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Right heart remodeling in end-stage pulmonary arterial hypertension and the impact of treatment intensity

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Background: Research on the limits of compensatory right heart remodeling and the effects of pulmonary artery hypertension (PAH) targeted therapies on these mechanisms is limited.

Method: Chest x-ray and echocardiographic data were collected from 143 deceased patients with PAH confirmed by right heart catheterization at their end-stage disease. Right heart remodeling was compared across different PAH treatment strategies.

Results: This study of 143 deceased PAH patients (49 ± 17 years, 74.1% female) characterized right heart remodeling at the time of death. Mean cardiothoracic ratio (CTR), right atrial area (RAA) and mid-cavity RV linear dimension (RVD) measured by echocardiography were 0.61 ± 0.09, 27 cm^2 (median 27, IQR 21–38), and 4.97 ± 0.97 cm, respectively, with extremes of 0.88, 102 cm^2, and 7.50 cm. Intensive therapy resulted in larger CTR (0.63 ± 0.08 vs. 0.60 ± 0.09, $p = 0.016$), RAA (30 [(24–40)] vs. 25 [(19–34)] cm^2, $p = 0.020$), and RVD (5.30 ± 0.97 vs. 4.65 ± 0.85 cm, $p < 0.001$) compared with non triple therapy. After adjusting for confounders, intensive therapy independently predicted increases in CTR (0.03, 95% CI 0.00-0.05, $p = 0.054$), RAA (6.63 cm^2, 95% CI 1.46-11.80, $p = 0.013$), and RVD (0.66 cm, 95% CI 0.34-0.98, $p < 0.001$).

Conclusion: These findings suggest that more aggressive PAH treatment is associated with greater right heart remodeling, highlighting the complex relationship between therapeutic intervention and disease progression in PAH patients.

KEYWORDS

pulmonary arterial hypertension, death, right heart remodeling, treatment intensity, targeted therapies

Introduction

Pulmonary arterial hypertension (PAH) encompasses various conditions characterized by elevated pulmonary vascular resistance (PVR), including idiopathic, heritable, and PAH associated with connective tissue disease or congenital heart disease (1–3). Persistent elevation in pulmonary artery pressure increases right

ventricular afterload, triggering adaptive changes to maintain cardiac output (4). Over time, chronic pressure overload eventually leads to maladaptive right ventricular (RV) remodeling, marked by myocardial cell proliferation and fibrosis. This structural and functional remodeling represents a critical turning point in PAH progression (5). RV remodeling not only alters cardiac morphology but also impairs contractility, decreasing cardiac output and potentially leading to right heart failure, a major cause of mortality in PAH (6).

Significant advancements in drug therapies have markedly impacted right heart remodeling and improved the prognosis for patients with PAH (7). Current treatments target four main signaling pathways: endothelin-1 (8, 9), nitric oxide (10–12), prostacyclin (13), and the Activin/morphogenetic protein(BMP) pathway (14). While monotherapy options exist, combination therapies (7), including current triple and emerging quadruple drug regimens, have demonstrated greater efficacy. For those who remain unresponsive to these advanced therapies, lung transplantation remains a last resort.

Despite these therapeutic advances, disease progression, irreversible RV remodeling, and death still occur. Currently, limited research explores the limits of RV remodeling compensation and the impact of targeted therapies on these compensatory mechanisms. Therefore, further investigation is warranted to determine how these pharmacological strategies affect the limits of RV adaptation and to elucidate whether these limits vary among PAH patients.

Methods

Study design and patient selection

This retrospective cohort study was conducted in department of pulmonary circulation, Shanghai Pulmonary Hospital. All patients diagnosed with PAH in our department undergo regular follow-up, and for those whose deaths are confirmed during this follow-up period, we gather their information. We collected clinical data at baseline and the last visit data of these patients, encompassing demographic characteristics, laboratory test results, echocardiographic findings, chest radiographs and hemodynamic data. Our study adhered to the principles of the Declaration of Helsinki and received approval from the ethics committee of Shanghai Pulmonary Hospital (approval number: K16-293).

Patients had to meet the following criteria to be included in the study: (i) diagnosis between January 1, 2013, and June 30, 2024; (ii) confirmed diagnosis of Group 1 PAH, defined as mean pulmonary arterial pressure (mPAP) >20 mmHg, pulmonary artery wedge pressure(PAWP) <15 mmHg and pulmonary vascular resistance(PVR) > 2WU by right heart catheterization (RHC) at the time of diagnosis; (iii) visit data available within one year before death; (iv) death confirmed by telephone or visit. Patients who did not meet the diagnostic criteria for PAH and those lacking relevant visit data within one year before death were excluded.

Clinical, functional and hemodynamic characteristics

A comprehensive evaluation of clinical data was performed, including demographic information such as age, sex, as well as medical and family histories. The hemodynamic data were collected, including mPAP, PAWP and right atrial pressure (RAP). The cardiac index (CI) was determined by measuring cardiac output (CO) with the standard thermodilution technique and divided by body surface area. PVR was calculated using the formula: (mPAP-PAWP)/CO (15).

Cardiothoracic ratio and echocardiography assessment

The cardiothoracic ratio (CTR) on a chest x-ray is determined by comparing the width of the heart to the width of the chest (16). All patients underwent CTR measurements at both baseline and during their last visit.

All echocardiographic data were acquired using commercially available equipment (Vivid 7, GE Healthcare) in standard views. Measurements were obtained from the mean of three consecutive beats based on the American Society of Echocardiography Guidelines (17). The echo parameters and derived assessments that we focused on common and widely available for daily clinical practice, including RA area, mid-cavity RV linear dimension(RVD), left ventricular end diastolic diameter (LVEDD), left ventricular ejection fraction (LVEF), left ventricular end-diastolic eccentricity index (LV-EId), pulmonary arterial systolic pressure (PASP), tricuspid annular plane systolic excursion (TAPSE), and presence of pericardial effusion.

Statistical analyses

All statistical analyses were performed using SPSS version 20.0 software (IBM Corp., Armonk, NY, USA) and GraphPad Prism version 8 (GraphPad Software Inc., La Jolla, CA, USA). Categorical data are presented as numbers and percentages, while continuous data are presented as either mean ± SD or median with interquartile range (IQR), depending on the data distribution. Continuous data were compared using Welch Two Sample *t*-test or one-way ANOVA for parametric data, and Wilcoxon signed-rank/ Kruskal–Wallis rank sum test for nonparametric data. Linear regression analysis is used to describe the relationship between intensity of PAH therapy and the extent of heart remodeling. Multiple models were constructed, each adjusting for a different set of covariates to provide a nuanced understanding of how these covariates influence the observed association. A p-value of <0.05 was considered significant for all statistical tests.

Results

Characteristics of study population

A total of 143 deceased PAH patients met the inclusion and exclusion criteria. Demographic, classification, hemodynamic,

baseline right ventricular morphology and function, treatment, and cardiac remodeling data of the study population are presented in Table 1. The average age was 49 ± 17 years, with 37 (25.9%) males and 106 (74.1%) females. Time from symptom onset to death was 6.3 ± 4.5 years, and time from diagnosis to death was 3.4 ± 3.6 years. PAH classifications were idiopathic (63, 44.1%), heritable (4, 2.8%), connective tissue disease (51, 35.7%), portal hypertension (2, 1.4%), congenital heart disease (20, 14.0%), and PVOD/PCH (3, 2.1%).

TABLE 1 Clinical characteristics of deceased patients with PAH.

Characteristic	$N = 143$[a]
Age, yr	49 ± 17
Female	106 (74.1%)
Symptom-to-death interval[b], yr	6.3 ± 4.5
Diagnosis-to-death interval[c], yr	3.4 ± 3.6
PAH Classifications	
Idiopathic	63 (44.1%)
Heritable	4 (2.8%)
Connective tissue disease	51 (35.7%)
Portal hypertension	2 (1.4%)
Congenital heart disease	20 (14.0%)
PVOD/PCH	3 (2.1%)
Baseline Characteristics[d]	
RHC	
MPAP, mmHg	57 ± 16
PAWP, mmHg	7.1 ± 4.4
RAP, mmHg	6.1 ± 5.0
CI, L/min/m^2	2.60 ± 1.11
PVR, Wood units	13 ± 7
SVO_2, %	58 ± 14
Chest x-ray and Echocardiography	
CTR	0.62 ± 0.09
RAA, cm^2	26.72 ± 12.77
LVEDD, cm	3.56 ± 0.73
LV-EId	1.55 ± 0.35
TAPSE	1.57 ± 0.36
PAH therapy	
Mono-therapy	20 (14.0%)
Double-therapy	56 (39.2%)
Triple-therapy	67 (46.9%)
Cause of death	
Sudden death	41 (28.7%)
Right heart failure	89 (62.2%)
Other[e]	13 (9.1%)

[a]Data are presented as mean ± standard deviation for continuous variables and number (percentage) for categorical variables.
[b]Time was calculated from initial onset of PAH-related symptoms to time of death.
[c]Time from the date of PAH confirmation by right heart catheterization (RHC) to death.
[d]All clinical parameters reflect the patients' terminal status, with the exception of hemodynamic measurements obtained during baseline RHC.
[e]Non-cardiovascular causes of death comprised: Infectious complications ($n = 6$); Massive hemoptysis ($n = 3$); Intracranial hemorrhage ($n = 2$); Post-transplant mortality ($n = 1$); Procedural complications during colonoscopy ($n = 1$).
PAH, pulmonary arterial hypertension; PVOD, pulmonary veno-occlusive disease; PCH, pulmonary capillary hemangiomatosis; RHC, right heart catheterization; MPAP, mean pulmonary arterial pressure; PAWP, pulmonary artery wedge pressure; RAP, right atrial pressure; CI, cardiac index; PVR, pulmonary vascular resistance; SvO_2: Mixed venous oxygen saturation; CTR, cardiothoracic ratio; RAA, right atrial area; LVEDD, left ventricular end-diastolic diameter; LV-EId, left ventricular end-diastolic eccentricity index; TAPSE, tricuspid annular plane systolic excursion.

At diagnosis, right heart catheterization demonstrated mPAP of 57 ± 16 mmHg, PAWP of 7.1 ± 4.4 mmHg, RAP of 6.1 ± 5.0 mmHg, CO of 3.08 ± 2.23 L/min, CI of 2.60 ± 1.11 L/min/m^2, PVR of 13 ± 7 Wood units, and a mixed venous oxygen saturation (SvO_2) of 58 ± 14%. For baseline Chest x-ray and Echocardiography, we obtained data on some indicators, with CTR being 0.62 ± 0.09, RAA being 26.72 ± 12.77, LVEDD being 3.56 ± 0.73, LV-EId being 1.55 ± 0.35, and TAPSE being 1.57 ± 0.36. With respect to PAH-specific treatments, 20 (14.0%) received monotherapy (14 on phosphodiesterase type 5 [PDE5] inhibitors, 6 on endothelin receptor antagonists [ERAs]), 56 (39.2%) received double therapy (all on PDE5 inhibitors plus ERAs), and 67 (46.9%) were treated with triple therapy (ERAs, PDE5 inhibitors, and prostacyclin analogues). The primary cause of death was right heart failure in 89 (62.2%) patients. Sudden death accounted for 41 (28.7%) deaths. Other causes of death included infection ($n = 6$), hemoptysis ($n = 3$), cerebral hemorrhage ($n = 2$), transplant-related death ($n = 1$), and colonoscopy complications ($n = 1$).

Right heart remodeling at the time of death

At death, chest radiography showed a CTR of 0.61 ± 0.09. Echocardiography revealed RAA of 27 cm^2 (median 27, IQR 21–38), RVD of 4.97 ± 0.97 cm, LVEDD of 3.40 cm (median 3.40, IQR 3.00–4.00), and LV-EID of 1.56 (median 1.56, IQR 1.34–1.75) (Table 2). Notably, the extreme limits of compensatory remodeling in end-stage disease included a CTR as high as 0.88, an RAA of 102 cm^2, and an RVD of 7.50 cm. Figure 1 illustrates the frequency distribution of right ventricular remodeling parameters at death.

Before death, varying treatment strategies were associated with different degrees of right heart remodeling (Table 2). Monotherapy (20 patients) resulted in a CTR of 0.60 ± 0.09, RAA of 21 cm^2 (median 18, IQR 18–32), and RVD of 4.19 ± 0.87 cm; double therapy (56 patients) showed a CTR of 0.60 ± 0.09, RAA of 26 cm^2 (median 20, IQR 20–34), and RVD of 4.79 ± 0.80 cm; and triple therapy (67 patients) led to a CTR of 0.63 ± 0.08, RAA of 30 cm^2 (median 24, IQR 24–40), and RVD of 5.30 ± 0.97 cm. Statistical analysis indicated significant differences between treatment groups for RAA ($p = 0.037$) and RVD ($p < 0.001$), and a near-significant difference for CTR ($p = 0.054$). LVEDD and LV-EID remained relatively consistent across the different treatment approaches.

Compared with those who were insufficiently treated, patients receiving intensive combination therapy had a significantly larger RVD (5.30 ± 0.97 cm vs. 4.65 ± 0.85 cm, $p < 0.001$) and RAA (30 [24–40] cm^2 vs. 25 [19–34] cm^2, $p = 0.020$) (Table 3, Figure 2). However, no significant differences were observed in LVEDD or LV-EID. The CTR was slightly higher under intensive combination therapy (0.63 ± 0.08 vs. 0.60 ± 0.09, $p = 0.016$).

Impact of PAH therapy on right ventricular remodeling limits

Linear regression analysis demonstrated a clear association between the intensity of PAH therapy and the extent of right

TABLE 2 Compensatory cardiac remodeling in PAH patients under different treatment strategies.

Characteristic	Total $N = 143$	PAH target therapy			p
		Mono-therapy $N = 20$[a]	Double-therapy $N = 56$[a]	Triple-therapy $N = 67$[a]	
CTR	0.61 ± 0.09	0.60 ± 0.09	0.60 ± 0.09	0.63 ± 0.08	0.054[b]
RAA, cm^2	27 (21, 38)	21 (18, 32)	26 (20, 34)	30 (24, 40)	0.037[c]
RVD, cm	4.97 ± 0.97	4.19 ± 0.87	4.79 ± 0.80	5.30 ± 0.97	<0.001[b]
LVEDD, cm	3.40 (3.00, 4.00)	3.80 (3.20, 4.50)	3.20 (2.80, 3.90)	3.40 (3.00, 4.05)	0.059[c]
LV-EId	1.56 (1.34, 1.75)	1.43 (1.37, 1.69)	1.56 (1.32, 1.72)	1.57 (1.34, 1.85)	0.514[c]

[a]Mean ± SD; Median (IQR).
[b]One-way ANOVA.
[c]Kruskal–Wallis rank sum test.
PAH, pulmonary Arterial Hypertension; CTR, cardiothoracic Ratio; RAA, right atrial Area; RVD, mid-cavity right ventricular linear dimension; LVEDD, left ventricular end-diastolic diameter; LV-Eid, left ventricular end-diastolic eccentricity index.

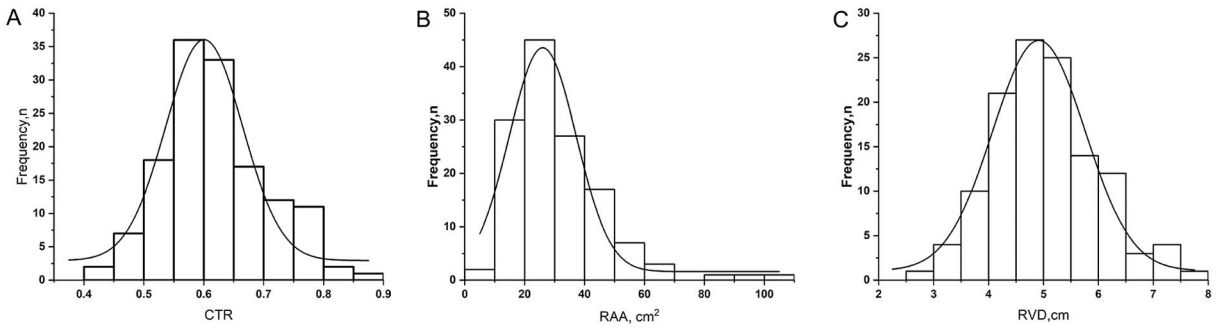

FIGURE 1
Frequency distribution of right ventricular remodeling parameters at the time of death in patients with pulmonary arterial hypertension. The histograms show the distribution of (A) CTR (cardiothoracic ratio measured from chest x-ray), (B) RAA (Right Atrial Area measured by echocardiography, cm^2), and (C) RVD (Mid-cavity Right Ventricular Linear Dimension by echocardiography, cm). The superimposed curves represent unimodal probability density functions fitted to the respective histograms.

TABLE 3 Compensatory cardiac remodeling in PAH comparing insufficient and intensive therapy approaches.

Characteristic	PAH target therapy		p
	Insufficiently treated $N = 76$[a]	Intensive combination $N = 67$[a]	
CTR	0.60 ± 0.09	0.63 ± 0.08	0.016[b]
RAA, cm^2	25 (19, 34)	30 (24, 40)	0.020[c]
RVD, cm	4.65 ± 0.85	5.30 ± 0.97	<0.001[b]
LVEDD, cm	3.35 (2.93, 4.00)	3.40 (3.00, 4.05)	0.845[c]
LV-EId	1.55 (1.32, 1.71)	1.57 (1.34, 1.85)	0.299[c]

[a]Mean ± SD; Median (IQR).
[b]Welch Two Sample *t*-test.
[c]Wilcoxon rank sum test.
PAH, pulmonary arterial hypertension; CTR, cardiothoracic ratio; RAA, right atrial area; RVD, mid-cavity right ventricular linear dimension; LVEDD, left ventricular end-diastolic diameter; LV-Eid, left ventricular end-diastolic eccentricity index.

ventricular remodeling, as detailed in Table 4. Here, we defined intensive therapy as triple therapy, while non triple therapy is defined as insufficient treatment. Patients receiving intensive combination therapy experienced significantly greater increases in CTR, RAA, and RVD compared to those receiving insufficient therapy. The analysis revealed that intensive therapy led to a 0.04 increase in CTR (95% CI 0.01–0.06, $p = 0.016$), a 6.12 cm^2 increase in RAA (95% CI 0.87–11.36, $p = 0.024$), and a 0.65 cm increase in RVD (95% CI 0.33–0.98, $p < 0.001$). Adjusting for age and sex (Model I) maintained the statistical significance of these findings, the increase in CTR was 0.03 (95% CI 0.00-0.06, $p = 0.016$), the increase in RAA was 5.67 cm^2 (95% CI 0.40–10.95, $p = 0.037$), and the increase in RVD was 0.63 cm (95% CI 0.31-0.95, $p < 0.001$). Further adjusting for PAH classifications (Model II) also demonstrated significant increases with intensive therapy for CTR (0.03, 95% CI 0.00–0.06, $p = 0.051$), RAA (6.85 cm^2, 95% CI 1.62–12.08, $p = 0.011$), and RVD (0.67 cm, 95% CI 0.35-0.99, $p < 0.001$). Finally, even after adjusting for cause of death in addition to age, sex, and PAH classifications (Model III), intensive therapy remained significantly associated with increased CTR (0.03, 95% CI 0.00-0.05, $p = 0.054$), RAA (6.63 cm^2, 95% CI 1.46–11.80, $p = 0.013$), and RVD (0.66 cm, 95% CI 0.34–0.98, $p < 0.001$).

Discussion

The present study demonstrates that patients with PAH exhibit varying degrees of right heart remodeling in the terminal

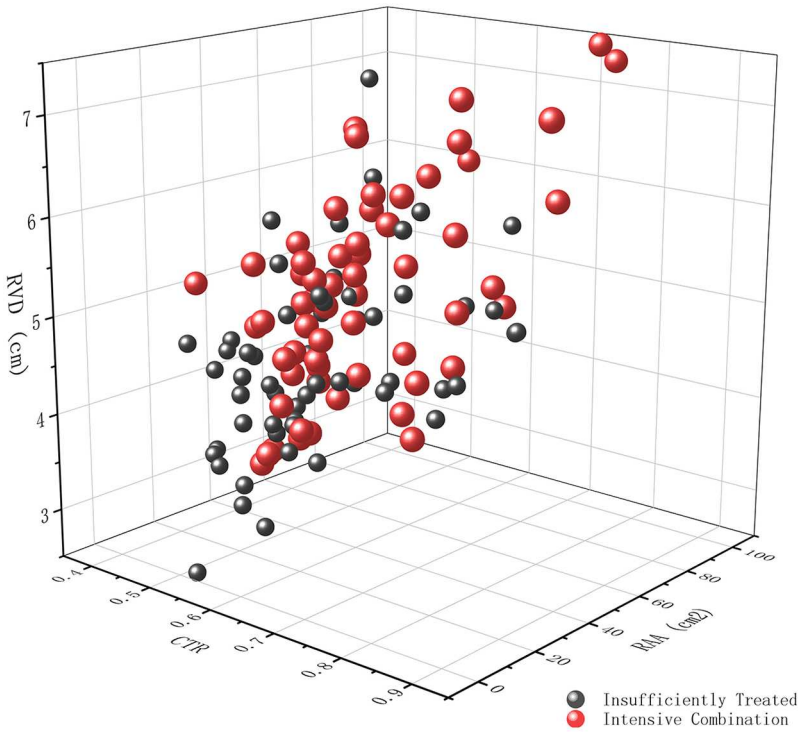

FIGURE 2
Three-dimensional scatter plot demonstrating the impact of treatment intensity on right ventricular remodeling. The plot depicts the relationship between cardiothoracic ratio (CTR) measured from chest x-ray, Mid-cavity Right Ventricular Linear Dimension (RVD, cm), and right atrial area (RAA, cm^2) measured by echocardiography, in patients receiving either insufficient treatment (dark grey spheres) or intensive combination therapy (red spheres).

TABLE 4 Association between PAH therapy intensity and compensatory cardiac remodeling (linear regression).

Characteristic	Unadjusted			Model I			Model II			Model III		
	Beta	95% CI	p	Beta	95% CI	*p*-value	Beta	95% CI	p	Beta	95% CI	p
CTR												
Insufficient therapy	Ref			Ref			Ref			Ref		
Intensive therapy	0.04	0.01, 0.06	0.016	0.03	0.00, 0.06	0.016	0.03	0.00, 0.06	0.051	0.03	0.00, 0.05	0.054
RAA												
Insufficient therapy	Ref			Ref			Ref			Ref		
Intensive therapy	6.12	0.87, 11.36	0.024	5.67	0.40,10.95	0.037	6.85	1.62, 12.08	0.011	6.63	1.46, 11.80	0.013
RVD												
Insufficient therapy	Ref			Ref			Ref			Ref		
Intensive therapy	0.65	0.33,0.98	<0.001	0.63	0.31,0.95	<0.001	0.67	0.35, 0.99	<0.001	0.66	0.34, 0.98	<0.001

Model I: adjusted for age and gender.
Model II: adjusted for Model I + PAH Classifications.
Model III: adjusted for Model II + PAH Classifications + Cause of death.
PAH, pulmonary arterial hypertension; CTR, cardiothoracic Ratio; RAA, right atrial area; RVD, mid-cavity right ventricular linear dimension; CI, confidence interval.

stage, with extreme cases showing CTR up to 0.88, RAA up to 102 cm^2, and RVD up to 7.50 cm. Intensive combination therapy (triple therapy) was significantly associated with more pronounced right heart remodeling compared to monotherapy or double therapy. Specifically, patients receiving triple therapy had larger CTRs, RAAs, and RVDs, as evidenced by both chest x-rays and echocardiography. Linear regression analysis confirmed that the intensity of PAH therapy independently correlated with increased right ventricular remodeling, regardless of age, sex, PAH classification and cause of death.

PAH is a progressive condition characterized by escalating pulmonary vascular resistance, which places an increased afterload on the right heart (2, 18, 19). In response, the right ventricle initially compensates by thickening its walls and enhancing contractility (19, 20). Over time, however, sustained pressure overload can lead to significant right heart enlargement,

a process intimately linked to patient survival (21–24). Although extreme cases of right heart remodeling in PAH are rarely documented, our findings indicate a remarkable capacity for structural adaptation, with right atrial areas reaching five to six times the upper limit of normal and right ventricular diameters exceeding twice the normal threshold (25). This degree of remodeling is shaped by an intricate interplay of factors, including neurohormonal activation, coronary perfusion, myocardial metabolism, disease onset rate, underlying etiology, and emerging genetic or epigenetic influences (20, 26, 27). Notably, our findings demonstrate that therapeutic strategies are another significant clinical factor influencing right heart remodeling. While cardiac dimensions are influenced by various confounding factors such as age (28), sex (29), PAH classification (30), and cause of death (31), our analysis demonstrates that even after adjusting for these factors, treatment intensity remains significantly associated with right heart remodeling.

PAH-targeted therapies have been shown to influence right heart remodeling (32–34). Novel agents like sotatercept improve right ventricular structure by reducing pulmonary vascular resistance (35), thereby prolonging the clinical course of PAH. Focusing on the concept of cardiac compensatory limits, our study elucidates the complex relationship between PAH-targeted therapy and right heart remodeling. We found a positive correlation between right heart size and treatment intensity, with significantly greater remodeling observed in patients receiving triple therapy before death compared to those without adequate treatment. Furthermore, the extent of right heart remodeling demonstrated a linear relationship with the duration of PAH management (data not shown). These results suggest that more comprehensive pharmacologic treatment allows for greater cardiac compensation, effectively extending right heart adaptation closer to its functional limits.

Right heart remodeling in PAH presents a complex duality. While the heart's initial remodeling response to increased pulmonary artery pressure is beneficial, enabling it to compensate and prolong survival (19, 36), especially with therapeutic intervention, this adaptive process eventually becomes detrimental. Prolonged remodeling leads to significant right heart enlargement, a key predictor of poor prognosis (37). This creates a critical challenge: While early intervention aims to reverse remodeling, the focus for advanced disease shifts to slowing its progression and maximizing the heart's compensatory capacity.

The emergence of "super-remodelers"—patients exhibiting extreme right heart enlargement despite prolonged PAH-targeted therapy—poses a significant challenge in lung transplantation decisions. While previous research suggests comparable outcomes between bilateral lung transplantation (BLT) and heart-lung transplantation (HLT) (38, 39), the decision-making process becomes more complex for these individuals. Although improved survival rates with PAH medications may be reducing the overall need for lung transplants, the rise of extreme right heart remodeling necessitates a closer look at optimal surgical strategies for this specific patient population. Further research focusing on the potential reversibility of this severe remodeling post-transplant is crucial for refining treatment approaches and determining whether BLT or HLT offers the best long-term outcomes.

This study has several limitations. First, the retrospective nature of our study design means that baseline assessments were performed at our center following referral, rather than at initial disease onset. This pre-referral treatment exposure fundamentally limits our ability to establish true baseline cardiac structural characteristics, and completely account for potential confounding effects of prior therapies on subsequent remodeling patterns. These factors may introduce systematic bias in our interpretation of treatment effects. Meanwhile the establishment of causal relationships was still influenced due to retrospective design and confounding by indication (sicker patients receive more therapy). Second, we lacked data on treatment changes over the disease course, hindering analysis of dynamic interactions between evolving treatment strategies and right heart remodeling progression. This prevented us from evaluating the impact of treatment modifications on remodeling over time. Third, cardiac remodeling at the time of death was assessed using chest radiography and echocardiography (40–42). While these modalities are readily available and accepted methods for evaluating right heart structure, the absence of MRI data limited our ability to fully characterize end-stage remodeling, especially in cases with extreme enlargement.

Conclusion

Right heart remodeling in PAH progresses throughout the disease course, culminating in significant changes in the terminal stage. PAH-targeted therapies influence the extent of this cardiac remodeling, effectively pushing the limits of compensatory adaptation. This influence is independent of age, sex, PAH classification, and cause of death. While these therapies enhance the heart's compensatory capacity, allowing it to reach structural extremes, this phenomenon presents a complex duality. The emergence of "super-remodelers," patients exhibiting extreme right heart enlargement despite prolonged PAH-targeted therapy, underscores the challenges in managing advanced PAH, particularly regarding decisions surrounding lung transplantation.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary Material, further inquiries can be directed to the corresponding authors.

Ethics statement

The studies involving humans were approved by the ethics committee of Shanghai Pulmonary Hospital. The studies were conducted in accordance with the local legislation and institutional requirements. Written informed consent for

participation was not required from the participants or the participants' legal guardians/next of kin in accordance with the national legislation and institutional requirements.

Author contributions

S-GG: Supervision, Writing – original draft, Writing – review & editing, Methodology. Q-HZ: Writing – original draft, Investigation, Data curation, Supervision. J-YZ: Writing – review & editing, Data curation, Formal analysis. QZ: Writing – review & editing. RZ: Formal analysis, Writing – review & editing, Methodology, Data curation, Investigation. H-LQ: Investigation, Data curation, Writing – review & editing, Visualization. C-JL: Visualization, Data curation, Writing – review & editing. H-TL: Investigation, Writing – review & editing, Data curation, Visualization. W-HW: Data curation, Visualization, Writing – review & editing, Investigation. PY: Methodology, Data curation, Writing – review & editing, Investigation, Visualization. JH: Visualization, Data curation, Writing – review & editing. JX: Writing – review & editing, Investigation, Visualization, Data curation. J-ML: Visualization, Data curation, Writing – review & editing, Supervision. Q-HZ: Investigation, Supervision, Project administration, Writing – review & editing, Writing – original draft, Data curation, Methodology, Visualization. LW: Writing – original draft, Visualization, Data curation, Project administration, Formal analysis, Writing – review & editing, Methodology, Supervision.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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