Original Article

Diagnostic Modality for Evaluation of Right Ventricle in Chronic Thromboembolic Pulmonary Hypertension Patients

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Abstract

Background: Chronic thromboembolic pulmonary hypertension (CTEPH) is a progressive disease of pulmonary hypertension (PH) as a consequence obstructive of pulmonary arteries with thromboembolism. Augmented pulmonary vascular resistance and pulmonary artery pressure (PAP) can ultimately lead to the right ventricular dysfunction, which leads to adaptive and maladaptive changes. Right ventricle (RV) remodeling can cause clinical deterioration and RV failure. **Aims and Objectives:** We aimed to evaluate the RV functions with a new diagnostic modality 2-deoxy-2-(18F)-fluoro-D-glucose (FDG)-positron emission tomography (PET) in patients with CTEPH. **Materials and Methods:** We included 53 patients diagnosed with CTEPH who were planned to have pulmonary thromboendarterectomy (PEA) and did not have any contraindication for cardiac PET/computed tomography (CT). We performed transthoracic echo, cardiac PET/CT, 6-minute walk distance (6-MWT), and right heart catheterization 1 week before PEA surgery. **Results:** The patients divided into two groups according to RV/left ventricle (LV) FDG-PET uptake ratio, RV/LV ≤1, and RV/LV >1. Six-MWD was significantly higher in the RV/LV ≤1 group ($P = 0.005$). Pro-BNP was considerably higher in the RV/LV >1 group ($P = 0.041$). **Conclusion:** The present study aims to demonstrate the RV/LV FDG-PET uptake ratio could be used in the noninvasive diagnostic method in diagnosing, treatment strategy, and clinical follow-up in patients with CTEPH.

Keywords: Cardiac fluoro-D-glucose positron emission tomography, chronic thromboembolic pulmonary hypertension, pulmonary vascular resistance, right ventricular remodeling

Introduction

Chronic thromboembolic pulmonary hypertension is the development of progressive pulmonary hypertension (PH) due to occlusion of pulmonary vascular bed and formation of structural changes by recurrent and organized pulmonary thromboembolism or *in situ* (in place) thrombosis.[1] This causes increased pulmonary vascular resistance (PVR) and pulmonary arterial pressure in pulmonary vascular bed over time. Adaptive remodeling such as compensatory right ventricle hypertrophy and increased contractility occur against increased afterload in RV. In time, these compensatory mechanisms become inadequate, and functional deterioration progresses by maladaptive changes in RV.

As a consequence of increased RV afterload, a clinical syndrome called RV failure develops due to insufficient blood flow in pulmonary vascular bed during resting or exercise and increased systemic venous pressure.[2] This anatomical, physiological, and

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metabolic remodeling in RV is responsible for essential subclinical and clinical features of CTEPH, and RV functions determine mortality and morbidity. For these reasons, the development of novel diagnostic and therapeutic approaches to RV functions is gaining importance. In the analyses about PH in recent years, pulmonary vascular structure and right heart were analyzed as a combined group as a cardiopulmonary unit.[3] Three primary mechanisms may be cause adaptive and maladaptive changes resulting in RV failure. These are ischemia due to pulmonary arterial hypertension (PAH), mitochondrial remodeling, and metabolic shift.[4] The myocardial metabolism that changes from oxidative glycolysis to nonoxidative glycolysis in RV due to PAH can be used as a novel diagnostic modality for 2-deoxy-2-(^{18}F) fluoro-D-glucose-positron emission tomography/computed tomography (FDG-PET/CT) to evaluate RV functions. In our study, we aimed to assess the relationship between RV functions in CTEPH patients with a diagnostic modality, FDG-PET/CT, and functional capacity.

Methods

This study included patients with CTEPH between June 2013 and January 2015 and planned to have pulmonary thromboendarterectomy procedure at our center. The Ethical Committee of Marmara University Medical School evaluated our study, and no objections were found for conduction. Informed consent forms were obtained from patients who found to be eligible for the survey regarding their approval for participation. It was a prospective study. A total of 53 patients with an exact diagnosis of CTEPH according to a multidisciplinary assessment at our center, who had no contraindication for a cardiac PET examination (overweight patients, pregnant, etc.). Patients with moderate-to-severe valve diseases, left heart failure with any reason, chronic obstructive lung disease with FEV1 below 50%, chronic renal failure, diabetes mellitus, uncontrolled hypertension, coronary artery disease, and hypertrophic cardiomyopathy, and those that not approved to participate were excluded from the study.

Each patient had diagnostic workups 1 week before the operation. The same operator conducted all echocardiographic evaluations according to the recommendations of the American Society of Echocardiography guidelines[5] using a Vivid 7 Ultrasound System (General Electric, Horten, Norway). Right heart catheterization (RHC) was performed by the femoral approach using a Swan–Ganz catheter to confirm the diagnosis of PH. Cardiac output was calculated by the Fick method. Each patient presented the (6-MWD) according to the 6-MWD Protocol of American Thorax Surgery Society.[6] The Qanadli Score is calculated in acute pulmonary thromboembolism by pulmonary CT angiography and pulmonary angiography and based on thrombus load in the pulmonary arterial bed.[7] For the first time in this study, we use Qanadli score to calculated based on thrombus burden in pulmonary arterial bed in CTEPH patients. An integrated PET/CT system (Discovery-16 LS, GE Healthcare, USA) was used for imaging. It included include the entire free walls of the right and the (LV). Our center is used to 0.8 ratios as usual in right ventricle/LV ratio.[8,9] Data computing and assessment were performed on a workstation (Advantage Windows Workstation 4.5, GE Healthcare, USA) following the imaging. The volume of interest was drawn over the right and LV free walls, and myocardial glucose involvement levels on these walls were obtained by measuring semiquantitative maximum standardized uptake values (SUV). Right/LV glucose metabolism proportions were calculated by calculating right and LV maximum SUV levels [Figure 1a-c].

Statistical analysis

SPSS 20 software (SPSS 20.0 for Windows, SPSS Inc., Chicago, IL, USA) was used for the statistical analyses of the study. The one-sample Kolmogorov–Smirnov test evaluated the distribution of data. If numerical data were normally distributed, then presented as mean ± standard deviation; and if not normally distributed, then given as median (minimum–maximum). Chi-square test evaluated categorical variables. Customarily distributed numerical data were compared with Student's *t*-test, and nonnormally distributed statistical data was compared with the Mann–Whitney U-test. Pearson or Spearman's correlation tests were used for correlation analysis. The Pearson correlation was used in the linear relationship between two continuous variables. The Spearman correlation was used the monotonic relationship between two continuous or ordinal variables. P <0.05 values were considered as statistically significant.

Results

A total of 53 patients diagnosed with CTEPH by a multidisciplinary evaluation, and those planned to have PEA

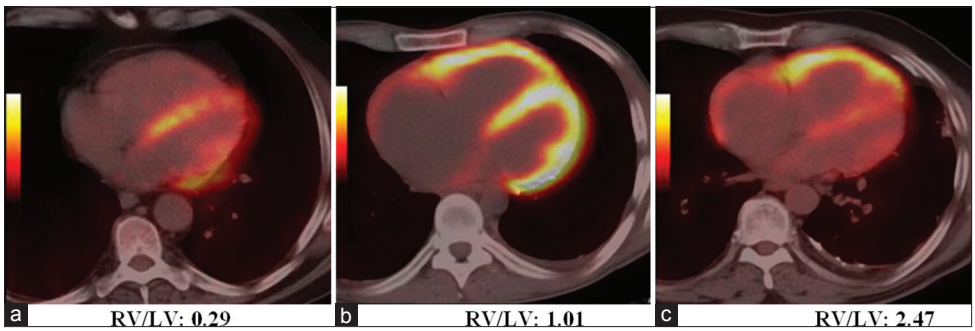

Figure 1: Sample of FDG PET uptake (a, b and c)

were included in the study. Mean age of the patients was 55 ± 13.8 years. Thirty-four patients were female (64.2%) and 19 were male (35.8%). General clinical characteristics and basal laboratory values of the patients are shown in Table 1. We have no data on their clinical symptoms and disease's duration.

Table 1: Demographic, and clinical datas of study population

Demographic and clinical datas	Means (*n*:53)
Blood pressure (mmHg)	
Systolic	120.0 (175-98)
Mean	92.8±17.4
Diastolic	75.4±11.1
BMI	27.8 (19.5-43.7)
6-MWT (meters)	266.5±161.7
Pace (beat/min)	86.6±14.1
Qanadli score	23.2±8.1
Symptom	
Present	43 (%81.1)
None	10 (%18.9)
WBC, ($\times 10^3/\mu L$)	7.6 (2.8-18.9)
Hemoglobin, (g/dL)	13.0±2.7
Hematocrit, (%)	38.8±6.1
Thrombocyte, ($\times 10^3/\mu L$)	233.5 (83-690)
Creatinine (mg/dL)	0.86±0.29
BUN (mg/dL)	19.0±9.2
D-dimer (mg/L)	0.4 ± (0.09-2.87)
Uric acid (mg/dL)	7.6±2.6
ProBNP (pg/ml)	986 (12-17020)
CRP (mg/L)	8.4 (0.9-75.0)

BMI: Body mass index, 6-MWT: 6 Minute Walk Test, CRP: C reactive protein, WBC: White blood cell

Table 2: Echocardiography and right heart catheterization parameters of study population

ECHO and RHC Parameters	Means (*n*:53)
TAPSE (mm)	14.4±4.3
MPI (mm)	0.63±0.17
RVS (mm)	10.7±3.1
RA area (cm^2)/LA area (cm^2)	23.9±7.7/16.1±4.3
RVEDD (mm)	40.1±6.7
LVEDD (mm)/LVESD (mm)	43.5±6.0/27.7±4.9
sPAP (mmHg)	71.5±28.4
Systolic Pulmonary Artery Pressure (mmHg)	76.5±27.3
Mean Pulmonary Artery Pressure (mmHg)	48.1±15.6
Diastolic Pulmonary Artery Pressure (mmHg)	29.2±11.9
Wedge (mmHg)	10.9±4.2
Cardiac Output (lt/dk)	4.2±1.7
Cardiac Index (lt/dk/m^2)	2.3±1.0
Transpulmonary gradient (mmHg)	38.0±15.6
Diastolic pulmonary gradient (mmHg)	18.5±10.9
PVR (woods)/SVR (woods)	10.4±6.3/21.8±9.0

RVEDD: Right ventricle end-diastolic diameter LVEDD: Left ventricle end-diastolic diameter; LVESD: left ventricle end systolic diameter; EF: Ejection fraction; RA: Right atrium area; LA: Left atrium area; sPAP: Systolic pulmonary arterial pressure; TAPSE: tricuspid annular plane systolic excursion; RVS: tricuspid annulus tissue Doppler systolic velocity; LV: Left ventricle

Decreases in RV systolic function parameters and increases incorrect heart diameters were observed before the operation in patients. PAP, PVR, and the transpulmonary gradient were found to be high, and cardiac output and cardiac index were found to be low in RHC [Table 2].

The patient population was separated into two groups according to right ventricle/LV FDG-PET uptake ratio. Groups formed according to the right ventricle uptake less than LV Group 1 (RV/LV ≤1) and proper ventricle uptake equals to and more than LV Group 2 (RV/LV >1). Twenty-seven patients were Group 1 and 25 patients were Group 2. Six-MWD, Qanadli score, Pro-BNP, Echo parameters, and RHC findings were compared between groups [Table 3]. Six-MWD was high in Group 1. The Qanadli score was calculated to be lower in Group 1, but it was not statistically significant. Pro-BNP was high in Group 1 when compared with Group 2. There were no significant differences between groups regarding echocardiography and RHC parameters [Table 3].

Correlation analyses were performed to determine the associations between clinical findings and RV/LV FDG-PET uptake levels in patients. A negative correlation was established between 6-MWD and RV/LV FDG-PET uptake ratio [Figure 2]. Furthermore, a positive relationship was found between increased Qanadli score, which determines the thrombus burden in the pulmonary arterial bed and RV/LV FDG-PET uptake ratio. There was a positive correlation between laboratory parameters of D-dimer and Pro-BNP and RV/LV FDG-PET uptake. There were no correlations between echocardiographic parameters of tricuspid annular plane systolic excursion (TAPSE), Myocardial Performance Index, and RV tissue systolic Doppler wave, which are frequently used to evaluate RV functions, and RV/LV FDG-PET uptake. There was a significant correlation between echocardiographic parameters of right ventricle area, LV diameter, and systolic pulmonary arterial pressure and RV/LV FDG-PET uptake [Figure 3]. There

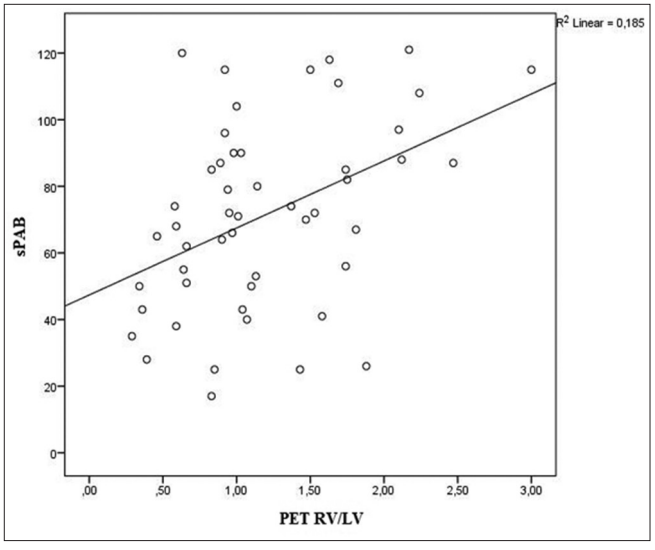

Figure 2: Relationship between 6-MWT and RV and LV FDG PET uptake

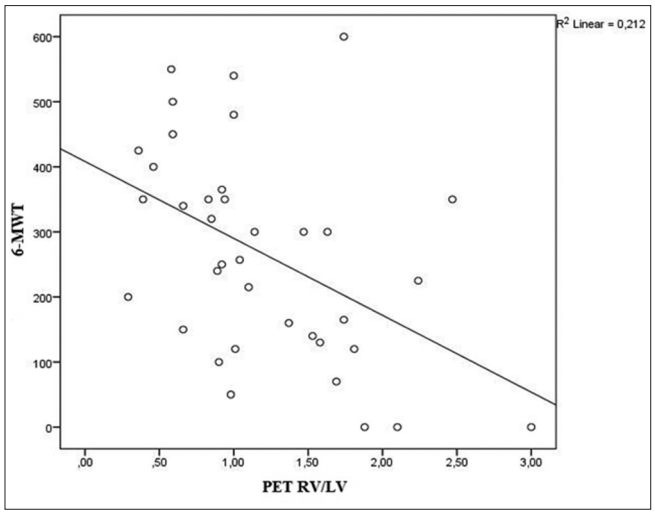

Figure 3: Correlation between echocardiographic parameters and FDG-PET uptake

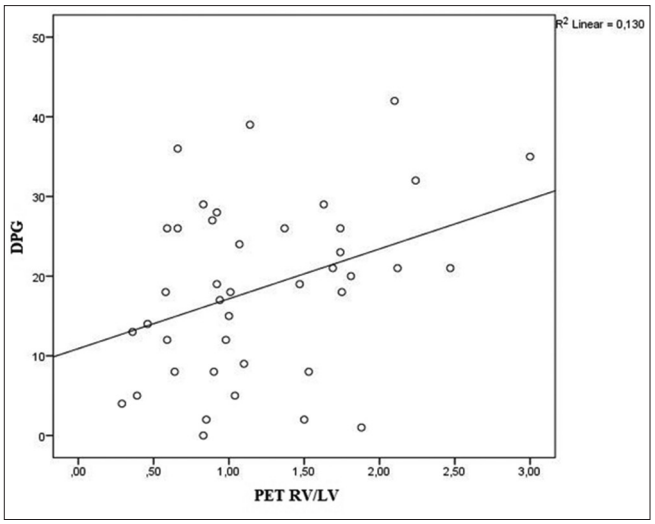

Figure 4: Relationship between diastolic transpulmonary gradient and FDG-PET uptake

was a significant correlation between RHC parameters diastolic PAP, diastolic pressure gradient and PVR, and FDG-PET uptake [Figure 4]. However, there were no significant correlations between other RHC parameters as cardiac output, cardiac index, and pulmonary capillary wedge pressure (PCWP) [Table 4].

Discussion

Noninvasive evaluation of RV functions, which have a crucial role in morbidity and mortality in PH, is essential for diagnosis, risk classification, and determining the therapeutic strategy prognosis of PH patients. PH causes remodeling in RV due to chronic pressure burden. The critical role of RV remodeling in prediction makes RV functions important in studies of PAH. However, the reviews on this topic remained inadequate to be reflected in the clinical approach to the disease. In our research, RV functions were evaluated in patients with CTEPH that planned to have PEA, by a diagnostic modality of FDG-PET/CT; and its associations with 6-MWD distance, Qanadli score, pro-BNP, other blood parameters, RHC parameters,

Table 3: Right ventricle FDG-PET uptake of study population

	RV/LV ≤1 (*n*=27)	RV/LV >1 (*n*=26)	*P*
6-MWT (meters)	337±143.1	191±148.8	0.005
Qanadli score	21.1±6.8	24.9±8.9	0.138
ProBNP (pg/ml)	448 (15-6791)	1799.5 (12-17020)	0.041
Mean Pulmonary Artery Pressure (mmHg)	45.7±17.0	50.4±14.2	0.298
PCWP (mmHg)	11.1±4.5	10.6±4.0	0.699
Cardiac Output (lt/dk)	4.4±1.5	3.9±1.8	0.296
Cardiac Index (lt/dk/m^2)	2.4±0.7	2.1±1.1	0.357
Transpulmonary gradient (mmHg)	35.0±17.6	40.7±13.2	0.250
Diastolic pulmonary gradient (mmHg)	16.0±10.1	20.9±11.3	0.147
PVR (woods)	9.2±6.0	11.6±9.9	0.170
SVR (woods)	21.6±8.2	22.1±9.9	0.858
TAPSE (mm)	14.8±4.6	14.0±4.1	0.552
MPI (mm)	0.65±0.09	0.62±0.22	0.684
RVS (mm)	11.3±3.1	10.1±3.0	0.203
RA area (cm^2)	21.8±7.4	26.0±7.6	0.06
LA area (cm^2)	16.6±3.9	15.7±4.4	0.487
RVEDD (mm)	38.6±5.2	41.6±7.6	0.142
LVEDD (mm)	45.3±6.0	41.8±5.6	0.039
LVESD (mm)	28.4±4.3	27.1±5.5	0.364
sPAP (mmHg)	66.2±27.8	76.4±28.7	0.211

RVEDD: Right ventricle end-diastolic diameter LVEDD: Left ventricle end-diastolic diameter; LVESD: left ventricle end systolic diameter; EF: Ejection fraction; RA: Right atrium area; LA: Left atrium area; sPAP: Systolic pulmonary arterial pressure; TAPSE: tricuspid annular plane systolic excursion; RVS: tricuspid annulus tissue Doppler systolic velocity; LV: Left ventricle, PCWP: Pulmoner capillary wedge pressure

Table 4: RV/LV FDG-PET uptake correlation findings

	r	*P*
Age (range) - year	0.200	0.156
6-MWT (meters)	-0.460	0.004
Qanadli score	0.358	0.023
D-dimer (mg/L)	0.585	0.002
ProBNP (pg/ml)	0.397	0.018
TAPSE (mm)	-0.215	0.138
MPI (mm)	-0.241	0.123
RVS (mm)	-0.270	0.072
RA area (cm^2)	0.393	0.005
LA area (cm^2)	-0.218	0.142
RVEDD (mm)	0.222	0.148
LVEDD (mm)	-0.467	0.001
LVESD (mm)	-0.337	0.018
sPAP (mmHg)	0.431	0.002
Systolic Pulmonary Artery Pressure (mmHg)	0.309	0.050
Mean Pulmonary Artery Pressure (mmHg)	0.244	0.092
Diastolic Pulmonary Artery Pressure (mmHg)	0.334	0.033
PCWP (mmHg)	-0.101	0.523
Cardiac Output (lt/dk)	-0.166	0.249
Cardiac Index (lt/dk/m^2)	-0.129	0.376
Transpulmonary gradient (mmHg)	0.319	0.042
Diastolic pulmonary gradient (mmHg)	0.360	0.021
PVR (woods)	0.297	0.038
SVR (woods)	0.107	0.469

RVEDD: Right ventricle end-diastolic diameter LVEDD: Left ventricle end-diastolic diameter; LVESD: left ventricle end systolic diameter; EF: Ejection fraction; RA: Right atrium area; LA: Left atrium area; sPAP: Systolic pulmonary arterial pressure; TAPSE: tricuspid annular plane systolic excursion; RVS: tricuspid annulus tissue Doppler systolic velocity; LV: Left ventricle; PVR: Pulmonary vascular resistance; SVR: Systemic vascular resistance

and echocardiography parameters were evaluated. Lundgrin *et al*.[10] determined in their study on PAH patients that there was an increase in the synthesis of hypoxia-inducible factor-1α in pulmonary vascular bed, and this factor caused a shift to nonoxidative glycolysis by affecting mitochondrial metabolism in RV myocytes, which partly explained the ischemic biochemical mechanism that developed in RV. Fang *et al*.[11] conducted a study on 25 patients with PH and 43 patients with PAH associated with congenital heart disease, and at the end of 2 years of follow-up, they compared the RV/LV FDG-SPECT uptake rates and patients' prognosis and reported that patients with higher RV FDG uptake had a worse prognosis. Our study is conducted on patients in a subcategory of PH, the CTEPH patients, and RV/LV FDG-PET uptake ratios were compared with 6-MWD – which is an important parameter that related with functional capacity and prognosis of patients, echo parameters – which are frequently used, noninvasive, and easy-to-perform determinants of RV functions, RHC parameters – which are considered as the gold standard for hemodynamic measurements in PH, and Qanadli score – which determines the pulmonary artery thrombus burden. Based on significant associations with frequently used parameters that assess RV functions, FDG-PET uptake ratio was shown to be a valuable method that can be used for diagnosis and follow-up of patients with CTEPH. However, our theory must be supported with an extensive trial and proved by RHC.

Kepez *et al*.[12] reported in their study on CTEPH patients that decreased RV functions determined by echocardiography were correlated with 6-MWT, which is an indicator of functional capacity. In our research, 6-MWD distances were found to be lower in Group 2 patients that have increased RV FDG-PET uptake, when compared with Group 1 patients (P = 0.005). Farber *et al*.[13] reported in their study that 6-MWD had prognostic importance in PH patients, and temporally decreased 6-MWD was related to poor prognosis. In this study, 1-year survival was reduced to 68.4% in patients with 6-MWD <165 m.[11] The higher RV/LV FDG-PET uptake in patients with 6-MWD <165 m in our study showed the prognostic value of RV/LV FDG-PET uptake ratio (P = 0.008). Despite the primary pathology was on the pulmonary vascular bed as expected, the main reason for symptoms and decreased effort capacity in the disease is increased ischemia due to pressure load, and reduced RV functions. RV FDG-PET uptake can be an essential alternative diagnostic method and prognostic modality in cases that 6-MWD cannot be performed due to reduced effort capacity, advanced age, orthopedic barriers, or comorbid diseases. Functions of RV decrease progressively in patients with high thrombus burden due to theoretically higher PAP and consequently higher pressure load on RV. Qanadli score, which determines acute thrombus burden in pulmonary artery bed, was used for the first time in this study to assess chronic thrombus burden.[7] Qanadli score was found to be associated with RV FDG-PET uptake (P = 0.023). Higher PVR develops when thrombus amount increases in the pulmonary vascular bed. Increased PVR causes increased pressure load on RV, adverse remodeling in RV, and decreased RV functions. RV FDG-PET uptake is a valuable diagnostic modality candidate for indirectly showing thrombus burden in the pulmonary vascular bed, and predicting thrombus amount that can be removed by PEA from vascular bed during the planning of CTEPH treatment and subsequently postoperative clinical improvement. Pro-BNP, which is synthesized in myocardial cells that exposed to volume and pressure load, and which is a frequently used blood parameter in left heart failure, was found to be correlated with RV FDG-PET uptake as expected due to the high-pressure gradient. This shows that Pro-BNP is an essential parameter in clinical follow-up and treatment of CTEPH, which provides vital information about disease severity and can be used in the clinical monitoring of PH patients with these properties.

D-dimer is used in the diagnostic algorithm of acute pulmonary thromboembolism as a fibrin degradation product and more preferred in diagnostic exclusion of acute pulmonary thromboembolism. However, previous studies showed that it has no prognostic value in CTEPH patients, despite being related to disease prognosis in PH patients.[14,15] In our study, we found that serum D-dimer levels were associated with RV/LV FDG-PET uptake ratio (P = 0.002). The high levels of

D-dimer in patients with increased RV/LV FDG-PET uptake suggest that thromboembolism cycle and *in situ* thrombus cycle continues in particular in distal arterial bed. These high-risk patients with ongoing *in situ* thrombus cycle may have a higher risk regarding residual PH after PEA, particularly following distal arteriopathy.

In our study, we have evaluated the associations between echo parameters that assessed RV functions and RV FDG-PET uptake. Accordingly, FDP uptake was significant in patients with elevated systolic PAP and right atrium area. Recent studies about RV functions also reported similar findings, and most frequently used and most important parameter among those, the TAPSE, was accepted to show RV functions. Li *et al*.[16] evaluated RV functions by three-dimensional-real-time echocardiography and reported that RV ejection fraction and RV fractional area change are correlated with RV tissue Doppler systolic wave and myocardial performance index, but not with TAPSE. The authors suggested that oscillation of RV apex significantly decreases in a minimal volume or pressure load due to its elastic structure, and this yields TAPSE to be measured less that it is. The limited abilities of echo parameters that are frequently used in the evaluation of RV functions, and their changeability according to operator increases the importance of a more objective evaluation method, the RV FDG-PET.

Diagnosis and treatment of PH are primarily based on hemodynamic parameters of RHC. According to the European Society of Cardiology (ESC) 2015 PH diagnosis and treatment guidelines, mPAP ≥25 mmHg and PCWP ≤15 mmHg for precapillary PH and mPAP ≥25 mmHg and PCWP >15 mmHg values remained, the transpulmonary gradient was removed, and diastolic pressure gradient and PVR were added to criteria for revised PH diagnosis. This revision was made due to systolic and mPAP were affected by PCWP during the cardiac cycle.[15] A significant correlation between RV FDG-PET uptake and the diastolic PAP, PVR, transpulmonary gradient, and diastolic pressure gradient, which are all hemodynamic parameters of RHC that is the gold standard in diagnosis, treatment, and follow-up of PAH patients. However, there were no significant correlations between systolic and mean PAP, cardiac output and cardiac index, and RV FDG-PET uptake. As Vachiéry *et al*.[17] reported in their study that referenced in ESC 2015 guideline, systolic and mean PAP is affected by PCWP during the cardiac cycle. Transpulmonary gradient loses its significance in discrimination of PH as precapillary or postcapillary. However, diastolic PAP and diastolic pulmonary gradient show precapillary PH, since diastolic PAP is affected by PCWP minimally during the cardiac cycle. But, since mPAP, which is the primary diagnostic criteria of PH, is also indirectly affected from PCWP, a similar revision can be done for patients who are in the grey zone with mPAP 21–24 mmHg and can be subject to misdiagnosis due to doubts about the diagnosis. At this point, utilization of diastolic PAP for PH diagnosis by determining a reference range can be discussed, because diastolic PAP is affected very less than mPAP from PCWP. Furthermore, since we found that RV FDG-PET uptake is correlated with RHC parameters, which are the gold standard in PH diagnosis, and which were revised in new ESC PH guidelines; right ventricle FDG-PET/CT can be a diagnostic method that can be used along with RHC for PH diagnosis in the future.

Specific treatment in PH is applied by targeting pulmonary arterial bed. However, symptoms and prognosis of the disease are determined by right heart failure. Right ventricle-targeted therapies have not been evaluated in detail in patients with PAH and right heart failure. The most promising data are about metabolic modulation among right ventricle-targeted medications. Phase 1 and 2 trials of mitochondrial modulators like dichloroacetate have been completed in patients with metabolic changes in the right heart and pulmonary vascular bed in PH.[18] Today, research is needed about stem cell and gene therapies targeting RV, specifically in PH.

Limitations of the study

Significant limitations of this study are mainly about the low number of patients, which caused many parameters to have a marginal statistical significance that could not reach to relevance. The follow-up of patients after the operation could not be done, and associations of right ventricle FDG-PET with long-term prognosis could not be evaluated. Furthermore, right ventricle FDG-PET evaluations after surgery could not be performed, and more detailed data about RV functions could not be obtained.

Conclusion

Our study is particularly important for evaluating associations between right ventricle FDG-PET uptake and clinical characteristics, 6-MWD, Qanadli score, echocardiographic, and RHC parameters of CTEPH patients. Under the light of these data, right ventricle FDG-PET uptake was shown to be an innovative noninvasive method that can be used in diagnosis, treatment strategy, and follow-up of CTEPH patients undergoing PEA.

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Conflicts of interest

There are no conflicts of interest.

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