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The effects of left ventricular function on right heart in the patients with acute pulmonary embolism

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Abstract

The optimal treatment approach of haemodynamically stable patients with acute pulmonary embolism (PE) remains controversial. Absence of RV dilatation or the ratio of RVD/LVD (<0.9) identifies patients at low risk of all-cause mortality in acute PE. Normally, we know that both ventricles' motion and wall thickness may affect each other. In this study, we aimed to evaluate the effect of left ventricular functions on the findings of right ventricular dysfunction in the patients with acute PE. The present study was a retrospective cross- sectional design. The patients were firstly categorized according to early mortality risk stratification. Later, intermediate-high and high risk groups were re-categorized according to having or not having left ventricular dysfunction by echocardiography. The cardiac findings and measurements were obtained from both thorax computerized tomography angiography and echocardiography. A total of 200 patients with acute PE were included in the study. The ratio of RVD/LVD was found significantly higher in patients with normal LV function than the patients with LV dysfunction (p:0.030). But, the RV and LV wall thickness, D-septum were similar among the patient groups (p>0.05). The ratio of RVD/LVD was found significantly higher in patients with normal LV function and acute PE. We think that baseline LV function may affect the findings of RV during acute PE event. Especially when we evaluate intermediate-high risk patients by echocardiography, we should consider left ventricular function.

Keywords: Acute pulmonary embolism, treatment, left ventricular function, right ventricular dysfunction

Introduction

Acute pulmonary embolism (PE) occurs due to the obstruction of the pulmonary arteries and it is the third most frequent cardiovascular disease. The incidence of acute PE is approximately 100–200 per 100.000, and the incidence increases with age. Fatal and severe complications may occur due to acute PE and it has high morbidity and mortality [1]. Based on an epidemiological model in 2004, more than 317.000 deaths (with a whole population of 454.4 million) were attributed to acute PE in six European countries [2].

Acute PE affects both circulation and gas exchange. Right ventricular (RV) failure due to overpressure is regarded to be the most important cause of death in severe PE. It was shown that nearly 50% of first-time patients diagnosed with submassive PE have RV dysfunction at time of diagnosis [3]. When 30–50% of the total cross-sectional area of the pulmonary arterial bed is occluded by thrombus, pulmonary arterial pressure (PAP) increases [1]. Also during acute PE, some mediators such as thromboxane A2 and serotonin contribute to the increase in PAP [4].

The sudden increase in PAP results in RV enlargement, and as a result the contractile properties of RV myocardium change. The interventricular septum displaces leftward and desynchronization of the ventricles occurs. Consequently, left ventricular (LV) filling is discontinued in early diastole, and cardiac output deteriorates. This causes to hypotension, hemodynamic collapse, cardiogenic shock and mortality [5].

RV dysfunction can be evaluated by echocardiography which gives quick and safe information on RV size and function. Determination of decreased RV ejection and depressed RV contractility by echocardiography are important clues for diagnosis of PE. Other findings of RV dysfunction are RV free wall hypokinesia or akinesia due to RV infarction and measurement of tricuspid annulus plane

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systolic excursion (TAPSE) [6,7]. However, echocardiographic results about RV in PE patients vary and its negative predictive value is 40–50%. In some cases, if cardiac evaluation with echo is normal, PE cannot be excluded with certainty [8,9]. On the other hand, RV dilatation or dysfunction findings are important for treatment for acute PE. Additionally, RV dysfunction can be assessed by thorax computerized tomography angiography (CTA) with evaluation of the right-to-left ventricular (RV/LV) diameter ratio in PE patients. Especially, multi-slice scanners allow accurate visualization of the cardiac chambers [6,10-12].

Thrombus burden in pulmonary artery is very important in prognosis. The RV / LV ratio is extremely correlated with the degree of pulmonary artery obstruction. The right ventricle, and hence the left ventricle, are affected when thrombus load is high [13]. The right ventricular wall is thinner than the left ventricular wall. Therefore, right ventricle is more dilated in the case of sudden load. Also, both ventricles' motion and wall thickness may affect each other. In our clinical observations, although the thrombus burden was high, the right ventricle did not expand as expected in some patients especially in the presence of left ventricular concentric hypertrophy or left failure. Thus, we aimed to evaluate the effect of left ventricular function on the findings of right ventricular dysfunction in patients with acute PE.

Material and Methods

The present study was a retrospective cross-sectional design and it was carried out between 2018 and 2019 in Ankara Yıldırım Beyazıt University, School of Medicine and Ankara Atatürk Training and Research Hospital. The regional committee of medical and health research ethics approved the study. All subjects gave their written consent to participate. The study population was selected according to ICD code I.26. A total of 265 patients with acute PE were screened and 200 patients who were hospitalized, diagnosed with PE by thorax CTA and patients who can achieve echocardiography results were included in the study. The data of this study were obtained by retrospectively examining medical files of the cases' with acute PE. Inclusion criteria were being older than 18 years old and having diagnosis of PE with thorax CTA. Exclusion criterion was being diagnosed as acute PE by other techniques except thorax CTA because of certain reasons such as having renal failure or pregnancy. Also, patients whose echocardiography results could not be obtained were excluded from the study.

A structured form was used for the study. Firstly, patients' demographic characteristics, initially hemodynamic parameters and laboratory findings [complete blood count, C-reactive protein, routine biochemical analysis (fasting blood sugar, urea, uric acid, creatinine, sodium, potassium, total protein, albumin, AST, ALT, cholesterol, HDL, LDL, triglyceride), D-dimer (normal value: < 0,55 mg/L), NT-pro BNP (normal value: <125 ng/L) , troponin (normal value: < 45 ng/L), CK-MB (normal value: < 5 µg/L), Myoglobin (normal value: < 110 µg/L) were recorded. Later, findings of electrocardiography, chest X-ray, thorax CTA and echocardiography were recorded.

The patients were firstly categorized according to early mortality risk stratification according to 2014 ESC guidelines. A high-risk PE is defined as suspected or confirmed PE in the presence of shock or sustained hypotension. An intermediate-risk PE is defined as suspected or confirmed PE with right ventricular dysfunction in the absence of shock. Echocardiographic findings of RV overload and / or dysfunction are described as enlarged right ventricle, increased RV / LV, McConnell sign and flattenned interventricular septum (1). Later, intermediate-high and high risk groups (candidates for thrombolytic therapy) were re- categorized according to having or not having left ventricular dysfunction by echocardiography (who has diastolic dysfunction, concentric hypertrophy, global or local hypokinesia, left ventricular relaxation dysfunction or ejection fraction (EF) less than 50%). Cardiac findings were obtained from both thorax CTA and echocardiography. Right and left ventricular diameter (RVD, LVD), wall thicknesses of right and left ventricles (RV, LV), the ratio of RV/LV diameter, aortic diameter, pulmonary artery (PA) diameter and the ratio of PA/aorta diameters were obtained retrospectively from patients' CTA images. The 2 axial sections that showed the maximal distance between the ventricular endocardium and the interventricular septum, perpendicular to the long axis of the heart, for the RV and LV, respectively, were identified. RVD axial and LVD axial were subsequently measured, and the RVD axial / LVD axial ratio was calculated. All thorax CTA was applied by 256 slice Siemens Somatom Definition Flash Single Slice 256. If value was 20, kVP value was 100, section thickness was 1 mm and pitch value was 0.9. The measurements were compared in the groups.

Statistical Analysis

The distribution of continuous measurements in the study was analyzed with Shapiro-Wilk test and normality graphs. All continuous and discrete measurements were expressed with median (minimum-maximum: min-max). Categorical variables were expressed numerically as percentages (%). In terms of continuous and discrete measurements, the risk groups were compared with the Jonckheere Terpstra test, which is the trend test for sequential groups, and otherwise with the Kruskal-Wallis test. After the Jonckheere Terpstra test, the Bonferroni correction was performed and after the Kruskal-Wallis test, Bonferroni-Dunn correction was applied. Patients with and without left ventricular dysfunction were compared with Mann- Whitney U test for numerical variables. The distribution of categorical variables in groups was analysed by chi-square tests. Column percentages were compared by ratio test and Bonferroni correction if necessary. In the absence of enough numbers in the two-way tables, Monte Carlo simulation results of 10000 repetitions were given. The level of statistical significance was accepted as $p < 0.05$. IBM SPSS Statistics 22.0 (IBM Corp. Released 2012. IBM SPSS Statistics for Windows, Version 22.0. Armonk, NY: IBM Corp.) was used for statistical analysis and calculations.

Results

A total of 200 patients, who were diagnosed with acute PE according to thorax CTA reports, were included in the study. Of the patients with a median age of 66 years (min-max: 19-94), 42.5% (n=85) were female (Table 1).

It was determined that 25.5% (n=51) of the patients were smokers, 30% (n=60) had stopped smoking and the rest had never smoked before. 60.5% (n=121) of the patients had at least one concomitant disease (Table 1). 45% (n=90) of the patients had cardiovascular diseases (CVD) (percentage of coronary artery diseases was 19%,

hypertension was 32%, diabetes mellitus was 15%, hyperlipidemia was 3%, left heart failure was 7.5% and atrial fibrillation was 2%).

The distribution of demographic and clinical characteristics of patients according to early mortality risk groups is given in Table 2.

Patients in the intermediate-high risk group were found to be older than the patients in the low-risk and intermediate-low risk groups ($p<0.05$). Gender and smoking were similar among the risk groups ($p>0.05$). The proportion of additional disease in patients with intermediate- high risk was higher than that in patients with low risk. The proportion of CVD was higher in patients with intermediate-high risk than those with intermediate-low risk.

Systolic and diastolic blood pressure was found to be lower in patients with high risk than other risk groups ($p<0.05$). D-dimer level was higher in patients with intermediate-high risk than in the low-risk group. NT-proBNP and Troponin were the lowest in low-risk patients, and the highest in intermediate-high and high-risk patients ($p<0.001$). CK-MB level was lower in low-risk and intermediate-low risk patients than in intermediate-high and high-risk patients ($p<0.001$). SpO2 level was lower in intermediate-high risk patients compared to low and intermediate-low risk patients and in high-risk patients compared to low-risk patients ($p<0.001$) (Table 2).

Table 1. Demographic and clinical characteristics of all patients

	Total (n=200)
Age, years [median (min-max)]	66 (19-94)
Gender, n(%) **Female**	85 (42.5)
Smoking history, n(%)	
Smoker	51 (25.5)
Ex-smoker	60 (30.0)
Never smoker	89 (44.5)
Comorbidity, n(%)	121 (60.5)
CVD	90 (45)
Others	80 (40)
SBP, (mmHg) [median (min-max)]	115 (70-180)
DBP, (mmHg) [median (min-max)]	70 (40-100)
D-dimer (mg/L), [n=192] [median (min-max)]	3,746 (0,25-38)
NT-pro BNP (pg/ml), [n=178] [median (min-max)]	337.5 (10-35000)
Troponin (ng/L), [n=192] [median (min-max)]	18 (3-794)
CK-MB (ng/ml), [n=196] [median (min-max)]	1.63 (0.06-18.85)
Myoglobin (ng/ml), [n=186] [median (min-max)]	32 (20-616)
SpO_2, [n=196] [median (min-max)],%	94 (65-98)
Risk groups, n (%)	
Low	63 (31.5)
Intermediate-low	69 (34.5)
Intermediate-high	46 (23.0)
High	22 (11.0)

CVD: Cardiovascular diseases, SBP: systolic blood pressure, DBP: diastolic blood pressure, BNP: Brain natriuretic peptid

Table 2. Demographic and clinical characteristics of patients according to the early mortality risk groups

	Low (n=63)	**Intermediate-Low (n=69)**	**Intermediate-High (n=46)**	**High (n=22)**	
	Median (min-max) n (%)	Median (min-max) n (%)	Median (min-max) n (%)	Median (min-max) n (%)	**p-value**
Age, years	63 (19-89)[1]	66 (20-90)[2]	74 (42-94)[1,2]	63 (30-88)	**0.001**
Gender, female	20 (31.7)	32 (46.4)	25 (54.3)	8 (36.4)	0.094
Smoking history					0.125
Smoker	21 (33.3)	19 (27.5)	6 (13.0)	5 (22.7)	
Ex-smoker	22 (35.0)	17 (24.6)	16 (34.8)	5 (22.7)	
Never smoker	20 (31.7)	33 (47.9)	24 (52.2)	12 (54.6)	
Comorbidity	32 (50.8)[1]	38 (55.1)	36 (78.3)[1]	15 (68.2)	**0.019**
CVD	24 (38.1)	26 (37.7)	29 (63)	11 (50)	**0.029**
Other	21 (33.3)	29 (42)	22 (47.8)	7 (31.8)	0.386
SBP, (mmHg) [median (min- max)]	120 (95-160)[1]	120 (70-180)[2]	110 (100-160)[3]	90 (70-170)[1,2,3]	**<0.001**
DBP, (mmHg) [median (min- max)]	80 (50-90)[1]	75 (60-100)[2]	70 (50-100)[3]	60 (40-90)[1,2,3]	**<0.001**
D-dimer (mg/L), [n=192]	3.02 (0.25-10)[1]	4. 23 (0.63-16)	8.24 (0.86-38)[1]	4.13 (0.42- 23.31)	**<0.001**
NT-pro BNP (pg/ml), [n=178]	101 (10-3109)[1,2,3]	370 (25-35000)[1,4]	1344.5 (10.49- 13918)[2,4]	978 (52-8331)[3]	**<0.001**
Troponin (ng/L), [n=192]	7.37 (3-318)[1,2,3]	16 (3-227)[1,4,5]	38.8 (14-377)[2,4]	62.5 (7.7- 794)[3,5]	**<0.001**
CK-MB (ng/ml), [n=196]	1.22 (0.06- 16.00)[1,2]	1.50 (0.30-7.10)[3,4]	2.11 (0.57-18.85)[1,3]	2.70 (0.60- 11.00)[2,4]	**<0.001**
Myoglobin (ng/ml), [n=186]	23 (21-120)[1,2]	34 (21-616)	37.68 (20-614)[1]	46 (21-580)[2]	**<0.001**
SpO_2, [n=196], %	96 (79-98)[1,2]	95 (82-98)[3]	90 (80-98)[1,3]	93 (65-98)[2]	**<0.001**

[1,2,3,4,5] $p<0.05$, CVD: Cardiovascular diseases, SBP: systolic blood pressure, DBP: diastolic blood pressure, BNP: Brain natriuretic peptid

The proportion of bilateral thrombus in the pulmonary artery was lower in the intermediate- low risk group than in the intermediate-high and high-risk groups (p <0.001) (Table3).

The number of affected lobar arteries was similar in the low-risk and intermediate-low risk groups (p=0.992). Although it was observed that the median number of segmental arteries increased as the risk level increased (p=0.037), there was no significant difference when pair- wise comparisons were performed.

Right ventricular diameter was higher in the intermediate-high risk group than in the low and intermediate-low risk groups (p<0.001). The ratio of RVD/LVD was significantly higher in intermediate-high and high risk groups compared to lower and intermediate-low risk groups (p<0.001). There was no significant difference between LVD, right / left ventricular wall thickness and aortic diameter in terms of risk groups (p>0.05). The main PA diameter was lower in the low-risk group than in the other three groups (p<0.001). The ratio of main PA diameter to aorta diameter was significantly higher in the patients with high risk compared to the patients with low risk (p<0.001). D-septum was high in the intermediate-high risk group than in the low and intermediate-low risk groups (p<0.001).

The proportion of the patients with normal right ventricle was highest (93.7%, n=59) in low- risk patients, and the lowest (0.0%) was observed with echocardiography in intermediate- high risk patients (Table 4).

Table 3. CT results of patients according to the early mortality risk groups

	Low (n=63)	**Intermediate-Low (n=69)**	**Intermediate-High (n=46)**	**High (n=22)**	
	Median (min-max),n (%)	Median (min-max),n (%)	Median (min-max),n (%)	Median (min-max),n (%)	**p-value**
Localization of Thrombus					
Bilateral	5 (7.9)	1 (1.4)[1,2]	11 (23.9)[1]	6 (27.3)[2]	**<0.001**
Right main	5 (7.9)	4 (5.8)	3 (6.5)	3 (13.6)	0.712
Left main	5 (7.9)	3 (4.3)	4 (8.7)	1 (4.5)	–
Lobar artery	35 (55.6)	28 (40.6)	30 (65.2)	15 (68.2)	**0.027[a]**
Segmental	62 (98.4)	69 (100.0)	46 (100.0)	21 (95.5)	0.404
Number of lobar arteries	1 (0-5)[1]	0 (0-5)[2,3]	2 (0-5)[1,2]	2 (0-5)[3]	**0.008**
Number of segmental arteries	4 (1-17)	4 (1-16)	6 (1-18)	9 (1-16)	**0.037[a]**
RVD, mm	35.6 (24.8-51.7)[1]	37.2 (24.4-57.0)[2]	44.3 (28.7-69.8)[1,2]	42.3 (30.2-65.1)	**<0.001**
RV wall thickness, mm	3.2 (1.8-6.4)	3.1 (1.6-7.5)	3.4 (2.1-8.0)	3.0 (1.6-5.1)	0.374
LVD, mm	42.4 (29.1-57.1)	42.5 (29.3-61.6)	41.8 (23.2-56.1)	38.7 (28.3- 50.8)	0.050
LVwall thickness, mm	7.6 (4.7-12.6)	7.6 (4.3-15.6)	7.4 (5.1-14.0)	7.5 (4.3-11.4)	0.779
RVD/LVD	0.82 (0.57-1.34)[1,2]	0.89 (0.57-1.47)[3,4]	1.06 (0.60-1.97)[1,3]	1.05 (0.73-1.78)[2,4]	**<0.001**
D-Septum	18 (28,6)[1]	17 (24.6)[2]	27 (60.0)[1,2]	9 (40.9)	**<0.001**
Aorta diameter, mm	34.2 (22.6-48.6)	35.2 (24.4-50.0)	36.1 (29.0-48.2)	34.3 (20.2- 47.6)	0.257
Main PA diameter, mm	26.4 (20.1-44.1)[1,2,3]	29.5 (22.3-53.2)[1]	31.1 (20.6-44.1)[2]	31.0 (22.3-39.3)[3]	**<0.001**
PA/Aorta	0.81 (0.58-1.13)[1]	0.81 (0.53-1.31)	0.86 (0.57-1.29)	0.89 (0.67-1.54)[1]	**0.001**

[1,2,3,4]p<0.05; [a]:There were no significant differences between pair-wise comparisons, RV: Right ventricle ; LV: Left ventricle; RVD: Right ventricular diameter; LVD: Left ventricular diameter, IVS: Interventricular septum, PA: Pulmonary artery

Table 4. ECHO results of the patients according to the mortality risk groups

	Low (n=63)	**Intermediate-Low (n=69)**	**Intermediate-High (n=46)**	**High (n=22)**	
	Median (min-max),n (%)	Median (min-max),n (%)	Median (min-max),n (%)	Median (min-max),n (%)	**p-value**
ECHO Right ventricle					**<0.001**
Normal	59 (93.7)[1,2,3]	25 (36.2)[1,4]	0 (0.0)[2,4,5]	5 (22.7)[3,5]	
Slightly dilated	4 (6.3)[1]	17 (24.6)[1]	4 (8.7)	3 (13.6)	
Advanced dilated	0 (0.0)[1,2,3]	27 (39.2)[1,4]	42 (91.3)[2,4,5]	14 (63.7)[3,5]	
ECHO TR					**0.001**
None	39 (61.9)[1]	28 (40.6)	15 (34.1)[1]	12 (54.6)	
1. degree	18 (28.6)	32 (46.4)	12 (27.3)	5 (22.7)	
2. degree	5 (7.9)	8 (11.6)	10 (22.7)	4 (18.2)	
3. degree	1 (1.6)[1]	1 (1.4)[2]	7 (15.9)[1,2]	1 (4.5)	
ECHO D septum	0 (0.0)[1,2]	4 (5.8)[3]	13 (28.3)[1,3]	4 (18.2)[2]	**<0.001**
ECHO sPAP,	33 (20-65)[1,2,3]	45 (25-90)[1,4]	55 (28-85)[2,4]	58 (26-75)[3]	**<0.001**
ECHO Left ventricle					0.192*
Normal	47 (74.6)	45 (65.3)	26 (56.5)	14 (63.7)	
Diastolic dysfunction	4 (6.3)	4 (5.8)	1 (2.2)	3 (13.6)	
Concentric hypertrophy	3 (4.8)	8 (11.6)	8 (17.4)	1 (4.5)	
Global hypokinesia	0 (0.0)	1 (1.4)	4 (8.7)	2 (9.1)	
Local hypokinesia	3 (4.8)	5 (7.2)	3 (6.5)	0 (0.0)	
LVRD	6 (9.5)	6 (8.7)	4 (8.7)	2 (9.1)	
ECHO MR					0.627*
None	57 (91.9)	58 (84.1)	41 (89.1)	18 (81.9)	
1. degree	5 (8.1)	8 (11.6)	4 (4.7)	3 (13.6)	
2. degree	0 (0.0)	3 (4.3)	1 (2.2)	1 (4.5)	
ECHO AR					0.763*
None	54 (87.1)	63 (91.4)	38 (86.4)	19 (84.6)	
1. degree	8 (12.9)	5 (7.2)	6 (13.6)	3 (13.6)	
2. degree	0 (0.0)	1 (1.4)	0 (0.0)	0 (0.0)	
EF,	65 (35-65)[1,2,3]	63 (30-65)[1]	60 (35-65)[2]	60 (30-65)[3]	**<0.001**
EF≥ 50%	62 (98.4)	61 (88.4)	37 (80.4)	20 (90.9)	**0.010**
EF< 50%	1 (1.6)	8 (11.6)	9 (19.6)	2 (9.1)	

1,2,3,4,5 p<0.05; * Monte Carlo simulation result based on 10000 samples.
TR: Tricuspid regurgitation, PAP: Pulmonary arterial pressure, LVRD: left ventricular relaxation disorder, MR: mitral regurgitation, AR: Aortic regurgitation, EF: ejection fraction, sPAP: Systolic pulmonary arterial pressure

Table 5. Demographic and clinical characteristics according to the left ventricular function in intermediate-high / High risk patients

	Intermediate high + High risk patients		
	Normal-Left ventricular function (n=38)	**Left ventricular dysfunction**	
	Median (min-max),n (%)	Median (min-max),n (%)	**p-value**
Age, years	66 (30-94)	73 (30-92)	0.198
Gender, female	19 (50)	14 (46.7)	0.785
Smoking history			0.398
Smoker	8 (21.1)	3 (10.0)	
Ex-smoker	12 (31.6)	9 (30.0)	
Never smoker	18 (47.4)	18 (60.0)	
Comorbidity			
CVD	21 (55.3)	19 (63.3)	0.501
Other	11 (28.9)	17 (56.7)	**0.021**
SBP (mmHg)	110 (70-170)	110 (80-155)	0.636
DBP (mmHg)	70 (40-100)	70 (40-120)	0.721
D-dimer (mg/L)	8.70 (0.42-38)	7.32 (0.86-16)	0.285
NT-pro BNP (pg/ml)	978 (36-13918)	1731.5 (10.49-10700)	0.183
Troponin (ng/L)	44.75 (7.7-377)	40.74 (14-794)	0.310
CK-MB (ng/ml)	2.27 (0.60-18.85)	2.23 (0.57-11.00)	0.958
Myoglobin (ng/ml)	33.25 (21-614)	57.40 (20-580)	0.765
SpO_2 (%)	92 (71-100)	94 (80-98)	0.217
Risk groups			0.258
Intermediate high	26 (56.5)	20 (43.5)	
High risk	14 (63.6)	8 (36.4)	

CVD: Cardiovascular diseases, SBP: systolic blood pressure, DBP: diastolic blood pressure, BNP: Brain natriuretic peptid

Table 6. CT and ECHO results according to the left ventricular function in intermediate-high / high-risk patients

	Intermediate high + High risk patients		
	Normal-Left ventricular function (n=40)	**Left ventricular dysfunction (n=28)**	
	Median (min-max),n (%)	Median (min-max),n (%)	**p-value**
RVD, mm	44.35 (30.2-65.10)	42.95 (28.7-69.80)	0.573
RV wall thickness, mm	3.25 (1.60-8.00)	3.10 (2.10-4.40)	0.067
LVD, mm	40.15 (23.2-51.2)	42.70 (28.3-53.0)	0.208
LV wall thickness, mm	6.90 (4.3-14.0)	8.05 (5.1-10.4)	0.831
RVD/LVD	1.09 (0.73-1.97)	1.04 (0.60-1.49)	**0.030**
IVS			0.357
Normal	16 (42.1)	16 (53.3)	
D-Septum	22 (57.9)	14 (46.7)	
Aorta diameter, mm	34.7 (29.0-47.6)	36.1 (20.2-48.2)	0.949
Main PA diameter	30.95 (22.30-43.7)	31.1 (19.30-44.10)	0.411
PA/Aorta	0.88 (0.67-1.29)	0.87 (0.57-1.54)	0.789
ECHO Right ventricle			0.193
Normal	3 (7.9)	2 (6.7)	
Slightly dilated	6 (15.8)	1 (3.3)	
Advanced dilated	29 (76.3)	27 (90)	
ECHO TR			0.273
None	20 (52.6)	9 (30)	
1. degree	8 (21.1)	9 (30)	
2. degree	7 (18.4)	7 (23.3)	
3. degree	3 (7.9)	5 (16.7)	
ECHO septum D-shape	12 (31.6)	5 (16.7)	0.153
ECHO PAP	60 (26-85)	55 (27-80)	0.273
ECHO Left ventricle			**<0.001**
Normal	40 (100)	2 (6.7)	
Diastolic dysfunction	0 (0)	4 (13.3)	
Concentric hypertrophy	0 (0)	9 (30)	
Global hypokinesia	0 (0)	6 (20)	
Local hypokinesia	0 (0)	3 (10)	
LVRD	0 (0)	6 (20)	
ECHO MR			0.133
None	35 (92.1)	24 (80)	
1. degree	3 (7.9)	4 (13.3)	
2. degree	0 (0)	2 (6.7)	
ECHO AR			0.460
None	34 (89.5)	25 (83.3)	
1. degree	4 (10.5)	5 (16.7)	
2. degree	0 (0)	0 (0)	
EF ≥ 50%	38 (100)	19 (63.3)	**<0.001**
EF <50%	0 (0)	11 (36.7)	
EF	60 (50-65)	55 (30-65)	**0.002**

RV: Right ventricular; LV: Left ventricular; RVD: Right ventricular diameter; LVD: Left ventricular diameter. IVS: Interventricular septum, PA: Pulmonary artery, TR: Tricuspid regurgitation, PAP: Pulmonary arterial pressure, LVRD: left ventricular relaxation disorder, MR: mitral regurgitation, AR: Aortic regurgitation, EF: ejection fraction

This proportion was higher in the low-risk group than in the other three groups (intermediate-low, intermediate-high- and high-risk groups) ($p<0.05$). In the low-risk group, the proportion of non-TY patients was higher than in the intermediate-high risk group ($p<0.05$). In the intermediate-low risk group, the proportion of patients with the third- degree TY was higher than in the low and intermediate-low risk groups ($p<0.05$). The proportion of patients with D septum was highest in intermediate-high-risk patients (28.3%, n=13). In echocardiography results PAP levels were lower in the low risk group compared to the other three groups; and it was significantly lower in the intermediate-low risk group than intermediate-high risk patients. Left ventricular, mitral failure and aortic failure results of echocardiography were similar among the groups ($p>0.05$). EF levels were higher in the low- risk patients than the other patients ($p<0.05$).

Syncope was seen in only 10 patients in high-risk patients and the difference was statistically significant when compared with other patients (p: 0,00). The proportion of patients receiving thrombolytic therapy were higher in high-risk patients compared to low and intermediate- low risk groups, also it was higher in intermediate-high risk patients compared to low-risk group ($p<0.05$).

When the patients in the intermediate-high and high-risk groups were grouped according to the left ventricular function, no significant difference was observed in terms of age, gender, CVD and cardiac markers ($p>0.05$, Table 5).

The ratio of RVD/LVD was found significantly higher in patients with normal LV function according to the patients with LV dysfunction (p:0.030). But, RV and LV wall thickness, D- septum, aorta diameter, main PA diameter and the ratio of main PA diameter to aorta diameter which were evaluated with thorax CTA were similar among the patient groups ($p>0.05$) (Table 6).

Discussion

In our study, we showed that the ratio of RVD/LVD was found significantly higher in patients with normal left ventricular function than in patients with left ventricular dysfunction. This suggests that the presence of underlying left heart disease may affect right ventricular findings on echocardiography. Thus, it should be considered when evaluating patients with acute PE. Also, RVD in patients with normal left ventricular function was wider than in the patients with left ventricular dysfunction.

In the light of the guidelines on the diagnosis and management of acute PE, while patients with hypotension and shock were classified as having high risk, patients with only cardiac involvement were classified as having intermediate risk and patients without no clinical findings as having low risk. Today, thrombolytic therapy is suggested for high-risk and intermediate-high risk patients [1]. Therefore, it is important to establish the risk classification of patients with acute PE. For risk stratification of patients with acute PE, echocardiography is recommended in current guidelines. Especially, echocardiography results are very important in determining intermediate-high risk group. Right ventricular dysfunction was found in 27-56% of normotensive patients with acute PE. The risk of 30-day early mortality and recurrence of PE increased significantly in intermediate-high risk group. The mortality rate varies between 5-15% in this group [1,10,14]. Also, cardiac biomarkers such as troponin and NT-proBNP and pulmonary severity index (PESI) are other important indicators for thrombolytic therapy in intermediate-high risk group [1]. In our cases, right ventricular dysfunction findings were observed in some patients in the low and intermediate-low group on echocardiography, whereas in the high-risk group, there were a few cases showing normal right ventricular findings. For this reason, we grouped our cases in accordance with ESC 2014 rules, in addition to echocardiography, using cardiac markers and PESI.

Venous thrombosis and PE develop as a consequence of the interaction between patient- or setting-related risk factors such as surgery, trauma, immobilization, pregnancy, oral contraceptive use or hormone replacement therapy. Also, venous thrombosis and PE may be viewed as part of the cardiovascular diseases and related to common risk factors such as cigarette smoking, obesity, hypercholesterolemia, hypertension and diabetes mellitus. It was shown that myocardial infarction and heart failure increase the risk of PE [1]. In our study, some of the patients had a significant number of coronary artery diseases, hypertension, diabetes mellitus, hyperlipidemia, left heart failure, and atrial fibrillation. In addition, the most important results of PE are on the heart. Due to the possibility of PE and CAD coexistence, it is likely that left cardiac functions and cardiac reserve will affect the results and prognosis of PE.

Depending on the previous cardiopulmonary condition and the degree of embolic occlusion, various echo findings may occur. As mentioned before, right ventricular dilatation, hypokinesia or D-septum on echocardiography are determinant factors in the treatment of the patient with PE. Also, dilatation of RV is dependent on the function of LV, which is a manifestation of interventricular dependence [15]. In our study, according to the echocardiography results, right ventricular mild dilatation was seen in a small number of patients and advanced dilatation in most patients in the intermediate-high risk group. Whereas; right ventricular advanced dilatation were seen lower in high risk group than the intermediate-high risk group.

Recently many studies which evaluate cardiac chamber diameters and the ratio of right ventricular diameter to left ventricular diameter from thorax CTA have been done and these measurements were used to determine the severity of PE. In a meta-analysis examining 36 studies, RVD was assessed with the ratio of RV/LV in most of the studies. Thirty- four studies reported RV/LV ratio on short-axis, four studies on the right-to-left ventricle volume ratio and one study on the right-to-left ventricle area ratio. In almost all of these studies, these values were found to be different in risk groups depending on the severity of PE and these differences were found to be significant. Also, ventricular dilatation was associated with 30-day mortality in all acute PE patients and RVD/LVD ratio of $\geq$ 0.9-1 was associated with an increase in three-month mortality rates [6,11,12,16-20]. Conversely, previous studies suggested that in the absence of shock or hemodynamic instability, RV dilatation does not adversely affect prognosis in patients with acute pulmonary embolism. Also, RV dilatation does not increase the risk of mortality and it is not an indication for thrombolytic therapy [21,22]. The reason for these contradictory results associated with mortality may have been due to ignored left cardiac functions. In our cases, the rate of RVD and RVD / LVD was significantly higher

in the intermediate-high risk and high risk group in the evaluation with thorax CTA.

Becattini et al showed that the positive predictive value of RV dilatation at CTA for death was low (10–15%). This finding was similar to that obtained by echocardiography and biomarkers. Therefore, the idea of using one of these markers to promote treatment in a single patient is probably inappropriate. In CTA, further risk stratification may be considered to improve clinical treatment in patients with RV dilatation. Whether echocardiography or troponin could improve the positive predictive value of CTA for death is currently undefined [6]. In a recent study, Ay et al evaluated the efficacy of troponin I, D-dimer, and lactate levels and RVD/ LVD ratio on thorax CTA in the risk classification of patients who were diagnosed with acute PE in Emergency Department. And, they demonstrated that lactate, troponin I, and RVD/LVD ratio may be used together for more correct risk stratification for the patients. In this study, RVD was greater than LVD in 83% of patients with intermediate risk group and D-septum was observed in 39% of the intermediate risk patients. Rest of the patients with intermediate risk had normal RVD and/or interventricular septum [16]. Interestingly, in our cases, RVD was found to be wider in the intermediate high risk group than in the high risk group.

In previous studies including the last study, a number of acute PE patients with intermediate-high risk had normal RVD and/or RV/LV ratios. These results support our hypothesis too. We demonstrated that the ratio of RVD/LVD was found significantly higher in patients with normal left ventricular function than in patients with left ventricular dysfunction. Also, pulmonary arterial pressure was measured high in patients with normal left ventricular function. This may have an effect on the expansion of the right ventricle in patients with normal left ventricular function. In patients with left ventricular dysfunction, the ratio of RVD/ LVD may be lower because of the larger left ventricular diameter. Hypothetically, the presence of pulmonary venous hypertension before acute PE may increase the afterload of the right ventricle in patients with left ventricular dysfunction. This concluded that right ventricle may have more easily tolerated sudden increase in pulmonary artery pressure because right ventricle accustomed to pressure.

The strength of our study is to draw attention to this issue for the first time. But our study had limitations too, such as the inclusion of a limited number of patients in the intermediate-high and high risk groups, and the design of the study as retrospectively.

As a result, the optimal treatment approach of haemodynamically stable patients with acute PE remains controversial. Risk stratification of the patients according to early mortality risk should be done to strengthen the decision of thrombolytic therapy. Absence of RV dilatation or the ratio of RVD/LVD identifies patients at low risk of all-cause mortality or with PE related complications. The ratio of RVD/LVD was found significantly higher in normal left ventricular function patients. But, the ratio of RVD/LVD may not be seen as expected in every patient. Acute PE may be seen as a part of cardiovascular disease in many patients and; thus baseline LV function may affect the findings of RV during acute PE event. Especially when we evaluate intermediate-high risk patients by echocardiography, we should consider left ventricular function. To show LV dysfunction's effect to RV in acute PE further investigation with larger number of patients is needed.

Conflict of interests
The authors declare that they have no competing interests.

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Ethical approval
The regional committee of medical and health research ethics approved the study. (Yıldırım Beyazıt University School of Medicine, Medical Research Ethics Committee- Number:26379996/40).

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