Original Research

Right ventricle performances with echocardiography and ^{99m}Tc myocardial perfusion imaging in pulmonary arterial hypertension patients

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Impact statement

In this study, we analyzed the clinical parameters for evaluating RV function, including right ventricle catheterization (RHC), echocardiography, and technetium 99m (^{99m}Tc) myocardial perfusion imaging (MPI) in normal Asian subjects and PAH patients ($n = 23$ for each group). Our results demonstrated that six RHC indexes, four echocardiography indexes and MPI index were significantly altered in PAH patients and correlated with the levels of mean pulmonary arterial pressure. Importantly, we evaluated the diagnostic performance of MPI and found that MPI has a strong diagnostic accuracy in PAH patients. The findings from this study will be of interest to clinical investigators who make diagnosis and therapeutic strategies for PAH patients.

Abstract

Right heart catheterization is commonly used to measure right ventricle hemodynamic parameters and is the gold standard for pulmonary arterial hypertension diagnosis; however, it is not suitable for patients' long-term follow-up. Non-invasive echocardiography and nuclear medicine have been applied to measure right ventricle anatomy and function, but the guidelines for the usefulness of clinical parameters remain to be established. The goal of this study is to identify reliable clinical parameters of right ventricle function in pulmonary arterial hypertension patients and analyze the relationship of these clinical parameters with the disease severity of pulmonary arterial hypertension. In this study, 23 normal subjects and 23 pulmonary arterial hypertension patients were recruited from January 2015 to March 2016. Pulmonary arterial hypertension patients were classified into moderate and severe pulmonary arterial hypertension groups according to their mean pulmonary arterial pressure levels. All the subjects were subjected to physical examination, chest X-ray, 12-lead electrocardiogram, right heart catheterization, two-dimensional echocardiography, and technetium 99m (^{99m}Tc) myocardial perfusion imaging. Compared to normal subjects, the right heart catheterization indexes including right ventricle systolic pressure, right ventricle end diastolic pressure, pulmonary artery systolic pressure, pulmonary artery diastolic pressure, pulmonary vascular resistance, and right ventricle end systolic pressure increased in pulmonary arterial hypertension patients and were correlated with mean pulmonary arterial pressure levels. Echocardiography parameters, including tricuspid regurgitation peak velocity, tricuspid regurgitation pressure gradient, tricuspid annular plane systolic excursion and fractional area, right ventricle-myocardial performance index, were significantly associated with the mean pulmonary arterial pressure levels in pulmonary arterial hypertension patients. Furthermore, myocardial perfusion imaging was not observed in the normal subjects but in pulmonary arterial hypertension patients, especially severe pulmonary arterial hypertension subgroup, and showed potential diagnostic properties for pulmonary arterial hypertension. In conclusion, mean pulmonary arterial pressure levels are correlated with several right heart catheterization and echocardiography markers in pulmonary arterial hypertension patients; echocardiography and ^{99m}Tc myocardial perfusion can be used to evaluate right ventricle performance in pulmonary arterial hypertension patients.

Keywords: ^{99m}Tc myocardial perfusion, BIOIMAGING, PULMONARY, pulmonary arterial hypertension, right heart catheterization, right ventricle

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Introduction

Pulmonary arterial hypertension (PAH) is a progressive disorder defined by the presence of increased mean pulmonary pressure. Despite of current advances in clinical management and therapies, PAH patients remain suffering from debilitating symptoms with high mortality.[1] It is widely accepted that right ventricle (RV) performances determine the clinical outcomes of PAH;[2–7] however, the indicators of RV dysfunction and their relationship with the disease severity of PAH remain to be defined.

Right heart catheterization (RHC) is the gold standard to diagnose PAH and evaluate RV function through invasively direct measurement of RV hemodynamic.[8,9] Although the procedure of RHC has been well standardized and has shown safe in PAH diagnosis,[2,10] it is an invasive procedure and requires appropriate techniques and result interpretation. Furthermore, RHC only provides hemodynamic information and is not suitable for long-term follow-up. Given the non-specific symptoms present in PAH patients, especially at the early stages, noninvasive examinations are needed to evaluate RV function. The advance in echocardiography and nuclear imaging has led to new insights into both anatomical and functional assessment in RV of PAH patients.[11] Importantly, nuclear imaging has recently emerged as a valuable tool to assess RV perfusion and metabolism in PAH patients.[12–14] However, there have been no noninvasive RV indexes well accepted for evaluating RV performance and predicting the clinical outcome of PAH patients and uncertainty remains on how RV performance can be analyzed in daily clinical practice to design management plans. Furthermore, it is unclear whether non-invasive parameters, such as index of nuclear imaging, are associated with the severity of PAH and RHC parameters. Therefore, it is crucial to analyze the RV non-invasive parameters and evaluate their correlation with PAH disease progression.

In this study, we first systemically evaluated the RV performance in 23 PAH patients (moderate and severe PAH groups) and 23 control subjects with RHC, electrocardiogram (ECG), transthoracic echocardiography, X-ray, and technetium 99m (^{99m}Tc) myocardial perfusion imaging (MPI). Next, we analyzed the correlation of RHC index, echocardiography parameters, and MPI index with the levels of mean pulmonary arterial pressure (mPAP). Furthermore, we calculated the diagnostic accuracy of MPI in PAH patients. Our results revealed that several RHC indexes and echocardiographic parameters are correlated with PAH severity and highlighted the potential use of MPI in diagnosing PAH, especially severe PAH.

Methods

Patient population

Twenty-three normal subjects and 23 PAH patients were enrolled in this study. The patients were diagnosed as PAH between January 2015 to March 2016 in our hospital. Twenty-three normal subjects were recruited as the control group. All the procedures were approved by our institutional ethic committee after receiving written informed consent from each participant. With the use of RHC, a diagnosis of precapillary pulmonary hypertension was made if the mPAP was higher than 25 mm Hg at rest and the PCWP was no more than 15 mm Hg. According to the levels of mPAP, PAH group was classified into two subgroups: severe group (>45 mmHg) and moderate group (36–45 mmHg). All the enrolled subjects were analyzed with a diagnostic evaluation, including inquires of clinical history, physical examination, chest X-ray, 12-lead ECG, RHC, two-dimensional echocardiography and ^{99m}Tc MPI. All the tests were performed according to the laboratory's quality control standards of our hospital.

Transthoracic echocardiography

All echocardiographic studies were performed as previously described.[15,16] Transthoracic echocardiographic evaluation was performed by an experienced certified sonographer with the use of the Acuson Sequoia 512 Ultrasound system (Acuson Sequoia^{TM} 512, Siemens, San José, CA) and 3.5 MHz transducers. Analysis of echocardiography parameters was made by one of four experienced noninvasive cardiologists without knowledge of patient group.

RHC. RHC was performed in supine position using a conventional pulmonary artery catheter and Edwards Vigilance Monitor for cardiac output measuring. The usual invasively measured hemodynamic parameters were recorded.

MPI. MPI was performed on all the subjects enrolled in this study as previously described.[17,18] Single photon emission computed tomography (SPECT) MPI was performed 60–90 min after intravenous injection of ^{99m}Tc (740–925 MBq, 20–25 mCi) using a dual-detector gamma camera (Millennium MG, General Electric, Elgems, Tirat Carmel Israel), equipped with a low-energy, all-purpose collimator, centered on the 140-keV photopeak with a 20% symmetrical energy window. Data were acquired in a 64×64 matrix along an elliptical orbit with six intervals over 180° (Toshiba-90B). Reconstruction was performed using a Butterworth-filtered back-projection algorithm without attenuation correction, and short-axis, horizontal long-axis, and vertical long-axis images were obtained. All of the scans were blindly reviewed by two experienced physicians. Myocardial perfusion was assessed visually using a 17-segment model. RV uptake of ^{99m}Tc was considered positive if any of the segments showed positive signal.

Statistics analysis

Continuous data were expressed as mean ± standard deviation (SD) and categorical data as percentage. Comparison between two groups was analyzed by unpaired Student's *t* test. Comparison among three groups was analyzed with one-way ANOVA followed by the Newman–Keuls test. Statistical differences were determined to be significant if $P < 0.05$. Data analysis was performed using SPSS version 10.0 (SPSS Inc., Chicago, IL) software. Sensitivity, specificity, and other values in diagnostic tests were calculated by

using RHC measurement (mPAP) as the universally accepted standard for the diagnosis of MPH (Table 2). A *post hoc* sample size calculation and inter and intraobserver variability coefficients calculation were performed by using PASS 11 and the results showed that the sample size of 23 cases in each group of this study reached the power = 0.9 requirement.

Results

Characterization of PAH patients

Twenty-three control subjects (6 men; 17 women; age 52 ±21) and 23 PAH patients (10 men; 13 women; age 40 ±18) were recruited in this study. PAH was diagnosed when mPAP at rest is more than 20 mmHg and the pulmonary capillary wedge pressure is no more than 15 mmHg, according to the established clinical criteria.[19,20] Table 1 summarizes the clinical, ECG, X-ray, and hemodynamic characteristics of the control group and PAH patients. The average mPAP pressure level was 14.26 ± 1.48 (mmHg) in the control subjects and 56.35 ± 13.19 (mmHg) in PAH patients. Compared to the control group, PAH patients had similar height, body weights, body surface areas, heart rates and respiration rates but showed slightly decreased transcutaneous oxygen saturation, suggesting impaired alveolar ventilation in PAH patients. Abnormal pulmonary second heart sound was present in 91.3% PAH patients and tricuspid auscultation zone systolic murmurs sound was detected in 43.5% PAH patients, neither of which was observed in the control subjects. Chest X-ray examination showed that heart enlargement and hilus hyperemia were detected in 78.3% and 48.5% of PAH patients, respectively, who also demonstrated a significantly elevated cardiothoracic ratio compared to the control group. ECG indexes including QT, proiosystole, paroxysmal supraventricular tachycardia (PSVT), tardy arrhythmia, ST segment changes, T wave change and atrioventricular block were not significantly changed in PAH patients.

Table 2. mPAP levels in the control and PAH groups.

	Control ($n = 23$)	Moderate PAH ($n = 7$)	Severe PAH ($n = 16$)	*P*
Group #	1	2	3	
mPAP (mmHg)	14.26 ± 1.48	42.57 ± 2.51	62.38 ± 22.29	<0.001**

Note: Moderate PAH: 36 < mPAP < 45 mmHg; Severe PAH: mPAP > 45 mmHg.
**$P < 0.01$.
PAH: pulmonary artery hypertension; mPAP: mean pulmonary arterial pressure.

Table 1. The demographic characters of the study groups (Mean ± SD, or *n*).

	Control ($n = 23$)	PAH ($n = 23$)	*P*
Male (%)	6 (26.1%)	10 (43.5%)	0.216
Age (year)	52.35 ± 21.41	40.22 ±18.32	0.225
Height (cm)	162.00 ± 6.79	164.04 ± 6.75	0.311
Weight (kg)	61 ± 9.95	63.35 ± 10.44	0.439
Body surface area (BSA, cm^2)	1.62 ± 0.17	1.66 ± 0.17	0.379
Heart rate (bpm)	76.78 ± 10.73	82.48 ± 12.04	0.097
Respiratory rate (per min)	20.30 ± 2.57	20.48 ± 1.56	0.783
Transcutaneous oxygen saturation	99.0% ± 0.8%	98.3% ± 0.9%	0.005**
Physical exam			
Abnormal lung auscultation (%)	0 (0%)	1 (4.34%)	0.312
Abnormal pulmonary second heart sound (%)	0 (0%)	12 (91.3%)	<0.001**
Tricuspid auscultation zone systolic murmurs intensity (0/1/2/3)	23/0/0 (100%/0%/0%)	13/2/3/5 (56.5%/8.70%/ 13.0%/21.7%)	0.005**
Pulmonary valve auscultation area intensity of diastolic murmur (normal/mild/moderate)	23/0/0 (100%/0%/0%)	18/4/1 (78.3%/17.4%/4.30%)	0.061
Enlarged liver lower bound (%)	0 (0%)	2 (8.70%)	0.148
X-ray imaging			
Heart enlargement (%)	0 (0%)	18 (78.3%)	<0.001**
Hilus hyperemia (%)	0 (0%)	10 (43.5%)	<0.001**
Cardiothoracic ratio	77.43 ± 9.64	79.13 ± 12.36	0.004**
ECG parameter			
QT(s)	0.41 ± 0.03	0.39 ± 0.04	0.132
Proiosystole (%)	1 (4.35%)	2 (8.70%)	0.550
PSVT (%)	0 (0%)	1 (4.35%)	0.312
Tardy arrhythmia (%)	0 (0%)	2 (8.70%)	0.148
ST segment changes (%)	2 (8.70%)	4 (17.4%)	0.381
T wave change (%)	2 (8.70%)	3 (13.0%)	0.636
Atrioventricular block (%)	0 (0%)	1 (4.35%)	0.312
RHC parameter			
mPAP (mmHg)	14.26 ± 1.48	56.35 ± 13.19	<0.001**

SD: standard deviation; PAH: pulmonary artery hypertension; ECG: electrocardiogram; RHC: right heart catheterization; mPAP: mean pulmonary arterial pressure.
**$P < 0.01$.

RHC in PAH

To assess the correlation between RHC indexes and mPAP levels, PAH patients were divided into two subgroups according to the mPAP levels (Table 2). RHC parameters are presented in Table 3, which showed that levels of right atrial pressure (RAP) and cardiac output (CO) were not significantly changed in PAH patients. Right ventricle systolic pressure (RVSP), right ventricular end diastolic pressure (RVEDP), pulmonary artery systolic pressure (PASP), pulmonary artery diastolic pressure (PADP), and pulmonary vascular resistance (PVR) increased in both PAH groups with the highest levels in the severe PAH patients. Pulmonary capillary wedge pressure (LPCWP), total peripheral resistance (TPR), and pulmonary vascular resistance index (PVSR) significantly increased in both PAH groups but without significant difference between the moderate and severe PAH groups. Notably, although PCWP level increased in both PAH groups, the average values were less than 12 mmHg. Compared to the control group, RV stroke volume was only significantly elevated in the moderate PAH group. Our results showed that RHC parameters, including RVSP, RVEDP, PASP, PADP and PVR, increased in the PAH patients and were positively correlated with mPAP levels.

Echocardiography in PAH

We next assessed RV morphology and hemodynamics characteristics with echocardiography (Table 4). We observed tricuspid regurgitation, suppressed systolic function and hypertrophy, indication of RV dysfunction in PAH. Moreover, tricuspid regurgitation peak velocity and tricuspid regurgitation pressure gradient were observed in two PAH groups and were positively related to mPAP levels. In sharp contrast, no tricuspid regurgitation was observed in any subject in the control group. Right atrium longitudinal diameter and horizontal diameter significantly increased in all PAH patients with the greatest level in the severe PAH group; however, right atrium area and right ventricular

Table 3. Comparison of the detailed RHC parameters between the control and PAH subgroups (Mean ± SD).

				P		
	Group 1	Group 2	Group 3	1 vs. 2	1 vs. 3	2 vs. 3
RAP (mmHg)	8.39 ± 2.73	5.71 ±2.50	8.31 ± 5.52	0.120	0.951	0.150
RVSP (mmHg)	27.70 ± 3.80	69.00 ± 5.80	90.44 ± 25.06	<0.001**	<0.001**	0.014*
RVEDP (mmHg)	5.04 ± 1.33	8.29 ± 2.06	12.13 ± 7.06	0.015*	0.003**	0.171
PASP (mmHg)	27.00 ± 3.61	68.57 ± 5.88	96.06 ± 12.19	<0.001**	<0.001**	<0.001**
PADP (mmHg)	7.96 ± 1.33	29.71 ± 2.14	46.44 ± 12.29	<0.001**	<0.001**	<0.001**
PCWP (mmHg)	7.61 ± 1.41	11.14 ± 2.73	10.19 ± 1.33	0.039*	<0.001**	0.791
CO (L/min)	5.73 ± 0.87	5.86 ± 0.69	6.14±1.16	0.746	0.192	0.524
TPR (dyne·s·cm^{-5})	205.52 ± 31.44	568.43 ± 161.83	827.81 ± 339.90	0.003**	<0.001**	0.064
PVR (dyne·s·cm^{-5})	95.35 ± 29.69	426.14 ± 158.96	695.69 ± 317.91	0.004**	<0.001**	0.04*
PVRI (dyne·s·cm^{-5})	153.96 ± 52.38	712.71 ± 198.80	1155.81 ± 629.23	0.001**	<0.001**	0.057

RAP: right atrial pressure; RVSP: right ventricle systolic pressure; RVEDP: right ventricular end diastolic pressure; PASP: pulmonary artery systolic pressure; PADP: pulmonary artery diastolic pressure; PCWP: pulmonary capillary wedge pressure; CO; cardiac output; TPR: total pulmonary resistance; PVR: pulmonary vascular resistance; PVRI: pulmonary vascular resistance index.
*$P < 0.05$, **$P < 0.01$.

Table 4. Comparison of echocardiography parameters between the control and PAH subgroups (Mean ± SD).

				P		
	Group 1	Group 2	Group 3	1 vs. 2	1 vs. 3	2 vs. 3
Tricuspid regurgitation peak velocity (cm/s)	0.00 ± 0.00	3.71 ± 0.22	4.44 ± 0.34	<0.001**	<0.001**	<0.001**
Tricuspid regurgitation pressure gradient (mmHg)	0.00 ± 0.00	55.43 ± 6.78	79.19 ± 12.01	<0.001**	<0.001**	<0.001**
PASP (mmHg)	0.00 ± 0.00	69.00 ± 7.64	94.19 ± 12.01	<0.001**	<0.001**	<0.001**
Right atrium longitudinal diameter (mm)	37.78 ± 2.28	43.43 ± 3.21	49.00 ± 4.47	0.008**	<0.001**	0.001**
Right atrium horizontal diameter (mm)	32.91 ± 2.09	36.14 ± 3.02	40.25 ± 4.58	0.028*	<0.001**	0.009**
Right atrium area (cm^2)	12.35 ± 1.23	13.71 ± 1.38	15.81 ± 2.17	0.123	<0.001**	0.036*
Right ventricular outflow tract (mm)	24.43 ± 1.65	27.43 ± 2.88	30.94 ± 3.43	0.096	<0.001**	0.071
RVWT (mm)	3.35 ± 0.49	5.00 ± 1.00	5.06 ± 0.68	0.012*	<0.001**	0.998
TAPSE (mm)	20.91 ± 1.20	15.29 ± 1.11	12.88 ± 1.50	<0.001**	<0.001**	<0.001**
Right ventricular myocardial perform index	0.38 ± 0.03	0.57 ± 0.08	0.79 ± 0.10	0.001**	<0.001**	<0.001**
FAC (%)	47.90 ± 3.22	35.33 ± 2.89	28.83 ± 2.87	<0.001**	<0.001**	<0.001**

PASP: pulmonary artery systolic pressure; RVWT: right ventricular wall thickness; TAPSE: Tricuspid annular plane systolic excursion; RV-MPI: right ventricular myocardial performance index; FAC: fractional area change.
*$P < 0.05$, **$P < 0.01$.

outflow tract only significantly increased in the severe PAH group. Right ventricular wall thickness also significantly increased in both PAH groups but with no significant difference between the moderate PAH and severe PAH groups. Tricuspid annular plane systolic excursion (TAPSE) and fractional area change significantly decreased in the PAH groups with the lowest level in the severe PAH group, whereas RV-myocardial performance index showed the opposite change with the highest level in the severe PAH group.

MPI in PAH patients

MPI with ^{99m}Tc was further performed to assess RV perfusion. As shown in Figure 1, in the control group, tracers were only enriched in the left ventricles but not in RVs. In contrast, increased perfusion in RV was observed in both severe and moderate PAH patients. Further quantitation revealed that RV perfusion was observed in 71.4% (5 in 7 patients) of moderate PAH patients and 100% of severe PAH patients (16 in 16 patients, Table 5). These results

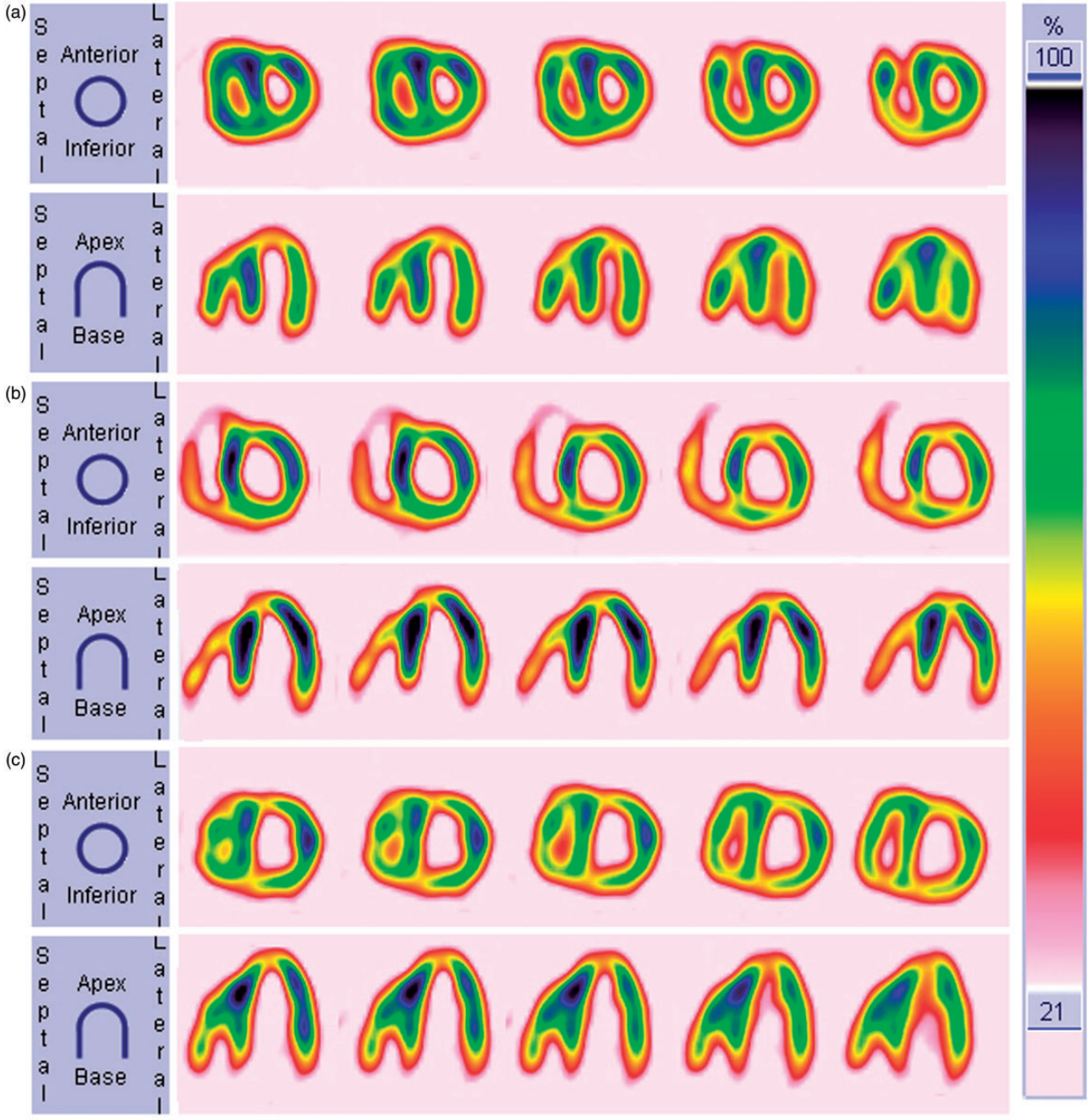

Figure 1. MPI images of PAH patients and control subjects. Representative MPI images from standard short-axis and long-axis projections of myocardial single photon emission computed tomography (SPECT) with 99mTC in severe PAH (a), moderate PAH (b) and control subjects (c). Each group included five representative examples from the same subject. Right ventricle (RV) perfusion was not observed in control subjects but showed increased perfusion areas in PAH patients. (A color version of this figure is available in the online journal.)

Table 5. Diagnosis of MPI in relation to the mPAP criteria for PAH.

		PAH			
		Negative	**Moderate**	**Severe**	**Sum**
MPI					
−	Count	23	2	0	25
	% within the group	92.00%	8.00%	0.00%	100.00%
+	Count	0	5	16	21
	% within the group	0.00%	23.81%	76.19%	100.00%
Sum					
Count		23	7	16	46
% within the group		50.00%	15.22%	34.78%	100.00%

MPI: myocardial performance index; PAH: pulmonary artery hypertension; mPAP: mean pulmonary arterial pressure.

Table 6. Cross tabulation of MPI compared with PAH diagnosed by RHC.

As compared with MPA from RHC	**Sensitivity**	**Specificity**	**PPV**	**NPV**	**PLR**	**NLR**
Severe	1.00	0.83	0.76	1.00	6.00	0.00
Severe and moderate	0.91	1.00	1.00	0.92	NA	0.09

PPV: positive predictive value; NPV: negative predictive value; PLR: positive likelihood ratio; NLR: negative likelihood ratio; RHC: right heart catheterization.

suggest that the presence of RV hypertrophy may be positively correlated with the mPAP pressure levels in PAH patients.

Diagnostic performance of MPI index in PAH

To further assess the accuracy of MPI index in the diagnosis of PAH and determine the correlation between MPI index and PAH disease progression, diagnostic test was performed to calculate the diagnostic accuracy of MPI index in PAH. As shown in Table 6, the sensitivity of MPI was 1 in the severe PAH group and 0.93 in all the PAH patients, respectively. The specificity of MPI was 0.83 and 1 in severe PAH patients and all the PAH patients, respectively. The total positive likelihood was 0.76 in the severe PAH group and 1 in all the PAH patients. The negative likelihood was 1 in the severe PAH group and 0.92 in all the PAH patients, respectively. These results supported the diagnostic potential of MPI index in PAH, especially severe PAH.

Discussion

PAH is characterized by the presence of increased lung vascular resistance, which results in a strikingly elevated RV afterload.[21] To maintain the systolic function of RV, an initial myocardial hypertrophy is followed by maladaptive and progressive contractile dysfunction, and eventual chamber dilation and RV failure, which is accompanied by increased filling pressure and diastolic dysfunction, diminished cardiac output and increased tricuspid regurgitation.[22,23] Meanwhile, there is lack of determinants and management of RV failure. Therefore, it is essential to identify the markers to assess and monitor RV function in PAH patients. In this study, we systemically analyzed the parameters of RHC, echocardiography, and ^{99m}Tc MPI in PAH patients and evaluated the correlation of these indexes with mPAP levels. Our results may provide the clinical evidence to identify standard markers to assess RV performance, prognosis, and therapeutic management strategies in PAH patients in the future.

RHC acts as the gold standard and has been widely used for PAH diagnosis, disease severity assessment, determination of prognosis and response to therapy in clinical practice. Previous studies have identified the prognostic role of RHC parameters, including RAP, cardiac output, mPAP levels, and PVR in PAH patients.[2] Consistently, we found that PVR increased in PAH patients and severe PAH patients had the highest PVR level (Table 3). Interestingly, RAP did not show significant difference in the PAH population enrolled in this study; however, RVSP, RVEDP, PASP, and PVR were variable in PAH patients and correlated with mPAP levels (Table 3). Our results suggest that combination of RHC parameters might be used to assess RV function.

Echocardiography has been applied in clinical practice to provide valuable information for hemodynamics, morphology, and systolic/diastolic function of RV; however, there has been no echocardiographic gold standard of RV functional assessment. Previous studies have found that myocardial performance index, RV fractional area change, and TAPSE are correlated with the survival of PAH patients.[24–27] Consistent with these previous studies, our results showed that tricuspid regurgitation peak velocity, tricuspid regurgitation pressure gradient, right atrium longitudinal diameter and horizontal diameter, TAPSE, FAC, and RV-MPI were significantly changed in PAH patients and correlated with mPAP pressure levels (Table 4). The secondary tricuspid regurgitation and tricuspid regurgitation usually resulted from PAH have been shown to be independently associated with PAH; however, several studies have shown that remodeling of the RV instead of mPAP levels is the major mechanism responsible for the

tricuspid regurgitation in PAH.[28,29] It will be important to assess RV remodeling in PAH patients.

MPI techniques have shown advantages over other non-invasive imaging methods.[30] In this study, we used MPI with ^{99m}Tc to examine RV perfusion and observed increased RV perfusion in PAH patients, which indicates the presence of RV hypertrophy (Table 5, Figure 1). The RV hypertrophy was also supported by the increased RV wall thickness as measured by echocardiography (Table 4). Notably, RV wall thickness did not show significant difference between the moderate PAH and severe PAH group in echocardiography. Nevertheless, compared to moderate PAH group, the occurrence of MPI perfusion was significantly elevated in the severe PAH group, suggesting MPI has increased sensitivity to detect RV hypertrophy. Although previous studies have validated the use of SPECT and PET to evaluate RV hypertrophy,[31,32] ischemia,[13,33,34] and fatty acid metabolism,[35–37] the association of MPI index with the severity of PAH and other clinical diagnostic parameters of RHC remains to be evaluated in PAH patients. Our study showed the performance and diagnostic potential of MPI in MPH diagnosis, especially for severe MPH. Our findings suggest that MPI may be included as diagnostic criterion for early detection of PAH as an alternative, non-invasive imaging method (Table 6). Nevertheless, the relatively small patient number may be deemed as a limitation of the study due to the difficulty to recruit the PAH patients.

Taken together, in this study, we systemically analyzed the parameters of RHC, echocardiography, and MPI in normal subjects, moderate, and severe PAH patients. Our results showed that several indexes, including MPI index, are significantly correlated with mPAP levels and PAH severity. Our study may provide the insights for establishing standards of RV assessment in PAH patients.

Authors' contributions: Jie Liu and Yong-Yue Zhang equally contributed to the conception and design of the research; Lei Fei contributed to the design of the research; Guang-Qing Huang and Xiao-Ke Shang contributed to the acquisition and analysis of the data; Mei Liu and Zhi-Jun Pei contributed to the interpretation of the data; and Jie Liu drafted the manuscript. All authors critically revised the manuscript, agree to be fully accountable for ensuring the integrity and accuracy of the work, and read and approved the final manuscript.

DECLARATION OF CONFLICTING INTERESTS

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