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Original Article

Pulmonary vascular performance and pulmonary function in patients with pulmonary arterial hypertension associated with connective tissue disease using intravascular ultrasound

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Abstract: This study was designed to explore the application of IVUS, to evaluate the changes in pulmonary vascular performance in patients with PAH-CTD, to study the relationship between pulmonary vascular performance and hemodynamics, and to evaluate the pulmonary function of PAH-CTD patients. 60 patients highly suspected of having PAH-CTD treated in our hospital from June 2014 to June 2019 were recruited as the study cohort. After undergoing RHC and IVUS, the patients were divided into three groups, namely the PAH-CTD group (n = 27), the other types of PAH group (n = 18), and the control group (n = 15). The patients in the PAH group were divided into the proximal remodeling subgroup (n = 21) and the distal remodeling subgroup (n = 24) according to IVUS. IVUS was used to analyze 480 pulmonary artery segments, and a statistical analysis was performed to evaluate and compare the pulmonary vascular performance and the pulmonary function among the patients in each group. The IVUS results showed that, compared with the control group, the MWT in the PAH-CTD group and the other types of PAH group was higher than it was in the control group (both $P < 0.01$). The FFR results showed that there was a significant power correlation between the FFR results and the IVUS results (both $R^2 > 0.4$, $P < 0.01$). The pulmonary vascular mechanical properties of the patients in the PAH-CTD group and in the other types of PAH group were worse than they were in the control group and showed a higher stiffness index β. In the pulmonary function results, the FEV1, FVC, FEV1/FVC and PAP values in the PAH-CTD group were higher than they were in the other types of PAH group, but the FEV1, FEV1/FVC and PAP values were lower than they were in the control group. IVUS can play an important role in evaluating pulmonary vascular performance in PAH patients. The pulmonary vascular performance of the PAH patients deteriorated, and the PAH-CTD group did better than the other types of PAH group. There was a positive correlation between pulmonary function and pulmonary vascular performance.

Keywords: Intravascular ultrasound, pulmonary hypertension, pulmonary function, fractional flow reserve

Introduction

Pulmonary hypertension (PH) is a group of diseases characterized by an abnormal increase in pulmonary arterial pressure (PAP), which can increase the pulmonary artery and right ventricle pressure and eventually lead to right heart enlargement, right ventricular wall hypertrophy, and right heart failure and death. Pulmonary arterial hypertension (PAH) is the most lethal type of PH [1-4], and the median survival time of PAH patients under current PAH drug therapy is only 7 years [5]. PAH is a common complication in patients with connective tissue disease. PAH associated with connective tissue diseases (PAH-CTD) mainly includes systemic lupus erythematosus (SLE)-related PAH, scleroderma (SSc), mixed connective tissue disease (MCTD), rheumatic arthritis (RA) and Sjogren's syndrome [6].

The diagnosis and evaluation methods of pulmonary hypertension mainly include right heart catheterization, lung biopsy, and pulmonary angiography. At present, right heart catheterization (RHC) is still the "gold standard" for the

evaluation and diagnosis of PAH, but it cannot detect abnormal pulmonary vascular performance, nor can it distinguish the slight differences of pulmonary vascular performance between the different types of PAH. Lung biopsy can accurately evaluate pulmonary vascular lesions, but because of the heterogeneity of pulmonary vascular lesions in patients with PH, and the greater trauma of biopsy, its clinical application is limited [7-12]. Intravascular ultrasound (IVUS) is a new imaging technique combining noninvasive ultrasound and invasive cardiac catheterization, and currently, it is mostly used in coronary heart disease research. However, a large number of studies at home and abroad have shown that IVUS can not only evaluate the function of pulmonary vessels, but it can also quantitatively and qualitatively analyze the functional changes of pulmonary vessels, so it plays an important role in evaluating the morphological changes and mechanical properties of PAH pulmonary vessels [13]. The distribution of the pulmonary vascular remodeling in the pulmonary vessels is uneven, and it is not only reflected in the changes in the vascular performance of the remodeling site. In fact, the overall pulmonary vascular performance is abnormal. However, most of the IVUS studies on PAH pulmonary vascular performance in the world emphasize the changes at the remodeling site while they ignore the abnormality of the overall performance, so they cannot accurately reflect pulmonary vascular performance.

Fractional Flow Reserve (FFR) refers to the ratio of the maximum blood flow that can be obtained in the myocardial region supplied by the blood vessels to the theoretically maximum blood flow that can be obtained under normal conditions in the same region under the condition of coronary artery stenosis, i.e., the ratio of the mean pressure in the stenotic distal coronary artery (Pd) to the mean pressure in the coronary artery ostium aorta (Pa) in the state of myocardial maximal hyperemia. FFR is widely used to evaluate the degree of coronary artery stenosis, and it is reported in the literature that FFR can also be used for the study of the pulmonary artery. Therefore, in this study, IVUS and FFR were used to analyze the proximal and distal segments of the pulmonary vessels, and the mean value of the two was calculated to ensure the consistency of the overall pulmonary vascular performance. Direct measurement and indirect calculation were used to study the changes in pulmonary vascular performance and pulmonary function.

Materials and methods

Research cohort and groups

We reviewed the medical histories and echocardiograms of 60 patients highly suspected of having PAH-CTD who were treated in People's Hospital of Xinjiang Uygur Autonomous Region from June 2014 to June 2019, and these patients were recruited as the study cohort. Inclusion criteria: ① Patients who met the diagnostic criteria for pulmonary hypertension and whose diagnosis was confirmed by a pathological examination, and ② Patients who agreed to participate in the treatment and research. Exclusion criteria: ① Patients suffering from chronic diseases or malignant tumors in the heart, brain, or other parts, ② Patients treated with other methods in the past three months that might affect the results of this study, ③ Patients with psychosis, and ④ Patients with incomplete medical records. RHC and IVUS examinations were performed after acceptance into the study. According to RHC, the laboratory tests, and the diagnoses of the People's Hospital of Xinjiang Uygur Autonomous Region, 27 patients were diagnosed with PAH-CTD (the PAH-CTD group), and 18 patients were diagnosed as having other types of PAH (10 cases of idiopathic pulmonary artery hypertension, 4 cases of portal pulmonary hypertension, 4 cases of congenital heart disease-related pulmonary hypertension), and 15 patients without PAH (the control group). The study was approved by the local medical ethics committee, and all the selected patients signed informed consent forms.

RHC and IVUS examinations

RHC (8.5F, Baxter Healthcare, Edwards Critical Care Division, Deerfield, IL, United States) was performed according to the Guidelines for the Diagnosis and Treatment of Pulmonary Hypertension [14] in the European Heart Journal to determine the patients' pulmonary artery hemodynamics. The measurements included: right atrial pressure (RAP), right ventricular pressure (RVP), pulmonary artery systolic pressure (sPAP), pulmonary artery diastolic pressure (dPAP), mean pulmonary artery pressure

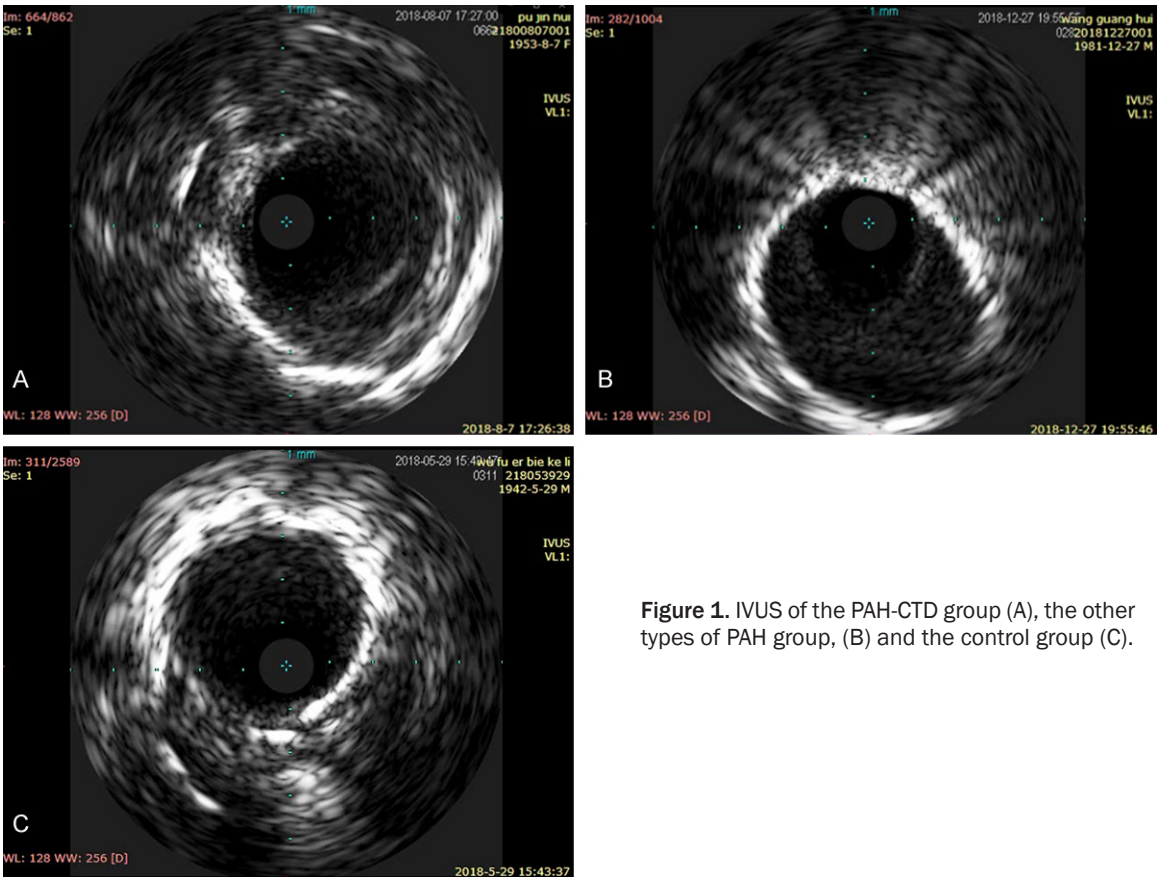

Figure 1. IVUS of the PAH-CTD group (A), the other types of PAH group, (B) and the control group (C).

(mPAP), pulmonary artery wedge pressure (PAWP), cardiac output/cardiac index (CO/CI), etc. The formula of PVR was: PVR = (mPAP-PAWP)/CO, and the formula of pulmonary artery pulse pressure difference (PPP) was PPP = sPAP-dPAP. The blood oxygen saturation of the vena cava, right atrium, right ventricle, and the pulmonary artery and the systemic circulation were measured. IVUS examinations were performed immediately after the RHC and pulmonary angiography (or the acute pulmonary vasodilator test) when the pulmonary artery pressure was restored (**Figure 1**). The lower pulmonary artery segment was measured using a 40 MHz US catheter (Boston Scientific, US) with an axial resolution of 43 μm. With reference to Bressollette et al. [15], typical pulmonary vascular performance abnormalities were usually in the lower lung, and the degrees of abnormality were similar in the left lung and the right lung. Therefore, two segments from the left and right pulmonary artery lower segments were taken from each patient , for a total of 4 segments measured from each patient, and the mean value was recorded for the statistical analysis.

The US catheter was delivered to the distal end of pulmonary artery and returned to the proximal end of pulmonary artery at a speed of 0.5 mm/s. The iLabTM system (Boston Scientific, United States) was used to read the image data to ensure that all the image quality was good (there was a complete circumferential boundary between the media and inner walls of the outer membrane of the pulmonary vessel), and the image data was recorded and saved with a Sony DVD.

FFR examinations

After the IVUS examination, a suitable guide tube was placed along the puncture vessel into each patient's pulmonary artery opening, the pressure wire was sent to the pulmonary artery opening through the guide tube, and the pressure measured by the pressure wire was corrected to be consistent with the pressure measured by the guide tube, then the pressure wire was sent to the distal end of the patient's lesion blood vessel. During the operations, we carefully avoided letting the guide wire contact the blood vessel wall, which would ultimately affect

the accuracy of the examination result. After an intravenous infusion of adenosine triphosphate 140 μg/kg·min until the patient's blood vessels reach their maximal hyperemia, the distal pressure and proximal pressure were measured using the pressure wire, and the FFR value was calculated. In order to ensure the accuracy of the data analysis, the examination and the determination of the FFR results were all completed by a highly-qualified interventional cardiologist with the main treatment qualification or higher and who was trained in FFR technology.

Measurement and calculation of pulmonary vascular performance

Using the single-blind method, two experienced operators independently measured the pulmonary vessel segments using imap software (ImageJ Ver 1.44, NIH, United States) without knowing any of the clinical or hemodynamic data. All the pulmonary vessels were divided into two segments: diameter < 5 mm for the distal segment and diameter > 5 mm for the proximal segment. A total of 480 pulmonary vessel segments were measured (216 in the PAH-CTD group, 144 in the other types of PAH group, and 120 in the control group).

Since IVUS cannot distinguish the pulmonary vascular adventitia, the study adopted the data on the diameter of the pulmonary vessel lumen (including the pulmonary vascular intima and media), including the diastolic and systolic total vascular (pulmonary vascular intima and media) areas (VAd and VAs), vessel diameters (VDd and VDs), lumen areas (LAd and LAs), lumen diameters (LDd and LDs), and minimum lumen diameters (MLDd and MLDs), mean vessel diameter = (VDd+VDs)/2, mean wall thickness (MWT) = [(VDd+VDs)/2-(LDd+LDs)/2]/2, percentage of MWT (WTP) = (2 × MWT) × 100%/VD. If the WTP of the distal segment of a pulmonary artery in the PAH patients was higher than it was in the proximal segment, it was included in the distal remodeling group (n = 21), otherwise it was included in the proximal remodeling group (n = 24).

The pulmonary vascular mechanical performance indexes included compliance, distensibility, elastic modulus, and stiffness index β [16-20], and the calculation method of each index was as follows: Compliance = (VAd-VAs) × 100/PPP; Distensibility = (VAd-VAs) × 100%/PPP × VAd; Elastic modulus = PPP × VDd/(VDd-VDs); Stiffness index β = Ln (sPAP/dPAP)/[(VDd-VDs)/VDd].

Measurement of lung function

A Quark PFT4 pulmonary function instrument (COSMED, Italy) was used to measure the pulmonary function indexes FEV (forced expiratory volume in 1 second) and FVC (forced vital capacity). A Compaq RT-6800 color Doppler ultrasonic cardiograph was used to measure PAP (pulmonary artery pressure). The relationship between pulmonary vascular performance and pulmonary function was analyzed based on four indexes: FEV1 (forced expiratory volume in the first second), FVC (forced vital capacity), FEV1/FVC (%) (ratio of forced expiratory volume in the first second to forced vital capacity) and PAP (pulmonary artery pressure).

Statistical analysis

SPSS 19.0 software was used for the statistical analysis. Unless otherwise specified, continuous variables were represented as the mean ± standard error; independent samples t-tests and paired samples t-tests were used for the comparisons of non-normal distribution continuous variables, and one-way ANOVA was used for the comparison of the normally distributed data. Regression analysis, the test curve fitting model, and the POWER model were used to analyze the correlation between pulmonary vascular performance and hemodynamics. The main endpoint was all-causes of death. Bilateral $P < 0.05$ was considered statistically significant.

Results

Baseline data and hemodynamic test results

As shown in (**Table 1**), SLE accounts for 52% (14/27) of the most common causes in the PAH-CTD group, and IPAH accounts for 67% (12/18) in the other types in the PAH group.

There was no significant difference in the hemodynamic indexes between the PAH-CTD group and the other types of PAH group (**Table 2**), but the hemodynamic indexes of the patients in the PAH-CTD group and the other types of PAH group were significantly higher than they were in the control group ($P < 0.01$).

IVUS test results

No complications occurred in any of the patients after the IVUS examination. The mean vessel diameters of the patients in the PAH-

Table 1. Baseline data of the patients in each group

	PAH-CTD group	Other types of PAH group	Control group	χ^2/F	P
Number	27	18	15		
Age	46±16	43±13	45±16	0.212	0.810
Gender Female	24/3	17/1	15/0	1.964	0.375
Cases	14 cases of systemic lupus erythematosus 4 cases of systemic sclerosis 2 cases of Sjogren's syndrome 1 case of mixed connective tissue disease 1 case of rheumatoid	12 cases ofidiopathic pulmonary hypertension 3 cases of portal hypertension pulmonary hypertension 2 cases of Raynaud phenomenon	10 cases of systemic lupus erythematosus 3 cases of systemic sclerosis 1 case of rheumatoid arthritis 1 case of liver and lung syndrome	4.239	0.120

Table 2. The hemodynamic indexes of the patients in each group (±s)

Group	PAH-CHD group (n = 25)	Other type PAH group (n = 15)	Control group (n = 11)	F value	*P* value
RAP (mmHg)	7.5±6.2	8.6±3.2	6.5±1.2	0.634	0.48
RVP (mmHg)	29.6±6.5	31.52±10.9	11.0±3.5	27.900	< 0.01
sPAP (mmHg)	60.53±10.85	72.65±15.63	19.68±10.23	63.272	< 0.01
dPAP (mmHg)	30.58±10.6	42.56±8.55	10.86±6.54	37.051	< 0.01
mPAP (mmHg)	51.5±11.2	43.6±15.1	12.1±3.6	45.632	< 0.01
PAWP (mmHg)	11.05±5.1	13.00±3.8	10.65±2.7	1.246	0.15
CO (L/min)	4.5±0.9	5.9±1.4	6.1±1.3	10.666	< 0.01
PVR (Wood) unit	12.9±15.6	10.8±7.3	2.3±0.5	3.176	< 0.01

Note: RAP: right atrial pressure, RVP: right ventricular pressure, sPAP: pulmonary artery systolic pressure, dPAP: pulmonary artery diastolic pressure, mPAP: mean pulmonary artery pressure, PAWP: pulmonary artery wedge pressure, CO: cardiac output, PVR: pulmonary vascular resistance.

Table 3. The relationship between FFR and MWT

Group	MWT (mm)	FFR	R^2
PAH-CHD group (n = 25)	0.32±0.02	0.81	0.733
Other type PAH group (n = 15)	0.30±0.03	0.75	0.810
Control group (n = 11)	0.24±0.02	0.76	0.512
P value	< 0.01	< 0.01	

CTD group, the other types of PAH group, and the control group were basically the same (P > 0.05), which ensured the consistency of all the vessels and eliminated any interference or deviation caused by the differences in the pulmonary vessel diameters. Compared with the control group, the MWT of patients in the PAH-CTD group and in the other types of PAH group were both larger than the MWT in the control group (P < 0.01), and the WTP in the PAH-CTD group and in the other types of PAH group were both larger than the WTP in the control group (P < 0.01).

FFR test results

The study found that under the guidance of FFR, the incidence rate of primary endpoint events in the PCI group was significantly lower than it was in the drug treatment group when FFR ≤ 0.8. When FFR > 0.8, the drug treatment alone had a better curative effect. As shown in (**Table 3**), the FFR and IVUS test results show a significant power correlation.

The pulmonary vascular mechanical property test results

The patients' pulmonary vascular compliance in the PAH-CTD group and in the other types of PAH group was lower than it was in the control group. The distensibility was also lower than it was in the control group. The elastic modulus was higher than it was in the control group. The stiffness index β was higher than it was in the control group. The EM of the patients in PAH-CTD group was lower than it was in the other types of PAH group (**Table 4** all P < 0.01).

Analysis results of the correlation between the pulmonary vascular mechanical properties and hemodynamics

A nonlinear regression analysis of all patients' data (**Table 5**) shows that there is a significant power correlation between the pulmonary vascular mechanical properties and pulmonary

Table 4. Pulmonary vascular mechanical properties

Group	Compliance × 10^{-2} (mm^2/mm Hg)	Distensibility% (mm^2/mm Hg)	Elastic modulus	Stiffness index β (1)	EM (mm Hg)
PAH-CHD group (n = 25)	9.32±0.59	0.94±0.13	180.63±12.10	4.53±0.34	170.53±12.73
Other type PAH group (n = 15)	7.56±0.44	0.76±0.08	216.81±20.13	5.17±0.56	238.67±18.71
Control group (n = 11)	39.06±4.65	4.25±0.84	50.62±7.16	2.25±0.37	53.36±6.42
F value	844.967	313.767	470.429	164.882	571.857
P value	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001

Table 5. The relationship between the IVUS data and the hemodynamic measurements

Group	Compliance		distensibility		EM		Stiffness index β	
	R^2	*P*	R^2	*P*	R^2	*P*	R^2	*P*
sPAP	0.742	0.001	0.754	0.001	0.743	0.001	0.211	0.05
mPAP	0.682	0.001	0.618	0.001	0.672	0.001	0.195	0.12
PVR	0.582	0.001	0.547	0.001	0.500	0.001	0.186	0.09

Table 6. Pulmonary function test results (±s, %)

Group	FEV1 (L)	FVC (L)	FEV1/FVC (%)	PAP (mm Hg)
PAH-CHD group (n = 25)	0.81±0.35	1.4±0.41	57.14±6.24	53.15±7.53
Other types PAH group (n = 15)	0.78±0.24	1.3±0.62	55.64±7.10	52.15±6.57
Control group (n = 11)	0.86±0.52	1.3±0.47	59.45±5.1	54.69±4.88
P value	< 0.05	< 0.05	0.09	< 0.05

artery hemodynamics, and there are significant power correlations between sPAP and compliance, distensibility, elastic modulus and stiffness index β. There are significant power correlations between mPAP and compliance, distensibility, elastic modulus, and also between PVR and compliance, distensibility, elastic modulus.

Test results of pulmonary function

Compared with the other types of PAH group, the PAH-CTD group had higher FEV1, FVC, FEV1/FVC, and PAP values ($P < 0.05$), but compared with the control group, the PAH-CTD group had lower FEV1, FEV1/FVC, and PAP values, but the difference between FEV1/FVC groups was not statistically significant ($P = 0.09$) (**Table 6**).

Discussion

The results of this study demonstrate the important role of IVUS in the evaluation of pulmonary vascular performance. The trauma caused by IVUS is small, and the thickness of the vascular wall (intima and media) can be directly observed. Consistent with the results of previous studies, the pulmonary vascular remodeling in patients with PAH was significant, and their pulmonary vascular mechanical properties were significantly reduced [22, 23]. Changes in the mechanical properties may be affected by pulmonary vascular remodeling. A linear regression analysis indicated that the more severe the pulmonary vascular remodeling, the worse the pulmonary vascular mechanical properties. In addition, the distribution of pulmonary vascular remodeling in pulmonary vessels is uneven and not only reflected in the changes in the vascular performance of the remodeling site. In fact, the overall pulmonary vascular performance is abnormal. However, most of the IVUS studies on PAH pulmonary vascular performance emphasize the changes in the remodeling site, but they ignore the abnormality of the overall performance, so they cannot accurately reflect the pulmonary vascular performance [24, 25]. In this study, the IVUS examination showed that the proportion of patients with PAH distal remodeling was only 53% (24/45), and nearly half of the patients had pulmonary vascular proximal remodeling. Therefore, it is necessary to measure and aver-

age the data at both ends. Hemodynamic changes in PAH patients are similar, but to some extent, the pulmonary vascular performance of PAH-CTD patients is better than it is in other types of PAH patients, so it may be related to inflammatory dysimmunity and deserves further study [21]. Researchers have recently demonstrated that patients with PAH-CTD have significantly reduced endothelial metabolic function. Moreover, they showed that for a given cardiac index, patients with PAH-CTD have a lower functional capillary surface area. Such reduction in functional capillary surface area is directly correlated with the degree of Dlco reduction. These findings suggest that the reduction in Dlco in patients with PAH-CTD reflects a diminishing vascular area with reduced metabolic activity [22-26]. At the same time, we compared the results of FFR and IVUS and found them to be significantly correlated, suggesting that FFR can assist IVUS in evaluating pulmonary vascular performance. The statistical analysis results of this study also showed that there is a strong power correlation between pulmonary vascular performance and hemodynamics, indicating that pulmonary vascular performance may be significantly improved if intervention treatment is given at the early stage of PAH (when mPAP and PVR are both low). In addition, IVUS can better detect changes in pulmonary vascular performance at an early stage compared with hemodynamic changes determined by RHC.

Due to the non-specific early symptoms and signs of pulmonary hypertension, complex pathogenesis and poor prognosis, early screening, rapid diagnosis, and accurate assessment of the disease are particularly important. IVUS can safely and effectively evaluate the changes of pulmonary artery morphology and function in patients with pulmonary hypertension and provide important clues for the diagnosis, severity evaluation, treatment choice, and prognosis evaluation of pulmonary hypertension. At present, right heart catheterization (RHC) is still the "gold standard" for the evaluation and diagnosis of PAH, but it cannot detect abnormal pulmonary vascular performance, nor can it distinguish slight changes in pulmonary vascular performance between the different types of PAH, thus limiting its further application. However, IVUS makes up for this shortfall. A large number of studies at home and abroad have shown that IVUS can not only study the function of pulmonary vessels, but it also quantitatively and qualitatively analyzes the functional changes of the pulmonary vessels, which plays an important role in detecting and evaluating the morphological changes and mechanical properties of PAH pulmonary vessels. However, IVUS itself still has many problems and limitations, such as its high cost, its assessment of pulmonary artery vascular wall lesions in pulmonary hypertension has not been universal, and the relationship between structural changes and functional changes in pulmonary vascular walls has not been fully clarified, so it is necessary to further evaluate the clinical application value of IVUS in pulmonary hypertension. It has been proved that IVUS can accurately perform high-resolution imaging of small vessels and measure the diameter of the lumen and the thickness of the intima and media to evaluate the severity of vascular lesions and determine their composition, as long as it is done using appropriate operations. In the clinic, the pulsatility of the pulmonary artery can be directly observed in children with congenital heart disease complicated by severe pulmonary hypertension in the critical state, which provides an important basis for the selection of operative indications and the evaluation of the postoperative effect. With the emergence and continuous improvement of IVUS 3D reconstruction technology, forward-looking functions, virtual histology imaging technology, IVUS measurement of blood flow velocity and therapeutic application, its application value in pulmonary hypertension and other cardiovascular diseases will become more and more important.

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Disclosure of conflict of interest

None.

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