Journal of Experimental and Clinical Medicine
https://dergipark.org.tr/omujecm

Research Article

J Exp Clin Med
2022; 39(3): 733-737
doi: 10.52142/omujecm.39.3.27

Imaging of the right ventricle in predicting the development of chronic thromboembolic pulmonary hypertension (CTEPH)

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Received: 16.02.2022 • **Accepted/Published Online:** 14.08.2022 • **Final Version:** 30.08.2022

Abstract

There is increasing evidence in the literature emphasizing the importance of right ventricular (RV) imaging in the prognosis of pulmonary hypertension. We aimed to investigate the predictive role of RV dysfunction parameters assessed by echocardiography (ECHO) and thorax computed tomography (CT) in developing CTEPH. We included prospectively patients diagnosed with pulmonary embolism (PE). All patients underwent ECHO and CT within 24 hours after admission. We repeated CT and ECHO after six months and one year to assess the incidence of CTEPH and the predictive role of RV dysfunction factors in the development of CTEPH. We included twenty-two patients (seven male) with a mean age of 53.9±17.9 years; CTEPH developed in two patients during the follow-up. Baseline PO2 levels were significantly lower in patients with CTEPH (61.5±11.4 vs 77.8±25.2, $p<0.05$). The baseline RV diameter, RV EF, and systolic PAP levels evaluated by ECHO differed significantly in two patients who developed CTEPH. Two patients that developed CTEPH had the lowest RVS (-10.3% and -11.7%). This study claims that hypoxemia, decreased RV EF, RVS, increased systolic PAP values in ECHO, and increased RV/LV ratio evaluated in thorax CT indicate the severity of RV dysfunction in acute PE and may predict CTEPH development.

Keywords: Hypertension, echocardiography, pulmonary circulation, right ventricle

1. Introduction

Chronic thromboembolic pulmonary hypertension (CTEPH) is a rare pulmonary vascular disease caused by clot formation that occludes the vascular bed and may occur after a symptomatic acute pulmonary embolism (PE) event. There is an expected natural course following acute PE. The clot's complete or significant resolution is marked by improved pulmonary hemodynamics, gas exchange, and exercise tolerance. However, CTEPH may occur after a recurrent PE event and inadequate resolution of thrombus. CTEPH frequency was reported as 1-4% in PE survivors (1,2).

Clinical symptoms and signs of CTEPH are absent in early disease and may resemble acute PE or idiopathic pulmonary hypertension. Early diagnosis is essential in CTEPH because it is a disease that can be cured in the majority of patients who are eligible for pulmonary endarterectomy. However, routine screening for CTEPH after PE is not supported by current evidence (3).

Several risk factors have been reported in previous studies considered associated with the development of CTEPH (4). These risk factors mainly include comorbid conditions such as ventriculoatrial shunt, infected cardiac pacemaker, splenectomy, thyroid replacement therapy, and malignancy (5). Identifying simple, non-invasive, reproducible parameters that predict the development of CTEPH during PE evaluation is vital for the early diagnosis of the disease. There is increasing evidence in the literature emphasizing the importance of right ventricular (RV) imaging in the prognosis of pulmonary hypertension. However utility of these factors in the development of CTEPH after PE event is not evaluated (6-8). This study aimed to investigate the predictive role of RV dysfunction parameters assessed by echocardiography (ECHO) and thorax computed tomography (CT) in developing CTEPH.

2. Materials and Methods

According to thorax CT findings, we included prospectively patients admitted to our hospital and diagnosed with PE in this study while excluding the patients with different diseases such as scleroderma, COPD, left heart failure, sleep apnea, and connective tissue disease that may cause pulmonary

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hypertension (PH). We recorded patients' demographic characteristics, arterial blood gas analysis, D-dimer, and NT-proBNP levels. All patients underwent thorax CT and ECHO within 24hours after admission. We repeated thorax CT and ECHO after six months and one year to assess the incidence of CTEPH and evaluate the predictive role of RV dysfunction factors in the development of CTEPH. The same physician performed the ECHO examination within 24 hours after application using a 3.0 MHz transducer on a General Electric VingmedVividSystem7 device (Horten, Norway). We determined the right ventricular (RV) diameter, ejection fraction (EF), systolic pulmonary artery pressure (sPAP), acceleration time (ACT), tricuspid annular plane systolic excursion (TAPSE), right ventricular strain (RVS), the rate of change in myocardial diastolic and systolic peak.

The same radiologist performed thorax CT by intravenous opaque material in 0.5mm sections from the apex of the lung through Toshiba Aquilion (Tokyo, Japan) tomography on all study patients. We evaluated the primary PA diameter, RV diameter, right atrium diameter, RV wall thickness, septum wall thickness, and RV/LV ratio by CT.

In follow-ups, we suspected CTEPH in patients with a systolic PAP greater than 50 mmHg in ECHO and with chronic, organizing, and occlusive thrombus in the pulmonary arteries (PA) on thorax CT despite effective anticoagulant therapy[3]. We performed right heart catheterization to confirm the CTEPH diagnosis. The ethical committee of Kocaeli University approved the study, and we obtained written informed consent from all participants.

2.1. Statistical analysis

We conducted the statistical analysis of the data obtained in the study in the SPSS 16.0 program and expressed the results as mean ± standard deviation (SD). We used descriptive statistics and Chi-square tests to compare the demographic characteristics of the patients while using the non-parametric Wilcoxon and Friedman tests to compare the initial and control parameters and the Mann-Whitney U test to compare the intergroup meanings. The Pearson correlation test assessed the correlation between variables. We considered a p-value of less than or equal to 0.05 significant.

3. Results

Twenty-two patients (seven male) with a mean age of 53.9±17.9 years were diagnosed with PE. CTEPH developed in two patients during the follow-up, and both patients underwent pulmonary endarterectomy. We observed a significant improvement in clinical and functional parameters in the postoperative follow-ups.

The leading symptom was dyspnea in most patients (15 patients, 68.2%). Baseline demographic characteristics were not different in patients diagnosed with CTEPH compared to others; however, baseline PO2 levels were significantly lower in patients with CTEPH (61.5±11.4 versus 77.8±25.2 p <0.05) (Table 1).

Table 1. Comparison of laboratory findings between CTEPH and non-CTEPH patients

	CTEPH (+)	CTEPH (-)	p
D-dimer	0.95±0.4	3.89±3.53	>0.05
NT-ProBNP	165±26.8	159±281	>0.05
Troponin	0.05±0.01	0.06 ± 0.03	>0.05
PO2	61.5±11.4	77.8±25.2	<0.05

CTEPH: Chronic thromboembolic pulmonary hypertension, NT-ProBNP: NT-pro brain natriuretic peptide, PO2: Partial oxygen pressure

Control ECHO was available only in 18 patients because two patients died and two did not come to their follow-ups. Three patients had tricuspid regurgitation (TR) at the advanced stage, while no TR was present in seven patients. Systolic pulmonary artery pressure was higher than 50 mmHg in three patients, two of whom developed CTEPH in follow-ups. After treatment, sPAP and RV diameters decreased significantly. Furthermore, compared to baseline parameters, RVS, RV EF, and TAPSE values significantly increased in the 6th and 12th-month follow-up ECHO (Table 2).

Table 2. Baseline and follow-up echocardiographic characteristics of patients

	Baseline	6 month	12 month	p-value
RVS (%)	-16.88±3.76	-18.62±3.96	-19.16±3.16	0.001
RV diameter (mm)	28.58±3.32	28.31±7.85	25.72±3.67	0.001
RV EF, %	58.11±15.64	63.77±12.84	66.27±10.47	0.001
PAPMax (mmHg)	33.48±18.75	30.53±19.70	25.51±17.86	0.011
ACT (msn)	72.45±17.41	75.83±15.43	78.33±16.38	0.245
TAPSE (mm)	17.95±3.53	19.50±2.87	20.66±3.18	0.001

RVS: right ventricular strain, RV: right ventricle, PAPmax: systolic pulmonary artery pressure, ACT: acceleration time, TAPSE: tricuspid annular plane systolic excursion

In thorax CT, we detected thrombus originating from the right system in five, from the left system in four, and bilateral involvement in 13 patients. In the 6th and 12th months, control CT examination was available in 19 and 18 patients, respectively. Compared to baseline measurements, the main pulmonary artery (PA), RA, RV diameters, and RV/LV ratios significantly decreased on the 6th and 12th-month control CT (Table 3). We found a significant correlation between RV EF detected in ECHO and RV diameter detected in thorax CT (p:0.001). In thorax CT, RV strain in ECHO significantly correlated with septal flattening (p:0.035) and RV diameter (p:0.008). We observed that the RV/LV ratio evaluated in CT was correlated with all follow-up ECHO parameters (RV diameter, p:0.003; RV EF, p:0.007; PAP max, p:0.044; and RVS, p: 0.02).

Table 3. Baseline and follow-up thorax computed tomography characteristics of patients

	Baseline	6 month	12 month	p-value
Main pulmonary artery diameter (mm)	28.81±5.19	26.78±5.38	25.61±5.78	0.006
RV diameter (mm)	42.86±8.10	40.05±5.97	38.88±6.89	0.005
RA diameter (mm)	49.04±9.06	44.89±14.27	42.11±8.69	0.002
RV wall thickness (mm)	3.41±1.64	3.01±1.02	2.71±1.00	0.282
Septum wall thickness (mm)	10.75±3.10	10.65±1.89	11.05±2.04	0.740
RV/LV ratio	1.26±0.45	1.09±0.25	1.00±0.20	0.002

RV: right ventricle, RA: right atrium, LV: left ventricle

The baseline RV diameter, RV EF, and sPAP levels evaluated by ECHO were significantly different in two patients who developed CTEPH compared to others. We detected the lowest RVS values in these patients (-10.3% and -11.7%).

4. Discussion

This study suggests that hypoxemia, decreased RV EF, RVS, increased systolic PAP values in ECHO, and increased RV/LV ratio evaluated in thorax CT indicate the severity of RV dysfunction in acute PE and may predict CTEPH development.

The actual incidence and prevalence of CTEPH have not yet been fully defined and remain a controversial topic (3, 5). In recent studies, the incidence of CTEPH after acute PE has been reported to be around 4-5%. However, most experts believe real CTEPH varies from 0.5% to 2% after acute PE (1, 5, 9). In a study conducted by Ribeiro et al., 78 patients (5.1%) who had survived acute PE developed CTEPH at the end of a 1-year follow-up (2). Kayaalp et al. showed that CTEPH developed in five of 90 (5.5%) patients followed up for 1-2 years after acute PE (10). In another study, symptomatic CTEPH frequency in the first two years after a critical PE event was 3.8% in 223 patients followed up for an average of 7.8 years, and there were no new cases diagnosed with CTEPH after the first two years (1) . Dentali et al. included 92 patients with acute PE with a median follow-up time of 6 to 12 months and showed that CTEPH developed in 8 patients while half of these patients were asymptomatic (9). Our study included a relatively low number of patients; however, two patients (9%) out of 22 patients developed CTEPH. This data suggests that the prevalence of the disease might be higher than reported in the literature, and active screening after acute PE events may be beneficial on an individual basis by increasing the number of early diagnosed patients. However, it is clear that this is not a cost-effective method and is not supported by the current evidence. Therefore, it is necessary to identify the high-risk group and improve the follow-up parameters used in the early diagnosis of these patients.

Echocardiography (ECHO) is a non-invasive method widely used in screening PH. In the diagnosis of PH, the sensitivity of ECHO varies between 63-100%, and specificity ranges between 60-98% (11). Echocardiography should always be performed when PH is suspected; however, it is not sufficient to make a specific diagnosis and decide on treatment, and cardiac catheterization is required (3).

CTEPH is limited as it allows diagnostic evaluation only in symptomatic patients, carrying the risk of diagnosing disease in advanced stages. On the other hand, routine screening for CTEPH in asymptomatic survivors of PE is not cost-effective and is not recommended by current guidelines (3). Therefore, we need to determine predictive factors for CTEPH from the routine diagnostic workup in acute PE besides the above-mentioned clinical risk factors to compose a high-risk population in which follow-up for CTEPH is reasonable.

Previous studies evaluated several echocardiographic parameters to predict CTEPH development, such as PA pressure, RV diameter, RV EF, ACT, and TAPSE (12). However, assessment of RV function is complex because of the complexity of RV anatomy. Recently RV strain analysis by 2D speckle tracking ECHO has been introduced to evaluate RV function in PH. Shiino et al. demonstrated that RVS had a significant correlation with an invasively determined pulmonary hemodynamic parameter. It was a valuable indicator to detect increased mean PAP in patients with CTEPH (13). Strain is a parameter of RV myocardial deformation, and it has an excellent diagnostic and prognostic accuracy in patients with PH (14). Previous studies have shown that RVS markedly decreased in patients with PE compared to healthy controls and improved on the 15th day after treatment (14, 15). In our study, lower RVS values in patients with CTEPH suggest that ECHO follow-up should be planned in patients with low strain values, and CTEPH should be suspected if there is no improvement in RVS after the treatment. However, RVS measurement is still not widely used in routine clinical practice.

Nowadays, multislice thorax CT is the most commonly used imaging technique in diagnosing PE. It has been reported that thorax CT can evaluate RV structure and function and diagnose PE or CTEPH, which correlates with disease severity and ECHO follow-up parameters (16, 17). It has been shown that the ratio of RV/LV above 0.9 in thorax CT is associated with a poor prognosis in PE (18, 19). The study by Ende-Verhaar et al. showed that the risk of

developing CTEPH after pulmonary embolism is higher in patients with RV/LV ratio greater than 1 in thorax CT (20). In this study, both patients diagnosed with CTEPH had an RV/LV ratio greater than 1.0 in baseline thorax CT evaluation. In addition, we determined that this parameter was the best-correlated variable with the follow-up parameters in ECHO.

The most important limitation of our study was the relatively low number of patients. In addition, some follow-up parameters in patients with and without CTEPH do not differ in the statistically significant dimension and are attributed to the small number of patients. We believed that the number of patients was influential in elucidating the difference in variables such as pro-BNP, D-dimer, troponin, and CT findings. Nevertheless, we consider early detection of two CTEPH cases, appropriate surgical intervention, and improvement of their prognosis significant despite the small number of patients. Limiting the follow-up period to one year can constitute another limitation. Prolonging the follow-up time may allow early detection of new patients (1, 21).

CTEPH is a severe disease that may result in progressive right heart failure and death. It may follow acute PE events; however, routine screening of every asymptomatic survivor after acute PE is not practical and not recommended. This study suggests that hypoxemia, decreased RV EF, RVS, increased systolic PAP values in ECHO examination and increased RV/LV ratio evaluated in thorax CT indicate the severity of RV dysfunction in acute PE events and may predict CTEPH development. Control ECHO examination on the third or sixth month after the treatment in patients with one or more of these risk factors during acute PE events may provide an early diagnosis of CTEPH.

Conflict of interest

The authors declared no conflict of interest.

Funding

No funding was used for the study.

Acknowledgments

Ethical Approval: The Ethics Committee of Kocaeli University approved this study (date: 25.07.2011, No: KAEK 10/11). We conducted the study per the principles of the Declaration of Helsinki and obtained written informed consent from all participants.

Authors' contributions

Concept: İ.B., F.Y., Design: Y.T.G., İ.B., Data Collection or Processing: Y.T.G., İ.B., Analysis or Interpretation: İ.B., Y.T.G., F.Y., H.B., T.Ş., S.D., Literature Search: Y.T.G., İ.B., S.B., T.Ş., S.D., Writing: Y.T.G., İ.B., H.B.

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