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Original Article

Evaluation of incidence of chronic thromboembolic pulmonary hypertension after acute pulmonary embolism in patients admitted to Imam Reza Hospital, Tabriz, Iran (primary results)

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Abstract

Introduction: Chronic thromboembolic pulmonary hypertension (CTEPH) is a late complication of pulmonary thromboembolism, which is associated with high morbidity and mortality. Although the pathogenesis is not fully understood, the damage and frequency of this complication have a wide range. The aim of this study was to evaluate the incidence of CTEPH following the first episode of acute pulmonary embolism (PE).

Methods: In a cohort study, 101 patients with acute embolism who had undergone anticoagulant therapy were followed up for at least one year. Patients that presented symptoms of dyspnea were selected. Echocardiography was performed on these patients, and they were evaluated for symptoms of right heart failure and increased pulmonary artery pressure of more than 35 mmHg.

Results: 101 patients with a mean age of 85.2 ± 17.7 years, including 57 men (56.4%) and 44 females (43.6%), were treated for a diagnosis of acute PE and were followed up for one year. 77.2% of patients had an idiopathic PE and 22.8% had it as the underlying cause. During follow-up, 23 patients (22.8%) experienced dyspnea. Echocardiography was normal in 13 cases and 10 cases had signs of right heart failure and pulmonary artery pressure. The overall incidence of CTEPH was 9.9%. Demographic data and computed tomography (CT) angiography findings were not associated with higher incidence of CTEPH.

Conclusion: CTEPH is a serious complication of acute PE, and the incidence of pulmonary hypertension after pulmonary emboli is relatively high. Age and gender did not influence its occurrence. Moreover, there was no relationship between the findings of CT angiography in the initial PE and chronic pulmonary hypertension rate of incidence.

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Introduction

Chronic thromboembolic pulmonary hypertension (CTEPH) is one of the late consequences of pulmonary embolism (PE), which is accompanied by a high rate of morbidity and mortality. Previous studies have reported CTEPH in 0.1-3.8% of patients who had pulmonary thromboembolism. CTEPH is life-threatening because it occurs with intraluminal thrombus and fibrotic stenosis or the complete obstruction of pulmonary arteries.[1] Although the exact pathogenesis of the induced damage is not well-understood, the incidence and frequency of this condition have a wide range, in some cases 8.8% of PE patients. This wide range

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could be due to the variable criteria used for diagnosis in previous studies.[2,3] Generally, CTEPH is known as a treatable, life-threatening disease. Considering the high frequency of CTEPH (3.8% to 8.8%), it is very important for patients to receive long-term follow-up treatments after ceasing treatment with anti-thrombotic agents. Applying specific screening programs for CTEPH by echocardiography has been recommended as an assistive tool for on-time diagnosis in some studies.[3] CTEPH diagnosis is often delayed until complications and nonspecific symptoms appear. Many patients are diagnosed late at final stages with signs of dyspnea and hemoptysis.[4,5] Because CTEPH is a cause of pulmonary hypertension that can be treated by surgery, there is a need to determine the epidemiological condition of CTEPH, investigate which people are more prone to CTEPH, and diagnose these patients before they are affected by sequels such as right ventricle failure. The current study was performed to evaluate the incidence rate and reasons involved in pulmonary thromboembolic complications.

Methods

This study was performed with a cohort design in the educational and therapeutic center of Imam Reza Hospital, Tabriz, Iran, affiliated to Tabriz University of Medical Sciences, Iran. It was conducted on patients affected by acute PE with the assistance of the educational group of internal and pulmonary diseases and the cardiology department. The sample consisted of 101 hospitalized and treated patients with acute PE who met the criteria for entering the study. The terms for inclusion in the study were patient agreement, confirmation of acute embolism by pulmonary computed tomography (CT) angiography, and were referred for therapeutic follow-up. All the patients whose acute PE had been confirmed by CT angiography and did not have any history of embolism were included in the study. Exclusion criteria were patients with a previous history of pulmonary emboli, evidence of chronic embolism in CT angiography (as determined by the way the clot takes place on vascular walls), history of pulmonary hypertension secondary to other accompanying diseases such as chronic obstructive pulmonary disease (COPD) and interstitial lung disease (ILD), and connective tissue diseases.

Patient history was taken, and a questionnaire was provided to record information regarding age, sex, time of initial symptoms, familial background, and risk factors (e.g., operation record, oral contraceptive pills (OCP) consumption, motionlessness, cancer, cigarette use, repeated abortion). All the patients were followed up with three months after release from the hospital, and a complete history regarding the presence of CTEPH symptoms was taken, especially for dyspnea in resting condition, during activities, and continuously. Echocardiography was performed for patients who had a history of dyspnea. All the patients who had follow-up appointments every three months for a year, and people with dyspnea were invited for an interview and received an echocardiograph. All echocardiography were performed by the same cardiologist to reduce any personal bias. A patient who had pulmonary hypertension based on echocardiography without any evidence of other pulmonary disease or left heart disease underwent ventilation/perfusion scan. If at least one mismatch segmental defect was observed, the patient was considered as CTEPH. These patients underwent pulmonary CT angiography for evaluating the anatomical condition of the clot and indications for surgery. Finally, the incidence rate of hypertension and possible risk factors for its occurrence were determined. This study was performed under the observation of the Tabriz Medical Science University Ethical Committee after obtaining the required terms.

Quantitative data are presented as a mean ± standard deviation (SD), and qualitative data are shown as frequency and percentage. Student's independent t-test was used in order to compare the quantitative

data and a chi-square or Fisher's exact test was used for qualitative data. Assessment of risk factors involved in pulmonary hypertension incidence was performed by logistic regression model. Significance was considered as $P < 0.05$ in all cases. The data were analyzed using SPSS software (version 20, IBM Corporation, Armonk, NY, USA).

Results

This study investigated 101 patients with acute pulmonary thromboembolism and a mean age of 85.2 ± 17.7 years, among which the youngest and oldest were 18 and 88 years respectively. 57 patients were men (56.4%) and 44 were women (43.6%).

In their follow-up treatment, 23 cases (22.8%) had symptoms of dyspnea and underwent transthoracic echocardiography. In 13 cases (12.9%), the echocardiographic findings were normal and there was no evidence of pulmonary hypertension. In 10 cases (9.9%), the echocardiography findings were abnormal and suggestive of pulmonary hypertension. The echocardiography findings are shown in table 1.

As can be seen, the mean systolic pressure for right ventricles was too high and there was a right ventricular extension, which is indicative of pulmonary hypertension. Right ventricle function (RVF) was normal in four cases (40%) and abnormal and disturbed in six cases (60%). Due to the type of primary acute thromboembolism in patients with chronic pulmonary hypertension, anti-phospholipid diseases existed in just 1 case and 9 other patients (90%) were idiopathic. In patients who did not have chronic pulmonary hypertension, the frequency distribution of various background diseases involved in acute PE was idiopathic in 78 patients (77.2%). Other patients history included trauma caused by accident (30.4%), OCP use (4.3%), history of surgery (1.7%), being bedridden (17.3%), systemic lupus erythematosus (SLE) (4.4%), autoimmune polyglandular syndrome (APS) in 4.33%, and lower limb vascular thrombosis (17.3%).

Table 1. Echocardiographic findings in patients with chronic thromboembolic hypertension

Variable	Mean ± SD
LVEDD	42.3 ± 5.5
LVESD	23.9 ± 4.3
RAV	82.5 ± 5.2
RAA	23.4 ± 8.3
EF	53.1 ± 6.7
TAPSE	16.2 ± 3.5
IVC diameter	20.2 ± 4.3
PAP	44.5 ± 13.5
RVSM	7.4 ± 2.2
TRV	27.1 ± 1.7
RVSP	75.5 ± 20.7

LVEDD: Left ventricular end diastolic diameter; LVESD: Left ventricular end systolic diameter; RAV: Right atrial volume; RAA: Right atrial appendage; EF: Ejection fraction; TAPSE: Tricuspid annular plane systolic excursion; IVC: Inferior vena cave; PAP: Pulmonary arterial pressure; RVSM: Right ventricular size measure; TRV: Tricuspid regurgitant velocity; RVSP: Right ventricular systolic pressure; SD: Standard deviation

There was no significant difference between the patients affected by chronic pulmonary hypertension and other patients regarding the demographic findings, According to the regression model, no variable was involved in predicting the incidence of CTEPH. The findings of the primary CT angiography performed on patients are shown in table 2.

Table 2. Frequency distribution and comparison of demographic findings

Variable	CTEPH patients [n (%)]	Non-CTEPH patients [n (%)]	P*
Main artery	3 (42.9)	32 (35.2)	0.40
Segmental	0 (0)	31 (34.1)	0.20
Lobar	4 (57.1)	13 (25.3)	0.20
Saddle	0 (0)	5 (5.5)	0.20
Pulmonary infarction	1 (14.3)	44 (48.4)	0.80
Pleural effusion	1 (14.3)	51 (56.0)	0.30
Right pulmonary artery	3 (30.0)	29 (31.9)	0.10
Left pulmonary artery	0 (0)	7 (7.7)	0.10
Both lungs	7 (70.0)	55 (60.4)	0.10

*Chi-square test, CTEPH: Chronic thromboembolic pulmonary hypertension

No significant difference was observed between the two groups. Based on the regression model, none of the CT angiography findings were effective in predicting chronic pulmonary hypertension in patients with acute PE. In 10 cases of confirmed chronic hypertension, a mortality rate of 10% was seen with one death in the follow-up period. Surgery was performed in 6 cases (66.7%), and nonsurgical therapy was performed in 2 cases (22.3%). In 1 case, the patient did not agree to an operation.

Discussion

The real incidence and prevalence of CTEPH are not yet clear in the normal population. After acute PE, CTEPH incidence has been reported as 0.1% to 8.8%.[13] CTEPH is a serious side effect of acute PE; however, the pathophysiology and the exact mechanism have not yet been determined.[5,6] It may be due to referral embolisms or disturbances in the function of pulmonary artery endothelial. Patients affected by CTEPH face nonspecific manifestations resulting from right heart failure, and 40% of these patients may not have any history of thromboembolism.[6] In a study published in South Korea, a high incidence of CTEPH was reported in cases with acute PE, unlike previous studies.[7] In a study performed by Park et al., the incidence rate was reported as 6.1%. According to new studies, the incidence of pulmonary hypertension is higher after acute PE in the first year of follow-up. However, it was previously supposed that the low incidence and longer duration of primary acute episodes is less important as compared to CTEPH in patients with acute PE.[7]

In previous studies, cumulative incidence based on the time passed after the first episode of acute PE has been reported as 0.8% in the first year, 1.3% in the second year, and 1.5% in the third year.[8] In our study, patients with acute PE had symptoms of dyspnea in 22.8% of cases in the one-year follow-up after receiving treatment. According to echocardiograph investigation, 9.9% of patients had findings related to chronic pulmonary hypertension. This incidence rate was higher as compared to previous reports. In a study by Hoeper et al., an assessment of 78 patients with acute pulmonary thromboembolism showed that pulmonary hypertension and disturbance in right ventricular function was present in 4% of patients in the first year based on the findings of pulmonary echocardiography.[8] In a study conducted in Turkey by Kayaalp et al., CTEPH existed in 5.5% of patients after follow-up in the first and second years.[4] The main reasons for the significant changes in the incidence rate of CTEPH in studies using screening methods are the diagnostic methods, duration of follow-up, and sample size. In some studies, the presence of primary clinical signs such as dyspnea have been used as the primary screening method, and some others have used echocardiography of all patients with an acute primary embolism.

Primary echocardiography in patients with nonspecific manifestations, including dyspnea after acute PE, is an efficient tool for determining the occurrence of pulmonary hypertension.[9] Evaluating the right ventricular function and measuring the function and morphology of the right ventricle by echocardiography have shown to have a significant correlation with the incidence of CTEPH.[10] In Klok et al. investigation, echocardiography was used to determine the cases of CTEPH after acute PE in a screening program.[11] In this cohort study, all the patients who had a history of acute PE underwent echocardiography. People who had suspicious findings in their echocardiographs underwent accurate workup, including ventilation-perfusion scan and catheterization of the right heart.[11] Pulmonary hypertension existed in 19 cases based on clinical findings and in 10 cases based on an echocardiography screening program. In 4 cases, a definitive diagnosis of chronic pulmonary hypertension was done in work-up. Unlike other studies, the overall incidence rate was low at an estimated 0.57%. According to this study, a screening program with echocardiography is not required for all patients since the incidence of

CTEPH after acute PE is low. In our study, people with dyspnea were about 22%, while 23 people did not have dyspnea and incidence rate was also high, unlike Klok et al.[11] study.

Without therapeutic intervention, survival decreases significantly in these patients. In one study, the five-year survival of patients with chronic pulmonary hypertension and a mean pulmonary artery pressure of more than 40 mmHg was about 30%. In patients whose pulmonary artery pressure was higher than 50 mmHg, five-year survival has been stated as 10%, and the mortality rate is too high.[12] In another study, a mean pulmonary artery pressure of 30 mmHg was considered as the threshold for poor prognosis of the patients. In our study, the mortality rate was 10% in the first year of follow-up and the mean pulmonary artery pressure was about 44 mmHg, similar to previous echocardiography findings.[13,14]

In the study done by Dentali et al., pulmonary hypertension risk factors included an age of over 70 and a pulmonary artery systolic pressure higher than 50 mmHg.[3] Contrary to the findings of this study, Kayaalp et al. study did not find any relationship between age, primary treatment, and thromboembolism with CTEPH incidence.[4] The current study was also unlike Hoeper et al. study and there was no relationship between age, sex, and other demographic findings with the incidence of CTEPH after primary acute PE.[8] Moreover, none of the findings of CT angiography have been effective in predicting the occurrence of chronic pulmonary hypertension in patients with acute PE. In Park et al. study, an extension of the right ventricle, D-dimer, and mean of right ventricular systolic pressure (RVSP) were the risk factors related to CTEPH after acute PE.[7] The most important predictive factor for CTEPH with echocardiographic findings is a mean RVSP that has a relative risk of 1.05. In the findings of our study, the measurements of echocardiography variables were higher in people with dyspnea after acute PE in cases with pulmonary hypertension, similar to the results of Parks et al. study.[8]

Conclusion

Chronic pulmonary hypertension is a serious consequence of acute PE and its incidence is relatively high following the acute PE. Age and sex did not affect its incidence. There was no relationship between primary acute embolism and the occurrence of chronic pulmonary hypertension in CT angiography.

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Authors' Contribution

Farid Rashidi supervised the project and interventional treatment. Hussein Sate was responsible for echocardiography of patients with CTEPH. Nilsa Dourandish collected the data and contributed in paper writing. Ali Tabrizi performed the data analysis and contributed in academic writing.

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Conflict of Interest

Authors have no conflict of interest.

Ethical Approval

This study was approved by the Medical Ethics Committee of Tabriz University of Medical Sciences.

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