patients that developed CTEPH

Benign prostate hypertrophy	5 (7.24%)
Hypertension	31 (44.9%)
Diabetes mellitus	12 (17.39%)
Malignancy	6 (8.69%)
Hyperthyroid	2 (2.89%)
Chronic kidney failure	2 (2.89%)
Obesity	2 (2.89%)
Cerebrovascular disease	3 (4.34%)
Pneumonia	3 (4.34%)
Systemic lupus erythematosus	1 (1.44%)
Asthma	2 (2.89%)

CTEPH: Chronic thromboembolic pulmonary hypertension.

Table 3. Detected comorbidities in patients that did not develop CTEPH

Hypertension	40 (59.70%)
Diabetes mellitus	10 (14.92%)
Malignancy	1 (1.49%)
Chronic liver failure	4 (5.97%)
Obesity	6 (8.95%)
Cerebrovascular disease	5 (7.46%)
Pneumonia	3 (4.47%)
Asthma	4 (5.97%)

CTEPH: Chronic thromboembolic pulmonary hypertension.

Table 4. Arterial blood gas findings of the patients

	CTEPH (+) (n= 52)	CTEPH (-) (n= 60)	p value
pH	7.46 $\pm$ 0.06	7.44 $\pm$ 0.06	0.31
PaO_2 (mmHg)	56.30 $\pm$ 15.84	63.81 $\pm$ 15.03	0.012*
SaO_2 (%)	84.73 $\pm$ 12.63	89.40 $\pm$ 13.02	0.057*
PaCO_2 (mmHg)	32.68 $\pm$ 6.03	32.78 $\pm$ 6.38	0.93
HCO_3 (mEq/L)	21.96 $\pm$ 3.80	22.76 $\pm$ 3.42	0.24

CTEPH: Chronic thromboembolic pulmonary hypertension.

* Statistically significant.

Table 5. ECHO and CT findings of the patients and D-Dimer, troponin levels

	CTEPH (+) (n= 52)	CTEPH (-) (n= 60)	p value
PAB basal	56.46 $\pm$ 22.01	44.15 $\pm$ 13.59	0.001*
PAB 6 th month	51.51 $\pm$ 21.44	31.45 $\pm$ 3.11	0.000*
Thrombus localization			
Major pulmonary artery	28	33	> 0.05
Lobar pulmonary artery	10	12	> 0.05
Segmenter pulmonary artery	14	15	> 0.05
D-Dimer	3.56 $\pm$ 1.64	4.13 $\pm$ 2.18	0.11
Troponin	0.21 $\pm$ 0.35	0.14 $\pm$ 0.24	0.25

CTEPH: Chronic thromboembolic pulmonary hypertension. CT: Computed tomography, PAB: Pulmonary artery pressure.

* Statistically significant.

Table 6. Independent risk factors in the development of CTEPH

Covariate	b	SE	P	Exp (b)	95% CI of Exp (b)
Gender	-0.6183	0.3498	0.07717	0.5389	0.2724 to 1.0660
PaO ₂	-0.7516	0.5548	0.1755	0.4716	0.1599 to 1.3914
Previous DVT	-0.8658	0.7616	0.2556	0.4207	0.0953 to 1.8576

CTEPH: Chronic thromboembolic pulmonary hypertension, DVT: Deep vein thrombosis.

It has been previously thought that there was a 'honeymoon phase' between the clinical findings of CTEPH and acute PTE and that the clinical findings of CTEPH would manifest themselves many years later [11]. It is recommended by the guidelines that patients, in whom findings of PHT or right ventricle dysfunction is detected during hospitalization due to acute PTE, should undergo a follow-up echocardiography after discharge (usually 3-6 months later) in order to determine if PHT has improved [9]. In our study, CTEPH development was detected 6 months after the acute event and these cases were found to have a high sPAB value within a mean follow-up period of 21.2 months (6-60 months).

It has been previously believed that the developmental incidence of CTEPH after acute PTE was between 0.1% and 0.5% [12,13]. Further studies have detected that this rate is much higher. In a prospective study by Martive et al., it has been detected that the incidence of CTEPH is 9.0% [14]. In another more recent study, CTEPH incidence of 94 patients, whose mean follow-up period was 25.47 months (4-62 months), has been found as 14.4% [15]. In a study by Pengo et al., the incidence of symptomatic CTEPH in the follow-up of their 223 patients has been found as 1.0% 6 months later, 3.1% one year later and 3.8% 2 years later [6]. In a study carried out in our country, it has been reported that the incidence of symptomatic CTEPH during a mean follow-up period of 16.3 months was 4.6% and that CTEPH developed within a year after the acute event in most of the patients (80%). It has been indicated in the same study that diagnosis could be made in patients with symptomatic CTEPH in a mean 9.4 months. The researchers have stated that CTEPH manifested clinical symptoms especially within the first 1 year and presented a quiet picture in later years [16]. When the incidence of CTEPH detected in our study was compared to the literature, it was seen that the incidence detected in our study was prominently higher. When the reason for it was researched, we detected that the incidence of CTEPH was mostly given by including symptomatic patients. When we grouped our patients as symptomatic/asymptomatic, we saw that the incidence of symptomatic CTEPH was 7.14%.

Risk factors having a part in the development of CTEPH are multifold. One of these factors is the presence of residual thrombus. It is known that full thrombus resolution and full improvement in the pulmonary vascular bed occur in the 4th-8th [9]. weeks. It has been reported that there was full resolution after 4 weeks in 81% of the 69 patients with PTE, who were followed by CT angiography [17]. However, it has been detected in studies that full resolution is seen within this period of time in only 50% and 80% of the cases [17,18].

Residual perfusion defect has been established in 66% of 157 PTE patients whose perfusion scintigraphy was performed after a 3-month anticoagulant treatment [19]. In another study, residual perfusion defect has been confirmed in 29% of 254 PTE patients one year after diagnosis [20]. Residual chronic thrombus develops in many PTE patients; however, new studies need to be carried out in order to determine the clinical importance of this finding in the long term [21]. In this study where we included 112 PTE patients, we confirmed the presence of chronic thrombus in 13 patients (11.6%) in the 6th month. Out of these, 7 patients were in the symptomatic CTEPH group, 5 patients in the asymptomatic CTEPH group and one patient in the group where CTEPH did not develop. We determined in our study that the presence of residual thrombus in the 6th month was not a risk factor for the development of CTEPH.

It is known that recurrent thromboembolisms play a role in the development of CTEPH [22]. In a retrospective study by Bonderman et al., risk factors in CTEPH patients were investigated and splenectomy, previous venous thromboembolism, recurrent VTE, blood types apart from 0 and the presence of lupus anticoagulant/antiphospholipid anticorres were determined to be associated with CTEPH [23]. In a study conducted in our country, the incidence of CTEPH was determined higher in cases with previous PTE and idiopathic PTE [16]. Again in a study by Pengo et al., CTEPH was confirmed in three (5.2%) of the 58 cases with a history of DVT [6]. We also established in our study that history of DVT was an independent risk factor in the development of CTEPH.

Advanced age is thought to be a risk factor in PTE development [24]. However, data stating that age is a risk factor for the development of CTEPH are conflicting. While advanced age has been defined a relative risk factor in a study [14], other studies have shown that young age is associated with the development of CTEPH [6,25]. There are studies reporting that age is not a risk factor for the development of CTEPH [16,26]. We established in our study that CTEPH patients were significantly older than the patients without CTEPH: however, we also confirmed with regression analyses that age was not effective in the development of CTEPH.

The number of studies where gender has been investigated as a risk factor is limited. Female gender has been determined a risk factor in a study [23]. In our study, it was established that male gender increased the risk of development of CTEPH 4.59 times.

Different results have been obtained in studies investigating the correlation between CTEPH development and thrombus

localization. Korkmaz et al. have reported in their study that much thrombus load and CTEPH development have a significant relation; however, a significant relation has not been not reported between the localization of thrombus and CTEPH development [16]. In earlier studies, wide perfusion defects have been reported as risk factors in the development of CTEPH [6,27]. In our study, a correlation between the localization of thrombus and CTEPH development was not confirmed.

Increased PAB and right ventricular dysfunction are seen in nearly half of the PTE cases, which is also associated with early period mortality [26]. In a study conducted in our country, right ventricular dysfunction and high sPAB (> 35 mmHg) have been confirmed in 57% of acute PTE patients. In the same study, it has been confirmed that sPAB is higher in patients with CTEPH when compared to the ones without CTEPH [16]. In a study by Lang et al., it has been reported that high basal sPAB value is a risk factor for CTEPH [24]. In another study, high basal sPAB value, recurrent PTE, increased right atrium and ventricular diameter have been defined as high risk factors for the development of CTEPH [15]. Situations where PAB value is measured during an acute PTE and is higher than 50 mmHg have been found associated with persistent PHT development in the late period [27]. During acute PTE in our study, right ventricular dysfunction and high sPAP (50 mmHg and over) were detected in 35.7% of our patients. Basal sPAB values were determined to be significantly higher in cases with CTEPH when compared to the cases without CTEPH. Basal sPAB was detected high especially in all symptomatic CTEPH patients. However, high value of sPAB was not detected a risk factor in the development of CTEPH.

Hypoxemia is a vital clinical finding of PTE. Mechanisms playing role in the development of hypoxemia are V/Q imbalance, diffusion defect and intrapulmonary shaft development. Hypoxemia contributes to the development of PHT by increasing PVR. In our study, we confirmed that PaO₂ and SaO₂ values were prominently low in patients with CTEPH when compared to the patients without CTEPH.

One of the limitations to our study is that PAB was evaluated with ECHO rather than pulmonary artery catheterization. However, in ESC/ERS/ISHLT guidelines, an important correlation has been shown between the PAP value of 50 mmHg and higher on ECHO and the sPAP value of 50 mmHg and higher during pulmonary artery catheterization [9]. Another limitation to our study is that the number of patients that could not be followed was high. We do not know the number of symptomatic patients among the unfollowed cases. Another limitation is that cases with a disease causing PHT were excluded from the study since PHT does not develop in all of these disease, CTEPH that develop in these patients are overlooked or attributed to an additional disease.

In conclusion, CTEPH development after PTE occurs in rate close to 50%. Close monitoring of PTE and the appropriate length of use of anticoagulant therapy are vital to prevent the development of embolism and CTEPH.

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