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Left Ventricular Diastolic Function Assessment of a Heterogeneous Cohort of Pulmonary Arterial Hypertension Patients

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Abstract

Background: Pulmonary arterial hypertension (PAH) is known to trigger right ventricular (RV) remodeling that might compromise left ventricular (LV) filling due to inter-ventricular interdependence. In this study, we aimed to examine standard echocardiographic measurements of LV diastolic function in PAH patients.

Methods: In this retrospective study, we identified clinical as well as complete echocardiographic data from 128 chronic PAH patients to fully assess LV diastolic dysfunction (LVDD) using standard recommended Doppler guidelines. Accordingly, patients were divided into three groups: LVDD 0, LVDD 1 and LVDD 2.

Results: The mean age of the studied population was 57 ± 14 years with a mean pulmonary artery systolic pressure (PASP) of 55 ± 21 mm Hg. A total of 36% of the study patients had normal LV diastolic function. However, 64% had LVDD with LVDD stage 1 being the most common (48%). In terms of echocardiographic data, significant differences were found among the three LVDD groups in regards to PASP, LV end systolic and diastolic volumes, tricuspid annular plane systolic excursion, right ventricular fractional area change as well as many other tissue Doppler imaging parameters. Finally, just age and PASP were predictors of abnormal LV diastolic function ($P < 0.05$).

Conclusions: Impaired relaxation is a common abnormality in PAH patients. Additional studies are warranted to determine whether LVDD alters prognosis or is related to changes in the symptomatic profile of this group of patients.

Keywords: Pulmonary hypertension; Left ventricular function; Diastole; Echocardiography

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Introduction

Pulmonary arterial hypertension (PAH) is a conundrum of disease entities characterized by severe remodeling of distal pulmonary arterioles as a result of a complex interplay between genetic and molecular factors that ultimately elevates pulmonary artery (PA) pressures and thus increases right ventricular (RV) afterload [1-3]. This chronic unopposed increase in RV afterload initially causes progressive RV hypertrophy that will eventually lead to RV dilation and decreased contractility, as a result of the La'Place principle [4]. Ultimately, in many patients, these RV remodeling functional alterations cause eventual RV failure, the leading cause of death among PAH patients [5, 6].

Even though RV contractile abnormalities are the main focus of PAH echocardiographic evaluations, it is important to be cognizant of the fact that the RV does not function independently of the left ventricle (LV) [7]. Specifically, both ventricular chambers share the interventricular septum (IVS) with attachments at the anterior and posterior septum, have mutual encircling epicardial fibers, and are jointly enclosed within the intrapericardial space [8]. It is well characterized that in response to either RV pressure or volume overload, the IVS bows and flattens toward the LV [9, 10], with the greatest IVS shift occurring as a result of pressure overload as in the case of PAH. This shift of the IVS at the end-systole has been suggested to negatively affect LV filling [9-11]. In addition, the pericardium also plays an important part in affecting LV filling since the pericardium becomes stretched and less compliant as the RV dilates [12, 13]. Finally, LV diastolic abnormalities have also been attributed to intrinsic LV myocardial stiffening, fibrosis and myocardial fiber reorientation [14].

Even though data on LV diastolic dysfunction (LVDD) are limited among PAH patients, several correlations have been shown. First, symptomatic LVDD patients usually have increased PA pressures [15]. Second, the presence of LVDD has been closely correlated with worsening pulmonary hypertension (PH) in chronic obstructive pulmonary disease patients [16]. Third, autoimmunity not only is an important mechanism that may cause PAH, but also has been shown to result in

LVDD without elevation in PA pressures [17].

Since significant alterations in myocardial geometry and biventricular hemodynamics are known to occur in PAH patients that might alter LV filling dynamics and since LVDD echocardiographic data assessments in PAH patients have been somewhat limited, we sought to examine standard echocardiographic measurements of LV diastolic function, as recommended by both American Society of Echocardiography and European Association of Echocardiography, from a heterogeneous group of PAH patients at our institution [18].

Methods

Population studied

This was a retrospective study in which we queried our echocardiographic database searching for PAH patients who had been referred to our University of Cincinnati main echocardiographic laboratory and had a complete echocardiogram. The studied population was divided into three groups: LVDD 0, LVDD 1 and LVDD 2 accordingly to LV diastolic function stages recommended by published guidelines [18].

Inclusion criteria for this study required that all patients had available clinical information regarding PAH diagnosis as well as World Health Organization (WHO) group classification. Additionally, patients needed to be in normal sinus rhythm at the time of the echocardiographic study, and there was good visualization of the tricuspid regurgitation signal to estimate PA systolic pressures as well as adequate delineated RV outflow tract (RVOT) Doppler signal. A complete spectral Doppler study to examine LV diastolic function was acquired from our laboratory database.

Patients were excluded from final analysis if they had a history of a previous myocardial infarction, wall motion abnormalities, cardiac surgery, frequent premature or atrial contraction beats, left bundle branch block, moderate to severe left-sided valve disease involvement or known pericardial disease, and the presence of a pacer or defibrillator wire. Patients with LVDD stage 3 were also excluded, as the LV restrictive pattern associated with this stage and frequent number of patients with significant LV systolic dysfunction falling into this category could be important cofounders when assessing possible associations between LVDD and PAH.

The University of Cincinnati IRB office approved the study (protocol number 12061302). No written consent was needed to obtain since this was a retrospective analysis.

Echocardiographic studies

Two-dimensional echocardiographic studies were performed using commercially available systems (Vivid 7 and 9; GE Medical Systems, Milwaukee, WI, USA). Images were obtained in the parasternal and apical views with the patient in the left lateral decubitus position and in the subcostal view with the patient in the supine position using a 3.5 MHz transducer. Standard two-dimensional, color, pulsed, and continuous-wave Doppler data were digitally acquired in gently held end-expiration, and saved in regular cine loop format for subsequent offline analysis.

With regard to the particular aim of this study, the following echocardiographic parameters were measured: 1) LV end-systolic and end-diastolic volumes were traced from the apical four-chamber view and LV ejection fraction calculations were done using the Simpson's rule algorithm [19]. 2) Left atrial (LA) volume was calculated using the biplane area-length formula [19]. The areas were obtained from the two- and four-chamber views. The shortest length perpendicular to the axis of the mitral annulus was used for calculating the volume. Using this information, the atrial volume was calculated with the following formula: LA volume = $(8 \times A1 \times A2)/(3\pi L)$. The LA volume index was then calculated by dividing maximal LA volume by body surface area (BSA). 3) Mitral inflow velocity was obtained using pulsed-wave Doppler examination at a sweep speed of 100 mm/s from the apical four-chamber view by placing the sample volume at the tips of the mitral leaflets [18]. Mitral valve inflow deceleration time, peak velocity in early diastole (E-wave, LV relaxation), late diastole (A-wave, LA contraction) as well as the corresponding E/A ratios were measured, as previously described. 4) In terms of tissue Doppler imaging (TDI) of the lateral portion of the mitral annulus, early diastole (E) and late diastole (A) velocities were measured by placing the sample volume at the junction where the mitral valve plane intersects the LV free wall using images obtained from the apical four-chamber view. LV diastolic pressures were estimated using the mitral valve inflow E to mitral annular TDI E ratio. Finally, LV diastolic function was classified as normal (LVDD 0), impaired relaxation (LVDD 1), and pseudonormal (LVDD 2) following published recommendations as suggested by Nagueh et al [18]. 5) RV fractional area change (RVFAC) and maximal systolic excursion of the lateral tricuspid annulus were used to determine global RV systolic function [20-23]. 6) Finally, RV systolic pressures were estimated using continuous-wave Doppler to record the highest tricuspid regurgitation jet velocity and the pulmonary artery systolic pressure (PASP) was then calculated using the modified Bernoulli equation and an estimate of mean right atrial pressure using the diameter and collapse index of the inferior vena cava and the hepatic venous flow pattern [24].

Statistical analysis

The commercially available software Merge Cardio Workstation (Merge Healthcare) was used to calculate all echocardiographic measurements determined by a single observer. Baseline characteristics were compared between groups using analysis of variance (ANOVA) with Bonferroni correction for continuous variables, assuming equal variances and after testing for normality with Shapiro-Wilk test. To compare categorical data, Chi-square or Fisher's exact test (if an expected frequency was < 5) was the selected method. Additionally, multiple logistic regression test was performed to determine predictors of abnormal diastolic function. Intra- and inter-observer variability in our echo lab for this patient population has been previously reported [25, 26]. A P-value of less than 0.05

Table 1. Baseline Characteristics of Study Patients

Variables	LVDD 0 (n = 46)	LVDD 1 (n = 61)	LVDD 2 (n = 21)	P-value
Age (± SD), years	50 ± 14	63 ± 13	57 ± 14	< 0.001†
Gender (%)				
Female	37 (80%)	46 (75%)	17 (81%)	0.808
Male	9 (20%)	15 (25%)	4 (19%)	
BSA (± SD), m^2	1.98 (0.03)	2.01 (0.37)	2.21 (0.42)	0.034¶
Co-morbidities (%)				
Diabetes mellitus type 2	6 (13%)	13 (21%)	8 (38%)	0.07
Arterial hypertension	21 (46%)	35 (57%)	16 (76%)	0.06
Coronary artery disease	5 (11%)	13 (21%)	4 (19%)	0.39
Diagnosis of PH (%)				
WHO group I	23 (50%)	25 (41%)	9 (42%)	0.173
WHO group II	8 (17%)	7 (11%)	5 (24%)	
WHO group II	3 (7%)	8 (13%)	5 (24%)	
WHO group IV	8 (17%)	9 (15%)	0 (0%)	
WHO group V	1 (2%)	2 (3%)	0 (0%)	
WHO groups I, III	3 (7%)	6 (10%)	0 (0%)	
WHO groups II, III	0 (0%)	2 (3%)	0 (0%)	
WHO groups I, II, III	0 (0%)	1 (2%)	2 (10%)	
WHO groups II, III, IV	0 (0%)	1 (2%)	0 (0%)	

SD: standard deviation; BSA: body surface area; PH: pulmonary hypertension; WHO: World Health Organization; LVDD: left ventricular diastolic dysfunction. †Bonferroni test indicates significant differences between LVDD 0 and LVDD 1 and ¶LVDD 0 and LVDD 2.

was considered statistically significant. All statistical analyses were performed using STATA version 14.2.

Results

Using our study inclusion-exclusion criteria, of the 212 available echocardiograms queried, 128 met all criteria and comprised the study population. When LV diastolic function was assessed using standard echocardiographic measures, we found that 46 (36%) of the studied PAH cohort had normal LV diastolic function (LVDD 0). However, 82 (64%) patients had LVDD, with LVDD stage 1 or early relaxation abnormalities being the most commonly (61 (48%) patients) identified. Finally, just 21 (16%) patients were diagnosed with LVDD stage 2 or pseudonormal pattern.

Baseline characteristics of studied population are depicted in Table 1. The mean age of the included patients was 57 ± 14 (range 29 - 88 years) with 100 (77%) of the patients being female and a mean BSA of 2.03 ± 0.35 m^2. Most common listed co-morbidities were arterial hypertension (HTN) (57%), followed by diabetes mellitus (22%) and coronary artery disease (18%). Furthermore, group I (45%) was the most common PAH classification found among studied patients.

With regard to cardiovascular medications, the most commonly reported were diuretics (72%), beta-blockers (38%), angiotensin-converting enzyme inhibitors and/or angiotensin II receptor antagonists (34%), calcium channel blockers (26%), digoxin (5%) and nitrates (3%). In addition, 27% of the included individuals used either prednisone or some immunomodulator. In regard to active PAH vasodilator therapy, half of the study population was receiving either sildenafil citrate (Revatio) or Tadalafil, while 29% of the patients were treated with prostacyclin and/or endothelin receptor antagonist (ERA). Among all these patients, just 24% were on dual therapy with a vasodilator plus prostacyclin and/or ERA. Finally, 50% of the patients required home oxygen.

In terms of the measured echocardiographic variables, mean PASP was 55 ± 21 mm Hg, LV ejection fraction was 60±9%, LV end systolic volumes were 34 ± 17 mL, LV end-diastolic volumes were 81 ± 32 mL, LA volume index was 211.1 ± 161.3 mL/m^2, tricuspid annular plane systolic excursion (TAPSE) was 2.1 ± 0.5 cm, RV end-systolic areas were 21 ± 14 cm^2, RV end-diastolic areas were 41 ± 21 cm^2 and RVFAC was 50±12%.

Table 2 shows important echocardiographic data obtained from the study according to LV diastolic function. A one-way ANOVA test was performed to determine possible associations between echocardiographic variables and grades of LV diastolic function. Significant differences were found between PASP, LV end-systolic/diastolic volumes, TAPSE, RVFAC, MV E velocity, MV A velocity as well as MA TDI E /A and MV E/MA TDI E ratios.

Interestingly, after adjusting for important clinical and

Table 2. Relevant Echocardiographic Data From the Studied Population (± SD)

Variables	LVDD 0 (n = 46)	LVDD 1 (n = 61)	LVDD 2 (n = 21)	P-value (ANOVA)
PASP (mm Hg)	46 ± 15	62 ± 23	55 ± 16	< 0.001†
LVEF (%)	60 ± 9	60 ± 8	56 ± 9	0.106
LV end-systolic volume (cm^3)	34.2 ± 16.5	28.8 ± 12.2	45.4 ± 21.5	< 0.001¶, §
LV end-diastolic volume (cm^3)	84.3 ± 28.5	71.6 ± 23.2	103.3 ± 45	< 0.001¶, §
LA volume index (mL/m^2)	241.6 ± 196.1	178.6 ± 138.1	238.9 ± 124.1	0.093
TAPSE (cm)	2.2 ± 0.5	2.0 ± 0.5	2.1 ± 0.6	0.037†
RV end-systolic area (cm^2)	19.7 ± 13.3	21.6 ± 13.9	22.4 ± 15.9	0.696
RV end-diastolic area (cm^2)	40.8 ± 18.3	41.8 ± 23.2	41.1 ± 22.5	0.971
RVFAC (%)	54.1 ± 12.3	48.4 ± 12.3	46.8 ± 9.9	< 0.021†
MV E velocity (cm/s)	88 ± 21	70 ± 19	123 ± 37	< 0.001†, ¶, §
MV A velocity (cm/s)	59 ± 17	89 ± 21	96 ± 41	< 0.001†, ¶
MV DT (ms)	196 ± 58	210 ± 59	200 ± 63	0.664
MV E/a ratio	1.6 ± 0.7	0.8 ± 0.2	1.4 ± 0.6	< 0.001†, §
MA TDI E velocity (cm/s)	12 ± 3	8 ± 3	11 ± 3	0.083
MA TDI A velocity(cm/s)	9 ± 5	13 ± 10	9 ± 5	0.216
MA TDI E /A ratio	1.6 ± 0.9	0.9 ± 1.5	1.6 ± 0.9	0.016†
MV E/MA TDI E ratio	10 ± 13	8 ± 3	17 ± 10	< 0.001¶, §

SD: standard deviation; LA: left atrium; LV: left ventricle; RV: right ventricle; PASP: pulmonary artery systolic pressure; LVEF: LV ejection fraction; TAPSE: tricuspid annular plane systolic excursion; RVFAC: RV fractional area change; TDI: tissue Doppler imaging; MV: mitral valve; MA: mitral annulus; LVDD: LV diastolic dysfunction. †Bonferroni test indicates significant differences between LVDD 0 and LVDD 1, ¶LVDD 0 and LVDD 2, and §LVDD 1 and LVDD 2.

echocardiographic variables, just age and PASP were predictors of LVDD with an OR = 1.06, P = 0.001 and OR = 1.03, P = 0.030, respectively (Table 3).

Discussion

In this retrospective single center study aimed to examine LV diastolic function using standard echocardiographic measures, as recommended by both American Society of Echocardiography and European Association of Echocardiography, from a known heterogeneous group of chronic PAH patients, the following findings were identified. First, abnormal Doppler findings consistent with LVDD were present in 64% of our studied PAH patient population. Second, the most commonly identified LVDD Doppler pattern was early relaxation abnormality (48 % of patients) with a total of 16% of all PAH patients showing a pseudonormal pattern (LVDD 2). Finally, upon closer examination, just age and PASP predicted abnormal LV diastolic function.

Table 3. Stepwise Multiple Logistic Regression Analysis to Determine the Best Predictor of Abnormal LV Diastolic Function

Variables	OR	95% CI	z	P-value
Age	1.06	1.03 - 1.10	3.36	0.001
Gender	1.42	0.47 - 4.30	0.63	0.531
BSA	3.15	0.77 - 12.99	1.59	0.111
Arterial hypertension	1.13	0.44 - 2.89	0.26	0.795
Diabetes mellitus	1.17	0.35 - 3.90	0.26	0.796
Classification of PH	1.10	0.75 - 1.60	0.48	0.630
PASP	1.03	1.00 - 1.07	2.17	0.030
TAPSE	0.80	0.28 - 2.32	-0.41	0.684
RVFAC	0.97	0.94 - 1.01	-1.26	0.206

BSA: body surface area; PH: pulmonary hypertension; PASP: pulmonary artery systolic pressure; TAPSE: tricuspid annular plane systolic excursion; RVFAC: right ventricular fractional area change.

PAH is characterized by abnormal pulmonary vascular tone and reduction in the caliber of the pulmonary vessels known to increase RV afterload, as reflected by an increase in pulmonary vascular resistance and impedance that when unopposed contribute to progressive RV dilation and dysfunction [1-5]. Early in the course of PAH, uncoupling between the RV and pulmonary vasculature occurs, characterized by disruption of the normal relationship between RV and pulmonary arterial elastance [27]. This is then followed by a gradual decrease in overall cardiac output that occurs as a result of several factors including a reduction in LV filling due to a decrease in RV output [9-11]; a dilated RV further impairs the ability of the LV to augment RV ejection [28, 29]; and abnormal shift of the IVS towards the LV in the setting of an intact pericardium not only limits the available space for the RV to expand, but also influences LV filling as a result of an abnormal prolongation in RV contraction to continue beyond LV contraction causing additional encroachment on LV filling [12, 13, 30-33].

Even though anatomical explanations might account on the adverse influence that RV dilation has on LV filling as a result of an abnormal IVS curvature and LV filling, a direct compressive effect of a dilated RV on LV filling has been difficult to determine due to experimental limitations; however, two studies have provided supporting evidence. In a first study involving 21 patients with chronic LV failure, application of negative pressure to the lower extremities caused reduction in RV volume followed by paradoxical increase in LV filling [34]. In the second study, Kasner and associates demonstrated that unlike control subjects and patients with known LVDD, PAH patients demonstrated an initial increase in LV filling during occlusion of the inferior vena cava despite a reduction in LV end-diastolic pressure suggesting an improvement in diastolic compliance [35].

On the other hand, age-related changes in myocardial elastic recoil, ventricular load and diastolic stiffness as well as loss of peripheral vascular elasticity have been previously suggested as possible causes of subclinical diastolic dysfunction associated with aging [36]. In this regard, despite the small study sample, we found that age remained a predictor of LVDD in PAH patients after adjusting for possible cofounders. Though chronic HTN represents the most common cause of LVDD with up to 80% of older hypertensive patients having signs of impaired LV relaxation [37, 38], we found no significant differences with regards to LVDD among the patients included in our study. Furthermore, HTN was not a predictor of LVDD after adjusting for important clinical and echocardiographic variables.

The following study limitations need to be acknowledged. First, this was a retrospective study; however, the main goal was attained. Second, lack of a control group; however, our main intent was to examine Doppler patterns of LV diastolic function among a heterogeneous group of PAH patients. Even though prevalence of LVDD abnormalities in the general population has not been well characterized [39, 40], an even greater gap in knowledge exits regarding our understanding of LV diastolic function in PAH patients. However, data from Tonelli and associates seem to be in accordance with findings presented in our study as these investigators also found that impaired relaxation was observed in the majority of 61 patients with either advanced idiopathic or heritable forms of PAH [41]. Furthermore, in a cardiac magnetic resonance imaging study using tissue phase mapping metrics to assess LV diastolic function, these investigators found that these measures were significantly abnormal in PH patients [42]. Third, lack of concomitant right-sided hemodynamic pressures in our study to corroborate that the severity of PH based on echo-derived estimates was accurate might be a limitation. However, data from these PAH patients have been previously used to validate measures of myocardial and mitral annular tissue Doppler variables as well as speckle tracking interrogation of both the RV and LV [43-47]. Finally, it is important to mention that although recommendations for the evaluation of LV diastolic function by echocardiography have been recently updated [48], our findings are the result of an exploratory study prior to publication of the updated guidelines. Whether changes in current LVDD diagnosis criteria might alter its association with age and PASP in this patient population needs to be further clarified. However, current criteria neither take into consideration PAH variables nor age; hence, our results might remain unchanged.

Conclusion

Even though this study was not intended to provide anatomical or mechanistic explanations to explain the development of LVDD in PAH patients, our results not only seem to confirm but also expand our knowledge of LV diastolic function in PAH by identifying impaired relaxation as a common abnormality in these patients. Additional studies are now required to determine if impaired LV relaxation alters prognosis or is related to change in the symptomatic profile of PAH patients.

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Competing Interests

The authors report no competing interests.

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