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Differences in right ventricular dysfunction in patients with idiopathic pulmonary hypertension versus secondary pulmonary hypertension

Abstract

Introduction: Right ventricular (RV) function in the setting of pulmonary hypertension based on different etiologies has not been well studied. In this study, we evaluated the RV function in patients with idiopathic pulmonary hypertension (IPH) *versus* secondary pulmonary hypertension (SPH) due to congestive heart failure.

Material and method: Forty-five patients with pulmonary hypertension and New York Heart Association (NYHA) functional class II or III were enrolled. Of these, 22 were diagnosed with IPH and 23 with SPH. Echocardiographic data, including Doppler and Doppler based strain, were assessed according to the American Society of Echocardiography (ASE) guidelines for detailed evaluation of RV function in these two groups.

Results: Mean PAP was 60 $\pm$ 14.5 mm Hg in patients with IPH *versus* 43 $\pm$ 11.5 mm Hg in patients with SPH ($p = 0.001$). Considering conventional indexes of RV function, only Sm and dp/dt were significantly better in the first group compared with the second group (p-value for Sm $= 0.042$ and for dp/dt $= 0.039$). RV end diastolic dimension was significantly higher in the IPH group ($p = 0.013$). Using deformation indexes of RV function, the basal and mid portion of RV free wall strain and basal RV strain rates were significantly worse in the chronic systolic heart failure (PH-HF) group in comparison to the IPH group ($p < 0.001$ in basal RV strain, $p = 0.034$ in mid RV strain and $p = 0.046$ in basal RV strain rate respectively).

Conclusion: IPH has less impact on RV function in comparison to PH-HF. Considering both entities are in the category of RV pressure overload, we conclude that the etiology of pulmonary hypertension also plays an important role in RV function in addition to pressure overload.

Key words: pulmonary artery hypertension, pulmonary hypertension, right ventricular function, Doppler echocardiography, myocardial strain

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Introduction

The right ventricle can suffer from pressure overload due to pulmonary valve stenosis or from chronic pulmonary hypertension due to any cause. Initially, pressure overload will lead to myocardial hypertrophy and later, to progressive contractile dysfunction. Chamber dilatation will occur as a compensatory mechanism in order to maintain stroke volume despite reduced fractional shortening. As right ventricular function declines, right ventricular failure can occur. This failure manifests

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as increasing filling pressures, diastolic dysfunction, and reduced cardiac output. This can lead to annular dilatation leading to tricuspid regurgitation [1, 2]. Therefore, the right ventricular function and size are not only indicators of the severity and chronicity of pulmonary hypertension, but can also lead to symptoms and reduced long term survival. Right ventricular function is one of the most important factors for long term survival in patients with pulmonary arterial hypertension [3]. In general, the RV adjusts better to volume overload than to pressure overload. In atrial septal defect (ASD) and significant tricuspid regurgitation, the RV may tolerate volume overload much better without a significant decrease in RV systolic function.

Two examples of chronic pressure overload that are well tolerated by the RV include Eisenmenger syndrome and congenital pulmonary stenosis. Some studies have previously evaluated the RV function in RV volume and RV pressure overloads [4]. It has been shown that RV function is better preserved in pulmonary stenosis than in pulmonary hypertension [5], but a comparison of RV function in different types of pulmonary hypertension has not yet been evaluated.

Previously, we reported the usefulness of RV echo findings in predicting pulmonary vascular resistance in patients with IPH [6]. The aim of this study was to determine whether the RV function is similarly affected by different types of PH (idiopathic PH or PH secondary to left heart disease).

Patient selection

Forty-five patients were enrolled according to the following inclusion/exclusion criteria: The inclusion criteria were pulmonary hypertension with mean PAP ≥ 25 mm Hg found during right heart catheterization as well as New York Heart Association (NYHA) functional classes II or III. The exclusion criteria were comprised of atrial flutter/fibrillation (or any other arrhythmias) confounding the echocardiographic measurements, a history of previous cardiac surgery (such as coronary artery bypass grafting and/or any valve repair or replacement), severe tricuspid regurgitation, advanced documented lung disease and/or a poor echocardiographic window. We used echo finding for analysis and the cardiac catheterization findings as criteria for enrolling patients in the study. Approximately 50% of participants had been involved in previous studies at our institution.

2D echocardiography–derived parameters of RV function

All echocardiographic studies were performed with commercially available echocardiography systems equipped with a 3.5-MHz transducer (Vivid 7; GE Vingmed Ultrasound AS, Horten, Norway). Routine digital grayscale 2D and tissue Doppler cine loops were obtained at end-expiratory apnea from apical and parasternal views. Sector width was optimized to allow for complete myocardial visualization while maximizing frame rate regardless of heart rate. Frame rate was adjusted from 60 to 90 Hz. All measurements were obtained by an observer blinded to cardiac catheterization data.

Conventional echocardiographic assessment of RV performance

TAPSE was determined from an M-mode through the lateral tricuspid annulus by calculating the amount of longitudinal motion of the annulus at peak systole [7]. RV FAC was calculated as

$$\frac{\text{RV end–diastolic area} - \text{RV end–systolic area}}{\text{RV end–diastolic area} - \text{RV end–systolic area}} \times 100.$$

The RV endocardium was traced in systole and diastole from the annulus, along the free wall, to the apex and back along the interventricular septum using the apical four-chamber view. Attempts were made to trace the free wall beneath trabeculations. The RV isovolumic relaxation time (IVRTT), isovolumic contraction time (IVCT), and ejection time (ET) were measured by pulsed wave tissue Doppler from the lateral tricuspid valve annulus. The RV myocardial performance index (RVMPI, Tei index) was calculated as:

$$\frac{(\text{IVRTT} + \text{IVCTT})}{\text{ET}}.$$

We calculated RV dP/dt by measuring the time required for the TR jet to increase in velocity from 0.5 to 2 m/s. Using the simplified Bernoulli equation, this represents a 15 mm Hg increase in pressure. The dP/dt is therefore calculated as 15 mm Hg divided by this time (in seconds), yielding a value in millimeters of mercury per second [8].

Tricuspid annular peak systolic velocity

Doppler tissue imaging recordings were obtained from the modified apical four-chamber view with a high frame rate (> 150 frames/sec).

To avoid aliasing, the Nyquist limit was adjusted to the lowest level. Pulsed Doppler tissue imaging was performed at the lateral corner of the tricuspid annulus. The tricuspid annular peak systolic (Sa), early diastolic (Ea.), and atrial (Aa) wave velocities and Ea/Aa ratio were measured [9].

Strain rate imaging in the right ventricle

Real-time 2-D color Doppler myocardial imaging was recorded from the RV, using standard 4-chamber apical views at a high frame rate (> 150 FPS) and at the narrowest sector angle possible. The region of interest was placed at the basal and mid segments of the RV free wall and kept at the center of the ultrasound sector to ensure the accuracy of the angle with the long-axis motion to measure peak systolic longitudinal strain (RVSTR) and peak systolic longitudinal strain rate (RVSR). A sample volume of 7 mm to 10 mm was utilized for the calculation of longitudinal SR. The data obtained were stored in digital format and analyzed offline with dedicated software by an experienced person who was blinded to the clinical characteristics of the patients. For each variable, 3 representative beats were analyzed and the mean was calculated.

Statistical analysis

All the analyses were conducted using Statistical Package for Social Sciences (SPSS) software, version 22 (SPSS Inc., Chicago, IL, USA). A descriptive analysis of the demographic and echocardiographic data of the patients was performed. The categorical variables are presented as numbers and percentages and the quantitative variables as means ± standard deviation. Comparisons were made between the groups of patients using the chi-square test for the categorical data and the independent sample T test, as appropriate. All the P values were two-tailed, and a P value of < 0.05 was considered statistically significant. Interobserver and intraobserver variability were calculated as the absolute difference divided by the average of the two observations for all of the parameters. Eleven cases were analyzed for the calculation of the interobserver and intraobserver variability.

Results

Forty-five patients were enrolled in this study. Among them, 20 were females and 25 were males. Mean ± SD age was 38.3 ± 11.6 years (minimum 18 years and maximum 64 years respectively). In our study, Mean ± SD for mean PAP was 51.5 ± 15.5 mm Hg (minimum 33 mm Hg and maximum 88 mm Hg). For systolic PAP, the Mean ± SD was 78.5 ± 22 mm Hg (minimum 50 mm Hg and maximum 130 mm Hg). Based on two etiologies we separated our patients into 2 groups. Group 1 included patients with IPAH (N = 22) and group 2 was comprised of patients with PH secondary to chronic systolic heart failure (PH-HF) (n = 23). Mean ± SD of age in the first group was 35.5 ± 11.5 years. In the second group, the Mean ± SD was 41 ± 11.2 years ($p = 0.11$). Most of the patients in group 1 were females (68%), whereas only 21% of participants in the second group were female ($p = 0.002$). In the IPAH group, Mean ± SD for mean PAP was 60 ± 14.5 mm Hg in comparison to 43 ± 11.5 mm Hg ($p = 0.001$) in the second group. For systolic PAP the Mean ± SD in the first group was 93 ± 19.5 mm Hg in comparison to 64 ± 13.5 mm Hg in the second group ($p < 0.001$).

Considering conventional indexes of RV function, only Sm and dp/dt were significantly better in the first group in comparison to the second one (p-value for Sm = 0.042 and for dp/dt = 0.039). RVEDD was significantly higher in the IPAH group (4.36 ± 0.72 Cm in IPAH group in comparison to 3.91 ± 0.42 Cm in PH-HF group, $p = 0.013$). Although other indices of TAPSE and MPI were better in the IPAH group, they were not statistically significant (means in TAPSE in IPAH group was 15.2 ± 3.5 in comparison to 14.4 ± 4.4 in PH-HF group, $p > 0.5$). All indices of conventional indexes are shown in the Table 1. Considering deformation indexes of RV function, the basal and mid portion of RV free wall strain and basal RV strain rates were significantly worse in the PH-HF group in comparison to the IPAH group ($p < 0.001$ in basal RV strain, $p = 0.034$ in mid RV strain and $p = 0.046$ in basal RV strain rate respectively). Although FAC was better in the IPAH group, it did not reach statistical significance (FAC = 19.6 ± 5.5 in IPAH in comparison to 18.4 ± 8 in PH-HF, $p > 0.5$) (Table 1).

Discussion

It is well known that the most common cause of pulmonary hypertension is related to left ventricle failure. Reeves and Groves have shown that 44% of patients with coronary artery disease during coronary arteriography and right heart catheterization have pulmonary hypertension.

Table 1. Echocardiographic indices in patients with idiopathic (Group I) *versus* secondary (Group II) pulmonary hypertension

	Group I	Group II	P value
RVEDD (Cm)	4.3 ± 0.72	3.9 ± 0.42	0.013
TAPSE (mm)	15.2 ± 3.5	14.4 ± 4.4	0.52
Sm (Cm/s)	8.9 ± 2.4	7.6 ± 1.6	0.042
Dp/dt	490 ± 171	376 ± 173	0.039
MPI	0.8 ± 0.21	0.69 ± 0.3	0.17
FAC (%)	19.6 ± 5.5	18.4 ± 8	0.57
RV base Strain (%)	-19.7 ± 5.5	-14.7 ± 4.5	< 0.001
RV mid Strain(%)	-13.5 ± 2.9	-11.4 ± 3.2	0.034
RV base SR (S-1)	1.1 ± 0.47	0.91 ± 0.34	0.046
RV mid SR (S-1)	0.89 ± 0.49	0.69 ± 0.32	0.11

Our study showed that patients with pulmonary hypertension secondary to chronic systolic dysfunction have worse RV indexes of function. RV dysfunction in PH may have many underling etiologies: 1) Left ventricular failure increases pulmonary arterial afterload by increasing pulmonary venous and pulmonary arterial pressure. It is a protective mechanism against pulmonary edema; 2) The same pathological mechanism that causes left ventricular dysfunction could simultaneously affect the right ventricle; 3) Myocardial ischemia may involve both ventricles; 4) Left ventricular dysfunction can reduce coronary pressure in the right ventricle thus reducing right ventricular function; 5) Ventricular interdependence due to septal dysfunction can occur 6) leading to left ventricular dysfunction related to pericardial constrain.

In the failing RV, excessive sympathetic adrenergic stimulation can adversely affect ventricular remodeling and survival [10, 11]. In patients with PAH, elevated catecholamine levels have been found to be related to higher pulmonary vascular resistance and lower cardiac index [12, 13].

Furthermore, right ventricular wall stress and thickness appear to be inversely related [14] to RV function in IPAH patients. Abraham WT *et al.* have shown that the ACE DD genotype is significantly increased in patients with severe PPH in comparison to controls suggesting that some individuals could be genetically at risk for developing pulmonary hypertension [15]. The ACE DD genotype is related to preserved right ventricular function in PPH patients supporting the theory of the important role of Ang II in patients with RV pressure overload conditions. It is interesting to note that in a recent study [16] of patients with normal left ventricular function, right ventricular morphology was found to indicate the reason for increased afterload in patients with pulmonary hypertension. Furthermore, echocardiographic volumetric reconstruction and measurements of the right ventricle have shown improvement with successful treatment of pulmonary hypertension [17] suggesting that echocardiographic abnormalities can improve with successful treatment.

To the best of our knowledge, this is the first study assessing the relationship between these echocardiographic indices and the hemodynamic parameters indicative of RV failure. Based on our results, IPH has less impact on RV function in comparison to HF-PH. Considering both entities are in the category of RV pressure overload, we conclude that the etiology of pulmonary hypertension also plays an important role in RV function in addition to pressure overload.

Study limitation

The main limitation of our study was its relatively small sample size, which could limit the generalizability of our results. Myocardial strain and strain rate can be measured in all dimensions (longitudinal, radial, and circumferential) but we only quantified the longitudinal strain and SR. Hence, the RV myocardial ischemia, if present, would affect the strain and other RV functional parameters [11, 15]. Another limitation was our echocardiography system software which was validated for the LV but was not validated for the global longitudinal RV strain. Therefore, RV free wall 2D speckle strain analysis could not be performed.

Our study demonstrated that severe PAH seems to aggravate the RV function more severely compared to PS. However, to better elucidate the role of the RV echocardiography in assessing various types of the RV pressure overload states and its application to discriminate between idiopathic primary PAH and PS patients, further studies with a larger sample size of patients are needed.

Conflict of interest

None of the authors have any conflict of interest to disclose.

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