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RESEARCH ARTICLE

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Left ventricular underfilling in PAH: A potential indicator for adaptive-to-maladaptive transition

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Abstract

Pulmonary arterial hypertension (PAH) still remains a life-threatening disorder with poor prognosis. The right ventricle (RV) adapts to the increased afterload by a series of prognostically significant morphological and functional changes, the adaptive nature should also be understood in the context of ventricular interdependence. We hypothesized that left ventricle (LV) underfilling could serve as an important imaging marker for identifying maladaptive changes and predicting clinical outcomes in PAH patients. We prospectively enrolled patients with PAH who underwent both cardiac magnetic resonance and right heart catheterization between October 2013 and December 2020. Patients were categorized into four groups based on their LV and RV mass/volume ratio (M/V). LV M/V was stratified using the normal value (0.7 g/mL for males and 0.6 g/mL for females) to identify patients with LV underfilling (M/V ≥ normal value), while RV M/V was stratified based on the median value. The primary endpoint was all-cause mortality, and the composite endpoints included all-cause mortality and heart failure-related readmissions. A total of 190 PAH patients (53 male, mean age 37 years) were included in this study. Patients with LV underfilling exhibited higher NT-proBNP levels, increased RV mass, larger RV but smaller LV, lower right ventricular ejection fraction, and shorter 6-min walking distance. Patients with LV underfilling had a 2.7-fold higher risk of mortality than those without and LV M/V (hazard ratio [per 0.1 g/mL increase]: 1.271, 95% confidence interval: 1.082–1.494, $p = 0.004$) was also independent predictors of all-cause mortality. Moreover,

Abbreviations: 6MWD, 6-min walking distance; CMR, cardiovascular magnetic resonance; LVEDVi, left ventricular end-diastolic volume index; LVEF, left ventricular ejection fraction; LVESVi, left ventricular end-systolic volume index; LV M/V, left ventricular end-diastolic volume/mass; mPAP, mean pulmonary artery pressure; PAH, pulmonary arterial hypertension; PCWP, pulmonary capillary wedge pressure; PVR, pulmonary vascular resistance.; RAP, right atrial pressure; RVEDVi, right ventricular end-diastolic volume index; RVEF, right ventricular ejection fraction; RVESVi, right ventricular end-systolic volume index; RV M/V, right ventricular end-diastolic volume/mass.

Jiajun Guo and Jiaqi Wang contributed equally to this article.

patients with low LV M/V had a better prognosis regardless of the level of RV M/V. Thus, LV underfilling is an independent predictor of adverse clinical outcomes in patients with PAH, and it could be an important imaging marker for identifying maladaptive changes in these patients.

KEYWORDS
adaptative-to-maladaptive transition, cardiovascular magnetic resonance, LV underfilling, pulmonary arterial hypertension

INTRODUCTION

Pulmonary arterial hypertension (PAH) is a devastating physiological condition that is characterized by pulmonary vascular remodeling and, ultimately, leads to right heart failure and mortality. Despite the improvement in the management of PAH, patients continue to have poor prognosis.[1,2] In PAH patients, elevated pulmonary artery (PA) pressure leads to chronic right ventricular (RV) pressure overload, and RV adaption is considered one of the key determinants of short-term and long-term outcomes.[3,4] Reduced right ventricular ejection fraction (RVEF) and enlargement are recognized as significant indicators of RV maladaptation. However, it's still difficult to recognize the transition from adaption to maladaptation in PAH patients and better imaging biomarkers are needed.

RV concentric hypertrophy is generally considered an early adaptive response to PAH.[5–8] However, recent evidence indicates that not all instances of RV concentric hypertrophy in PAH patients are adaptive[9] and the adaptive nature of these changes should be interpreted in the context of ventricular interdependence.[3] Moreover, prolonged pressure overload can cause inadequate filling of the left ventricle (LV),[4,9,10] potentially leading to LV atrophic remodeling.[9] But in recent reports, higher LV end-diastolic volume correlated with better prognosis, indicating that a comprehensive consideration of both LV metrics and RV function may bring additive value in adaption-to-maladaptation evaluation in PAH patients.[9,11] Thus, we hypothesized that PAH patients with LV atrophic remodeling had a poor prognosis and LV atrophic remodeling can be a novel imaging biomarker for adaption-to-maladaptation recognition in PAH patients.

METHOD

Subjects and study design

A total of 190 participants diagnosed with PAH from October 2013 to December 2020 in West China Hospital were prospectively recruited. PAH was diagnosed in accordance with the 2015 European Society of Cardiology/European Respiratory Society (ESC/ERS) Guidelines.[12] The inclusion criteria were: (1) participants with mean pulmonary arterial pressure (mPAP) ≥25 mmHg, PA wedge pressure ≤15 mmHg, and pulmonary vascular resistance (PVR) >3 Wood units; (2) participants who underwent CMR within 72 h of right heart catheterization (RHC); and (3) participants aged 18 years or older. The exclusion criteria were: (1) participants with poor CMR image quality or with real-time cine; (2) participants with complex congenital heart disease types including transposition of the great arteries, double-outlet right ventricle (RV), tetralogy of Fallot, and single ventricle.

Image acquisition

Cardiac magnetic resonance imaging (MRI) was conducted on a 3.0-T scanner (Magnetom Tim Trio; Siemens Healthineers) using a 32-channel phased-array cardiac coil with breath-holding and electrocardiography gating. Cine images were acquired using steady-state free precession along consecutive short axes from the base to the apex, as well as two-, three-, and four-chamber views along the long axes, following a standardized protocol.[13] The scan parameters were as follows: field of view, 320–340 mm^2; repetition time, 3.4 ms; echo time, 1.3 ms; slice thickness, 8 mm with no gap; flip angle, 50°; acquisition matrix, 256 × 144; temporal resolution, 42 ms; and spatial resolution, 1.4 × 1.3 mm^2.

Image analysis

Biventricular volumes, ejection fraction, and mass were analyzed using dedicated software (QMass version 8.1; Medis Medical Imaging Systems) in accordance with the standardized protocol of the Society of Cardiovascular Magnetic Resonance postprocessing guideline.

Biventricular functional parameters were analyzed by meticulously delineating the endocardial and epicardial contours of the myocardium, including papillary muscles and trabeculations but excluding epicardial fat. The atrium was carefully excluded from the contours in basal slices. Biventricular mass and volumes were indexed to the body surface area (BSA). All image analyses were blindly executed by JG. (with 3 years of magnetic resonance imaging [MRI] experience) and JW (with 2 years of MRI experience). The controversial results were checked blindly by senior cardiac MRI reader YC. (with more than 10 years of CMR experience). Ventricular-arterial coupling was calculated as the ratio of RVSV to RVESV according to CMR.[14]

LV underfilling analysis

The LV mass to LV end-diastolic volume ratio (LV M/V) allows the distinction between LV underfilling and non-underfilling. The RV mass to RV end-diastolic volume ratio (RV M/V) allows the distinction between RV eccentric and concentric hypertrophy. All patients were categorized into four groups based on their LV and RV M/V values. The LV M/V values were stratified using the previously established normal values (0.7 g/mL for males and 0.6 g/mL for females),[15] while the median value was used to stratify the RV M/V values, given the lack of established normal values. Ventricular mass index (VMI) was computed by calculating the ratio of RV mass to LV mass.

Right heart catheterization

RHC was performed in a standardized manner using a 5F transfemoral catheter under local anesthesia. Hemodynamic measurements including the pressures in the superior vena cava, right atrium, RV, PA, and pulmonary capillary were recorded after obtaining stable readings. Blood samples were collected from the systemic and pulmonary circulations for the measurement of oxygen saturation. Cardiac output (CO) was calculated using the Indirect Fick method, and the cardiac index was determined as CO indexed to the BSA. PVR was calculated using the following formula: PVR = [mean pulmonary arterial pressure (mPAP) − pulmonary capillary wedge pressure (PCWP)]/CO.

Follow-up and clinical outcomes

Patient follow-up was conducted through regular clinical visits or telephone interviews every 3–6 months following the baseline visit, in accordance with current guidelines.[12] The primary endpoint was defined as all-cause mortality, while the composite endpoint included all-cause mortality and heart failure-related repeat hospitalization. Follow-up duration was calculated from the date of RHC until the occurrence of the event or the last contact.

Statistical analysis

The normality of variables was assessed using the Kolmogorov–Smirnov method, and all continuous variables were presented as mean $\pm$ *SD* or median with interquartile range. Categorical variables were expressed as percentages. The independent sample *t*-test and Mann–Whitney *U* test were utilized for comparing continuous variables, while the χ^2 test was used for categorical variables. Pearson's and Spearman's rank correlation coefficients were applied to evaluate bivariate correlation based on the normality of variables. Log-transformed values were used to analyze the N-terminal pro-brain natriuretic peptide (NT-proBNP). Variables associated with adverse cardiac events were identified using univariate Cox analysis. All significant variables from the univariate analysis were extracted and used as the starting set of variables. A "best subset regression" procedure was then performed on the set of variables, and the one with the lowest value of the Bayesian information criterion was ultimately selected. The Kaplan–Meier method was used to plot survival curves, which were compared using the log-rank test. A two-tailed *p* value of less than 0.05 was considered statistically significant. Statistical analyses were conducted using SPSS 26.0 (IBM) and R software (version 4.0.1, The R Project for Statistical Computing, Vienna, Austria).

RESULT

Patient demographic and other characteristics

A total of 190 patients with PAH were included, with a mean age of 37 years (Figure 1). Of these patients, 126 (66.3%) had shunt-related congenital heart diseases, 17 (8.9%) had connective tissue diseases, and 47 (24.7%) had idiopathic PAH. Details are presented in Table 1. Among the total patients, 76 (40%) had an LV M/V ratio that exceeded the normal value and were considered to have LV underfilling. No significant differences in sex and body mass index were observed between the two groups.

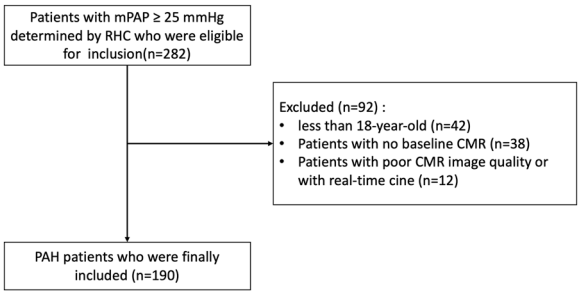

FIGURE 1 Inclusion and exclusion flowchart.

However, a higher proportion of patients with LV underfilling had a World Health Organization functional class (WHO FC) ≥3, as compared to those without LV underfilling (51.3% vs. 20.2%, respectively). Patients with LV underfilling showed significantly higher levels of NT-proBNP and shorter 6-min walking distance (6MWD) ($p < 0.001$ and $p = 0.001$, respectively), larger RV volumes and higher RV mass (all $p < 0.05$), but poorer ventricular-arterial coupling, lower cardiac index, lower SvO_2 and lower RVEF (both $p < 0.05$). However, no significant differences in LV mass and left ventricular ejection fraction (LVEF) were observed among the groups. There was also no significant difference in baseline medication between the two groups.

Relationship between LV M/V and other parameters

The correlation between LV M/V and several clinical and hemodynamic parameters was assessed. LV M/V showed a negative correlation with 6MWD ($r = -0.221$, $p = 0.003$), LVEDV index ($r = -0.678$, $p < 0.001$), left ventricular stroke volume (LVSV) index ($r = -0.620$, $p < 0.001$), RVEF ($r = -0.574$, $p < 0.001$), and RV-PA coupling ($r = -0.588$, $p < 0.001$). Furthermore, LV M/V was positively correlated with ln (NT-proBNP) ($r = 0.488$, $p < 0.001$), RVESV index ($r = 0.432$, $p < 0.001$), VMI ($r = 0.363$, $p < 0.001$), and RV mass index ($r = 0.344$, $p < 0.001$). The ratio of RVESV to LVESV was found to be strongly correlated with LV M/V ($r = 0.705$, $p < 0.001$). Further details can be found in Figure 2 and Table S1.

Follow-up and survival analysis

Following a median follow-up duration of 40.8 months (interquartile range: 25.2–60.3 months), 40 patients (21.1%) reached the primary endpoint of all-cause mortality, whereas 83 patients (43.7%) reached the composite endpoint. The results of univariate cox regression analysis were presented in Table 2 and Table S2. The risk of mortality was 2.7 times higher in patients with LV underfilling than those without. Furthermore, patients with adverse cardiac events demonstrated a higher level of WHO functional class, NT-proBNP, RV mass index, and larger RV volumes. Shorter 6MWD, lower RVEF, and lower ventricular-arterial uncoupling were observed in patients with adverse events. In the multivariable regression model, the model comprising three parameters exhibited the best performance for both primary and composite endpoints. WHO FC (hazard ratio [HR]: 2.189, 95% confidence interval [CI]: 1.316–3.640, $p = 0.003$), LV M/V (HR [per 0.1 g/mL increase]: 1.271, 95% CI: 1.082–1.494, $p = 0.004$], and ln (NT-proBNP) (HR: 1.722, 95% CI: 1.312–2.260, $p < 0.001$) were independent predictors of all-cause mortality. Similarly, WHO FC (HR: 1.603, 95% CI: 1.143–2.248, $p = 0.006$), LV M/V (HR [per 0.1 g/mL increase]: 1.185, 95% CI: 1.079–1.302, $p < 0.001$), and PVR (HR: 1.016, 95% CI: 1.001–1.030, $p = 0.031$) were independent predictors of the composite endpoint.

We identified that higher LV M/V value predicted worse outcomes (both $p < 0.0001$), while the RV M/V value, when considered alone, had limited prognostic value (both $p > 0.05$), as detailed in Figure S1. To further explore these findings, we divided patients into four groups based on their LV M/V and RV M/V values, as described earlier. Specifically, 56 were in the low-LV M/V-low-RV M/V group, 57 were in the low-LV M/V-high-RV M/V group, 39 were in the high-LV M/V-low-RV M/V group, and 37 were in the high-LV M/V-high-RV M/V group. Patients with low LV M/V and high RV M/V values had the most favorable prognosis (Figure 3). Subgroup analysis revealed that the effect of LV underfilling on event-free survival is similar in IPAH/CTD-PAH ($p = 0.002$) and CHD-PAH ($p = 0.008$) patients (Figure 4).

DISCUSSION

The study yielded several significant findings: (1) In the course of PAH, the RV underwent hypertrophy and enlargement while the LV was more likely to undergo volume change only; (2) LV underfilling was correlated with a more advanced disease stage and showed as an independent prognostic factor in PAH patients; (3) Once LV underfilling occurred, PAH patients were more likely to suffer from a poor prognosis regardless of the change of RV. LV underfilling might be important in the adaptative-to-maladaptive transition in PAH patients.

TABLE 1 Demographic, clinical, and CMR characteristics in all subjects.

	All ($n = 190$)	With LV underfilling ($n = 76$)	Without LV underfilling ($n = 114$)	p value
Age, year	37 ± 13	38 ± 14	36 ± 12	0.237
Males, *n* (%)	53 (27.9)	17 (22.3)	36 (31.6)	0.189
BMI, kg/m^2	21.2 ± 3.8	21.2 ± 3.5	21.1 ± 4.0	0.531
BSA, m^2	1.6 ± 0.2	1.6 ± 0.2	1.6 ± 0.2	0.985
NT-proBNP, pg/mL	510.0 (168.0–1767.0)	1170.5 (416.0–3119.3)	226.0 (79.8–631.0)	<0.001
6MWD, m	417.6 ± 114.8	376.9 ± 117.0	443.5 ± 106.1	0.001
WHO functional class, *n* (%)				
I	15 (7.9)	4 (5.3)	11 (9.6)	<0.001
II	113 (59.5)	33 (43.4)	80 (70.2)	
III	55 (28.9)	34 (44.7)	21 (18.4)	
IV	7 (3.7)	5 (6.6)	2 (1.8)	
PAH classification, *n* (%)				
CHD-PAH	126 (66.3)	35 (46.1)	91 (79.8)	<0.001
IPAH	47 (24.7)	29 (38.2)	18 (15.8)	
CTD-PAH	17 (8.9)	12 (15.8)	5 (4.4)	
Right heart catheterization				
RAP, mmHg	7.9 ± 4.6	8.3 ± 4.5	7.6 ± 4.7	0.441
mPAP, mmHg	60.4 ± 19.5	59.7 ± 20.6	60.9 ± 18.7	0.393
PCWP, mmHg	10.5 ± 4.4	10.2 ± 4.3	10.7 ± 4.5	0.619
PVR, Wood units	16.6 ± 14.1	19.6 ± 12.5	14.5 ± 14.8	<0.001
CI, L/min/m^2	2.1 ± 0.8	2.0 ± 0.8	2.2 ± 0.7	0.022
SvO_2, %	63.3 ± 8.8	61.6 ± 9.2	64.9 ± 8.0	0.008
CMR parameters				
LVEDVi, mL/m^2	84.6 ± 49.0	58.1.7 ± 24.6	101.7 ± 53.2	<0.001
LVESVi, mL/m^2	39.7 ± 27.3	26.2 ± 15.3	48.2 ± 30.1	<0.001
LVSVi, mL/m^2	46.1 ± 29.8	34.8 ± 27.8	53.5 ± 28.6	<0.001
LV massi, g/m^2	46.8 ± 21.8	44.3 ± 17.9	48.2 ± 23.9	0.299
LVEF, %	54.6 ± 10.3	55.5 ± 11.1	54.0 ± 9.8	0.230
RVEDVi, mL/m^2	131.9 ± 59.6	147.9 ± 70.8	121.2 ± 47.7	0.006
RVESVi, mL/m^2	86.1 ± 50.1	106.3 ± 58.9	72.7 ± 37.6	<0.001
RVSVi, mL/m^2	45.9 ± 23.2	41.5 ± 27.5	48.5 ± 19.5	<0.001
RV massi, g/m^2	33.1 ± 14.5	35.8 ± 13.3	31.2 ± 14.9	0.003
RVEF, %	36.4 ± 13.1	29.3 ± 13.3	41.0 ± 10.7	<0.001
RVEDV/LVEDV	1.9 ± 1.2	2.7 ± 1.2	1.4 ± 0.8	<0.001
RVESV/LVESV	3.2 ± 3.8	4.5 ± 2.3	2.3 ± 4.3	<0.001
VMI	0.76 ± 0.28	0.85 ± 0.30	0.69 ± 0.25	<0.001
RV-PA coupling	0.66 ± 0.38	0.49 ± 0.37	0.78 ± 0.34	<0.001
LV M/V, g/mL	0.61 ± 0.19	0.78 ± 0.16	0.49 ± 0.09	<0.001
RV M/V, g/mL	0.27 ± 0.09	0.26 ± 0.10	0.27 ± 0.08	0.441

(Continues)

TABLE 1 (Continued)

	All ($n = 190$)	With LV underfilling ($n = 76$)	Without LV underfilling ($n = 114$)	p value
Medications, n (%)				
Endothelin receptor antagonists	161 (84.7)	64 (84.2)	97 (85.1)	0.676
Phosphodiesterase 5 inhibitors	65 (34.2)	28 (36.8)	37 (32.5)	0.537
Prostacyclin analogues and prostacyclin receptor agonists	8 (4.2)	4 (5.3)	4 (3.5)	0.716
Diuretics	50 (26.3)	30 (39.5)	20 (17.5)	0.099
Monotherapy	113 (59.5)	45 (59.2)	68 (59.6)	0.798
Combination therapy	60 (31.6)	25 (32.9)	35 (30.7)	
No medication therapy	17 (8.9)	6 (7.9)	11 (9.6)	

Abbreviations: BMI, body mass index; BSA, body surface area; CHD-PAH, congenital heart diseases related pulmonary arterial hypertension; CTD-PAH, connective heart disease related pulmonary arterial hypertension; IPAH, idiopathic pulmonary arterial hypertension; LV massi, left ventricle mass index; LVEDVi, left ventricular end-diastolic volume index; LVEF, left ventricular ejection fraction; LVESVi, left ventricular end-systolic volume index; LVSVi, left ventricular stroke volume index; mPAP, mean pulmonary artery pressure; 6MWD, 6-min walk distance; PCWP, pulmonary capillary wedge pressure; PVR, pulmonary vascular resistance; RAP, right atrial pressure; RV massi, right ventricle mass index; RVEDVi, right ventricular end-diastolic volume index; RVEF, right ventricular ejection fraction; RVESVi, right ventricular end-systolic volume index; RV-PA coupling, right ventricular-pulmonary arterial coupling; RVSVi, right ventricular stroke volume index; VMI, ventricular mass index, calculated as RV mass/LV mass.

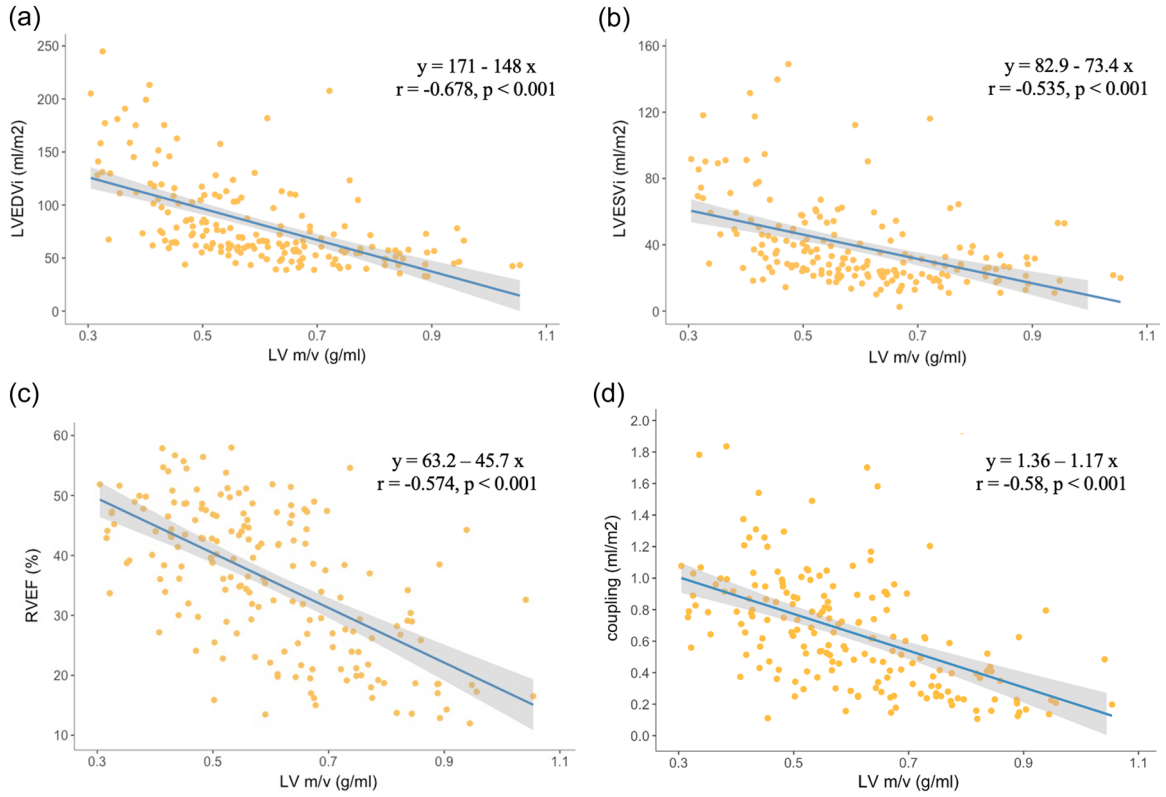

FIGURE 2 Correlation between LV M/V and CMR variables. (a) Relationship between LV M/V and LVEDVi; (b) relationship between LV M/V and LVESVi; (c) relationship between LV M/V and RVEF; (d) relationship between LV M/V and RV-PA coupling. LVEDVi, left ventricular end-diastolic volume index.

TABLE 2 Univariate and multivariate cox regression analyses of primary and composite endpoints in all patients with PAH.

	Primary endpoint		Composite endpoint	
Unadjusted	**Hazard ratio (95% CI)**	***p* value**	**Hazard ratio (95% CI)**	***p* value**
PAH classification				
IPAH	1.00 (ref)	–	1.00 (ref)	–
CHD-PAH	0.527 (0.251–1.104)	0.090	0.526 (0.324–0.854)	0.009
CTD-PAH	1.698 (0.635–4.535)	0.291	1.071 (0.503–2.281)	0.859
WHO FC				
I	1.00 (ref)	–	1.00 (ref)	–
II	2.177 (0.277–17.124)	0.460	1.199 (0.464–3.099)	0.708
III	3.975 (0.511–30.916)	0.187	1.754 (0.670–4.590)	0.252
IV	20.151 (2.346–173.112)	0.006	4.618 (1.443–14.782)	0.010
ln (NT-proBNP), pg/mL	2.009 (1.559–2.591)	<0.001	1.475 (1.268–1.716)	<0.001
6MWD, m	0.994 (0.991–0.997)	<0.001	0.997 (0.995–0.999)	0.001
LVEDVi, mL/m^2, per 10 increase	0.928 (0.839–1.027)	0.150	0.923 (0.864–0.986)	0.017
LVESVi, mL/m^2, per 10 increase	0.946 (0.814–1.098)	0.464	0.936 (0.848–1.033)	0.191
LVSVi, mL/m^2, per 10 increase	0.789 (0.632–0.985)	0.036	0.774 (0.667–0.899)	0.001
LVEF, %	0.978 (0.948–1.009)	0.160	0.979 (0.959–0.999)	0.038
RVEDVi, mL/m^2, per 10 increase	1.057 (1.012–1.104)	0.012	1.030 (0.993–1.069)	0.113
RVESVi, mL/m^2, per 10 increase	1.092 (1.044–1.142)	<0.001	1.067 (1.026–1.109)	0.001
RVSVi, mL/m^2, per 10 increase	0.776 (0.616–0.977)	0.031	0.823 (0.715–0.948)	0.007
RVEF, %	0.937 (0.911–0.964)	<0.001	0.958 (0.941–0.975)	<0.001
LV massi, g/m^2	1.008 (0.995–1.021)	0.219	0.999 (0.988–1.010)	0.893
RV massi, g/m^2	1.021 (1.003–1.039)	0.022	1.011 (0.996–1.026)	0.147
VMI	1.533 (0.502–4.685)	0.454	1.721 (0.811–3.656)	0.158
LV M/V, g/mL, per 0.1 increase	1.323 (1.184–1.479)	<0.001	1.229 (1.133–1.332)	<0.001
LV underfilling	3.690 (1.515–8.989)	0.004	2.082 (1.262–3.437)	0.004
RV M/V, g/mL, per 0.1 increase	0.844 (0.544–1.309)	0.448	1.030 (0.792–1.338)	0.828
RVEDV/LVEDV	1.415 (1.145–1.747)	0.001	1.313 (1.109–1.553)	0.002
RVESV/LVESV	1.252 (1.120–1.401)	<0.001	1.176 (1.078–1.283)	<0.001
RV-PA coupling	0.734 (0.639–0.843)	<0.001	0.848 (0.786–0.915)	<0.001
	Primary endpoint		**Composite endpoint**	
Adjusted	**Hazard ratio (95% CI)**	***p* value**	**Hazard ratio (95% CI)**	***p* value**
WHO FC	2.189 (1.316–3.640)	0.003	1.603 (1.143–2.248)	0.006
LV M/V, g/mL, per 0.1 increase	1.271 (1.082–1.494)	0.004	1.185 (1.079–1.302)	<0.001
PVR, wood units	–	–	1.016 (1.001–1.030)	0.031
ln (NT-proBNP)	1.722 (1.312–2.260)	<0.001	–	–

Note: PAH classification: 0—idiopathic PAH, 1—congenital heart diseases related PAH, 2—connective tissue diseases related PAH.

Abbreviations: CI, confidence interval; LV massi, left ventricle mass index; LVEDVi, left ventricular end-diastolic volume index; LVEF, left ventricular ejection fraction; LVESVi, left ventricular end-systolic volume index; LVSVi, left ventricular stroke volume index; 6MWD, 6-min walk distance; RV massi, right ventricle mass index; RVEDVi, right ventricular end-diastolic volume index; RVEF, right ventricular ejection fraction; RVESVi, right ventricular end-systolic volume index; RVSVi, right ventricular stroke volume index; RV-PA coupling, right ventricular-pulmonary arterial coupling; VMI, ventricular mass index, calculated as RV mass/LV mass; WHO FC, WHO functional class.

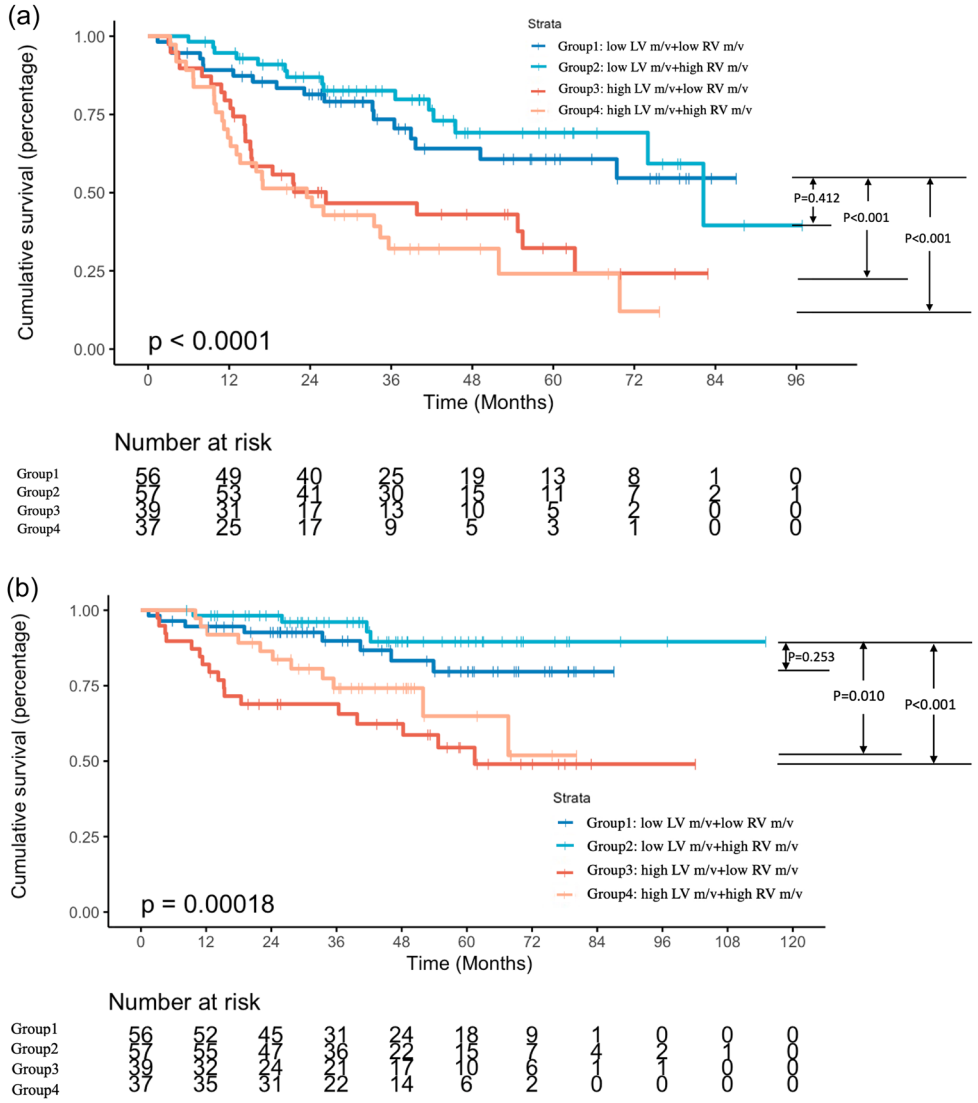

FIGURE 3 Survival differences of different remodeling phenotypes. (a) Shows event-free survival of different remodeling phenotypes; (b) shows survival of different remodeling phenotypes.

Despite the significant embryogenetic differences between the LV and RV, the so-called "laws of the heart" apply to both equally.[16] After the acute exposure to the increased afterload, ventricles adapt by increasing dimensions in obedience to Starling's law of the heart, which is known as "heterometric" response. A "homeometric" response then replaces the "heterometric" response, resulting in increased contractility according to Anresp's law. This preserves CO without ventricular dilatation and elevation in filling pressure, and ventricles undergo adaptive concentric hypertrophy. Finally, a heterometric response initiates again after "homeometric" response, leading to maladaptive ventricular dilatation and heart failure.[16–20] In previous studies, RV concentric hypertrophy was shown to be an adaptive change with optimal prognosis.[7,8,11,21] However, recent evidence suggested that not all RV concentric hypertrophy was adaptive[9] and the assessment of changes should be made in the context of ventricular interdependence.[3] This study sheds light on LV morphologic adaptation in patients with PAH by CMR. In the clinical course of the disease, LV suffered from shrinkage of cavity, elevated filling pressure, but without wall mass decrease, indicating the presence of LV underfilling but not LV atrophy. However, several other studies have demonstrated that left ventricular volume reduction precedes the loss of left ventricular mass.[22,23] Depending on the duration of exposure, patients undergo reductions in the end-diastolic volume of approximately 10%–20%, and reductions in mass of 5%–15%.[23] These changes might be attributed to both direct and indirect interactions between the RV and LV, which ultimately lead to

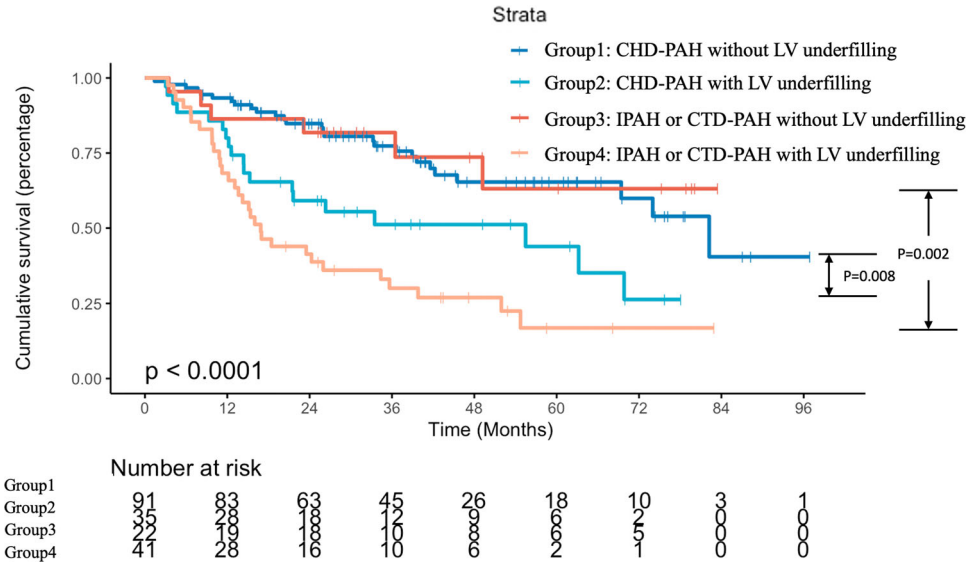

FIGURE 4 Event-free survival differences in different PAH classification and left ventricle underfilling. PAH, pulmonary arterial hypertension.

changes in LV morphology and function.[24] Interventricular interactions in PAH extend beyond mere mass and volume changes. As expected, patients with LV underfilling presented a more advanced disease stage and a poorer prognosis. Our results indicate that larger left ventricular end-diastolic volume (LVEDVi), higher LVSV, and LVEF are associated with a lower risk of cardiac adverse events.

In patients with severe PAH, the RV often undergoes dilatation at the expense of LV atrophy.[23] Despite this, the prognostic significance of LV underfilling and atrophic remodeling remains unclear and warrants further investigation. In this study, we observed a significant negative correlation between LV M/V ratio and RV stroke volume/end-systolic volume (SV/ESV) ratio, which is a noninvasive measure of RV-PA coupling.[25] RV-PA coupling reflects the ability of the RV to adapt to increased afterload in PAH,[26,27] suggesting that LV underfilling may represent maladaptive RV remodeling in certain cases. Given the negative interventricular interactions that result from ventricular competition for space, we hypothesized that PAH patients with concentric RV hypertrophy should be stratified based on the presence of LV underfilling. Our results revealed that the occurrence of LV underfilling pattern was associated with a higher risk of adverse cardiac events in PAH patients, irrespective of RV changes. Moreover, although CHD-PAH patients tend to have better outcomes compared to IPAH and CTD-PAH patients in previous studies,[28,29] in PAH patients without LV underfilling pattern, they presented with similar outcome.

Notably, although the RV M/V ratio has been established as a useful tool to differentiate between RV eccentric and concentric hypertrophy and predict outcomes in previous studies involving idiopathic and heritable PAH patients,[7,8,21] our study did not find any additional prognostic value of RV M/V in our congenital heart disease-related PAH-predominant population. The complexity of hemodynamic changes in PAH patients with congenital heart diseases, may account for this difference, as PAH patients with atrial septal defect may exhibit physiologically hypertrophied LV while those with ventricular septal defect may have LV volume overload due to shunting.[30] The presence of a shunt can result in both chronic volume and pressure overload of the RV, indicating that RV eccentric hypertrophy might not be the only marker for maladaptive recognition. Moreover, the median RV M/V ratio in our study was slightly lower than that in other studies, which may be attributed to the predominance of CHD-PAH patients, who are characterized by chronic volume overload of RV and a more dilated RV. Higher RV mass was related to poorer prognosis in our study, which calls into question whether RV hypertrophy is always adaptive. The prognostic value of RV mass is still controversial,[7–9] emphasizing the importance of considering both left and RVs to understand the adaptive pattern in PAH patients.

Limitations

This study included the relatively small sample size of PAH patients, limiting the ability to explore the potential ability of the LV underfilling in PAH patients' risk assessment. Our cohort was mainly composed of

CHD-PAH, younger and female patients. Moreover, clinical cohort only may not able to provide evidence on pathology mechanisms and treatment pathways. Therefore further researches with larger and more diverse participant groups, in vivo or in vitro models are warranted to validate and expand upon these initial findings.

CONCLUSION

In conclusion, the presence of LV underfilling is independently associated with adverse clinical outcomes in PAH patients and may serve as an important imaging biomarker for identifying maladaptive changes.

AUTHOR CONTRIBUTORS

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

All data in this study will be shared on reasonable request to the corresponding author (YCC) for research purposes once the data have been deidentified and all the main findings have been published.

ETHICS STATEMENT

This study was approved by the ethics committee of West China Hospital and registered in the Chinese Clinical Trial Registry (ChiCTR1800019314 and ChiCTR1900025518). All participants underwent the same CMR and RHC protocols and provided written informed consent.

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