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REVIEW

Beyond the right ventricle: left heart involvement in pulmonary arterial hypertension

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Abstract

Pulmonary arterial hypertension (PAH) is characterized by progressive remodeling of the pulmonary vasculature, leading to increased pulmonary vascular resistance and chronic right ventricular (RV) pressure overload. As RV dysfunction develops, ventricular interdependence alters the structural and functional relationship between the right and left ventricles. Although normal left-sided filling pressures define PAH, growing evidence indicates that left ventricular (LV) mechanics may be substantially affected. Leftward septal displacement, pericardial constraint, and reduced pulmonary venous return contribute to chronic underfilling of the left atrium and LV, impairing ventricular geometry and contractile dynamics despite preserved intrinsic myocardial function. However, secondary myocardial remodeling in advanced disease remains debated. These alterations may lead to subclinical or overt LV dysfunction and represent an underrecognized component of PAH pathobiology. Imaging markers such as LV global longitudinal strain, LV outflow tract velocity–time integral, and left atrial strain have emerged as potential indicators of left-sided involvement and may provide additional prognostic information. In this narrative review, we summarize current evidence on the pathobiological mechanisms linking RV dysfunction to left-sided cardiac alterations and discuss the role of ventricular interdependence in the coupling of the pulmonary circulation. Understanding this interaction may help redefine PAH as a progressive biventricular syndrome and may improve risk stratification and clinical assessment.

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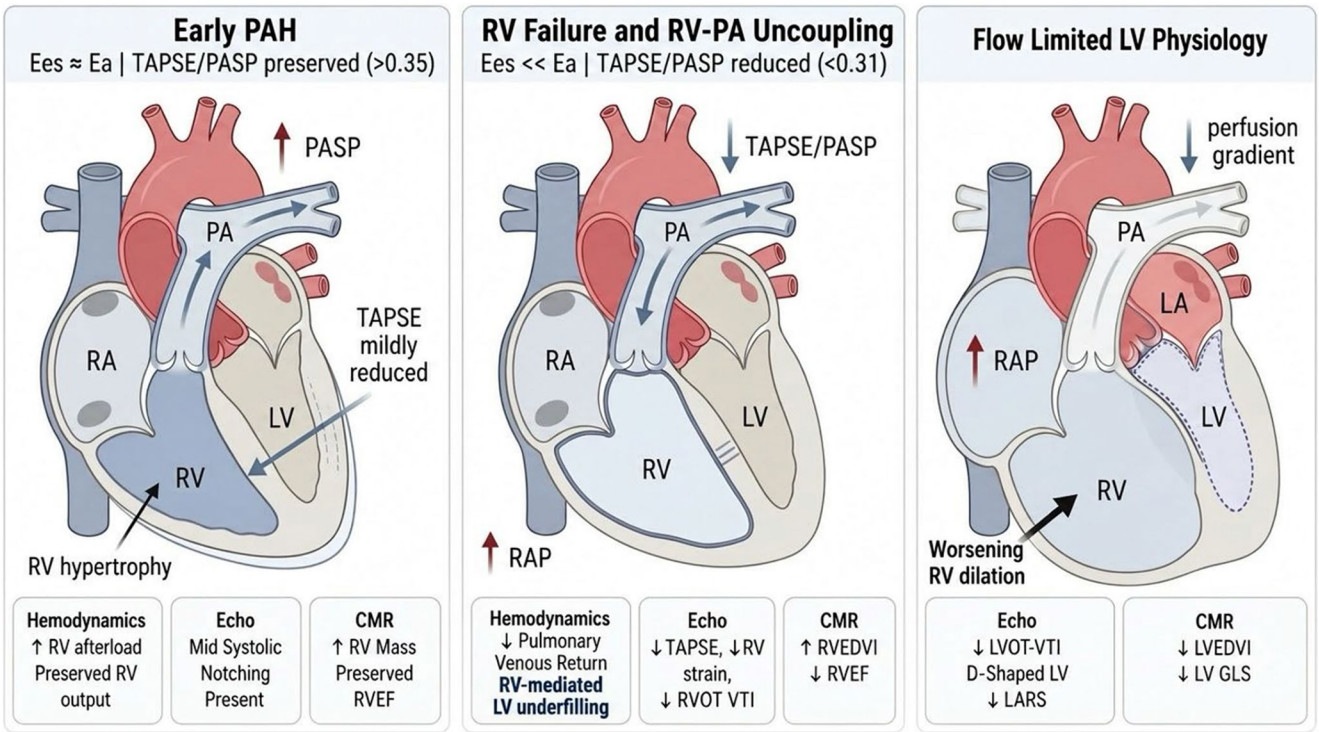
Graphical abstract

Central figure. Conceptual Models of Left Ventricular Dysfunction in PAH

Several mechanisms have been proposed to explain LV dysfunction in PAH. The most compelling and consistently supported is chronic underfilling: progressive RV pressure overload displaces the interventricular septum. It increases pericardial constraint, limiting LV diastolic filling and reducing pulmonary venous return, impairing LV mechanics despite preserved intrinsic myocardial function [1]. A second hypothesis suggests that sustained low mechanical workload induces structural atrophy, as evidenced by reduced LV mass and chamber dimensions [2,3]. A third, less established hypothesis proposes secondary intrinsic myocardial remodeling in advanced disease, whereby sarcomeric, metabolic, and molecular alterations may contribute to impaired contractility beyond loading abnormalities [4].While evidence exists for each, structural and molecular changes likely represent downstream consequences of prolonged ventricular interdependence rather than primary myocardial disease.

Abbreviations: CMR: Cardiac magnetic resonance; Ea: Arterial elastance; Ees: End-systolic elastance; LARS: Left atrial reservoir strain; LV: Left ventricle; LV-GLS: Left ventricular global longitudinal strain; LVEDVI: Left ventricular end-diastolic volume index; LVOT-VTI: Left ventricular outflow tract velocity time integral; PA: Pulmonary artery; PAH: Pulmonary arterial hypertension; PASP: Pulmonary artery systolic pressure; RA: Right atrium; RAP: Right atrial pressure; RV: Right ventricle; RVEDVI: Right ventricular end-diastolic volume index; RVEF: Right ventricular ejection fraction; RVOT-VTI: Right ventricular outflow tract velocity time integral; TAPSE: Tricuspid annular plane systolic excursion.



Keywords Pulmonary arterial hypertension · Ventricular interdependence · Left ventricle · Left atrium · Cardiac imaging · Pathobiology

Abbreviations

CMR	Cardiac magnetic resonance
CO	Cardiac output
LA	Left atrium/atrial
LARS	Left atrial reservoir strain
LAVi	Left atrial volume index
LV	Left ventricle/ventricular
LVEDV	Left ventricular end-diastolic volume
LVEF	Left ventricular ejection fraction
LV-GLS	Left ventricular global longitudinal strain
PA	Pulmonary artery/arterial
PAH	Pulmonary arterial hypertension
PAP	Pulmonary arterial pressure
PAWP	Pulmonary artery wedge pressure
PV	Pulmonary vein
PVR	Pulmonary vascular resistance

RV	Right ventricle/ventricular
RVEF	Right ventricular ejection fraction
SVI	Stroke volume index
TAPSE	Tricuspid annular plane systolic excursion
TR	Tricuspid regurgitation
TVI-LVOT	Time-velocity integral of the left ventricular outflow tract

Pulmonary arterial hypertension (PAH) is a progressive vascular disorder characterized by obliterative remodeling of the pulmonary arterioles, resulting in increased pulmonary vascular resistance (PVR), elevated pulmonary arterial (PA) pressures, and, ultimately, right ventricular (RV) dysfunction. Initial RV adaptation manifests as concentric hypertrophy to normalize wall stress. However, an increased persistent afterload leads to maladaptive remodeling, RV dilatation, tricuspid regurgitation, and progressive systolic dysfunction, which are hallmarks of RV-PA decoupling and right heart failure syndromes [5, 6]. As right heart strain worsens, the contractile dynamics between the ventricles change. Leftward septal shift and pericardial restraint impair left atrial (LA) and left ventricular (LV) filling, reduce preload, and blunt stroke volume, even in the absence of preexisting intrinsic left heart disease. These changes may lead to subclinical or overt LV dysfunction, a mechanism that is often underrecognized in PAH pathobiology. A recent meta-analysis demonstrated the prognostic value of left-sided parameters. The findings show that for each 1 mL/m² decrease in LV end-systolic or end-diastolic volume index on cardiac magnetic resonance imaging (CMR), mortality risk increased by 2.1% and 2.3%, respectively, despite no direct association with clinical worsening [7]. These findings underscore the functional interdependence between the RV and LV, driven by shared myocardial fibers, the interventricular septum, and the pericardial constraint. In light of the increasing acknowledgment of the interdependence between the right and left heart at the structural and molecular levels [5]. Therefore, we conducted a narrative review to summarize current knowledge on the pathobiology of RV and LV dysfunction, the role of the left heart in pulmonary circulation coupling, and the contribution of left-sided cardiac underfilling and left ventricular impairment in PAH.

Pathobiology of the right and left ventricles

Embryological and structural differences

Embryonic development of the human cardiovascular system occurs between the third and eighth weeks of gestation, and non-uniform heart development begins on the 16th day of gestation. Both ventricles differ in cellular origin, development, and molecular and genetic markers [8]. The first and second cardiac fields emerge after the translation of cardiac progenitor cells from the mesoderm to the anterior primitive vein. The first field forms the cardiac tube, which, in turn, gives rise to the LV and RV, contributing to the RV and outflow tract [9]. During fetal development, the RV accounts for 60% of total cardiac output (CO), and both ventricles have equal thickness and strength. The RV has fewer fibers and is considerably thinner than the LV. Most muscle fibers in the RV-free wall are transverse, with a small proportion of subendocardial longitudinal fibers that provide only 20–30% of the RV ejection fraction (RVEF). Approximately 80% of RV systolic function is induced by septal helicoidal fibers, which twist and shorten the longitudinal axis in the RV [10]. Additionally, the RV has a higher extracellular matrix content than the LV [11].

Physiological differences

The RV contractile process begins at the inlet, progresses through the trabeculated chamber, and culminates at the outflow tract via inward motion of the free wall, longitudinal shortening, and septal bulging. It operates under lower pressure, wall stress, and oxygen demand than the LV. Its efficient ventricular–vascular coupling requires only ~ 20% of the LV stroke volume to generate power [12]. PA pressure and PVR are 20% and 10% of systemic arterial pressure and systemic vascular resistance, respectively, resulting in lower RV oxygen consumption. The low pressures generated by the RV allow blood to perfuse the cardiac chambers throughout the cardiac cycle. Moreover, the collateral vessels of the RV are denser than those of the LV, and the RV has lower muscle mass. Lower oxygen consumption and blood flow result in a lower oxygen extraction reserve, making it more prone to ischemia. However, the RV is susceptible to acute increases in afterload due to its lack of coupling mechanisms. An increase in PA pressure raises intramural pressure, impeding blood supply during systole and increasing blood flow demands during diastole. When blood flow fails to meet an acute or chronic increase in oxygen demand, the RV workload increases [5].

Pulmonary vasculature, right heart driving forces, and hemodynamics

Pulmonary vasculature abnormalities

Vascular remodeling is a defining feature of pulmonary hypertension (PH), characterized by alterations in the vascular and functional systems that primarily affect the distal

pulmonary vasculature. In PAH, these changes are most prominent in the small pulmonary arterioles. When remodeling becomes widespread, PVR increases, pulmonary arterial pressures rise, and the RV initially develops adaptive responses that become maladaptive. A central element of this remodeling process is the progressive accumulation of vascular and inflammatory cells within the vessel wall and the surrounding perivascular space. A complex interplay of pathogenic signaling pathways drives this accumulation. These reflect dysregulated endothelial production of vasoconstrictors and vasodilators, impaired proliferative control of pulmonary concomitant artery smooth muscle cells and fibroblasts, and the influence of prothrombotic and inflammatory mediators [13].

Additionally, perturbations in signaling networks, particularly within the TGF-β/BMP axis, play a critical role in promoting and sustaining the remodeling phenotype. PAH disrupts the low-pressure, high-compliance pulmonary circulation [13, 14]. Owing to its distensible and recruitable capillary bed, the pulmonary vasculature can normally accommodate increased blood flow with minimal changes in pressure [10, 15]. However, in PAH, vessels become stiff, resistant, and noncompliant. Complex vascular lesions and disorganized angiogenic structures, possibly arising from bronchial or vasa vasorum origins, are hallmark features of advanced PAH. This "pseudo-neoplastic" transformation involves upregulation of oncogenes, downregulation of Kv channels, and suppression of mitochondrial and apoptotic signaling pathways [13].

Histologically, PAH is characterized by complex vascular lesions, a hallmark of the disease, and advanced vascular remodeling. Additional features include medial hypertrophy, adventitial fibrosis, endothelial proliferation, thrombosis, and complex vascular lesions, which reduce lumen diameter and increase vascular rigidity [13, 14]. There are four types of vascular lesions: Type 1, arising from supernumerary arteries and connecting to the vasa vasorum; Type 2 involves linking the pulmonary arteries to the peribronchial or bronchial circulation. While this can partially relieve suprasystemic pressure, it can also lead to desaturation; Type 3, occurring at abrupt distal arterial terminations with runoff into dilated pulmonary venules; and Type 4, characterized by obstructed arteries undergoing recanalization. In contrast, PVOD shows predominant venous and microvascular remodeling with patchy capillary hemangiomatosis (Fig. 1). According to Poiseuille's law, resistance increases in proportion to the fourth power of the vessel radius [16], and Laplace's law states that, for a given pressure, a smaller radius, without wall thickening, increases the wall tension. Initially, adaptive medial thickening may therefore become maladaptive, consequently leading to progressive vascular stiffening and remodeling [14].

In PAH, pulmonary veins (PV) shift from pulsatile inflow to steady capillary perfusion. The stroke volume/pulse pressure ratio (which is microvasculature-dependent) and PVR are inversely related. Together, they form a nearly constant resistance-compliance product, given by PVR × compliance. This equation describes the decline of PA pressure during diastole [17, 18]. Proximal PAs, acting as Windkessel reservoirs, lose their energy-buffering function due to increased pulse wave velocity and early wave reflection [19]. This mechanism induces late-systolic RV overload by altering Pascal's law, thereby resulting in labile, pulsatile afterload. The resistance-compliance time decreases, reflecting poor buffering and inefficient RV ejection [18]. Decreased ventricular–vascular coupling indicates significant uncoupling and impaired RV-PA interaction [12]. RV–PA coupling can be estimated noninvasively using the TAPSE (tricuspid annular plane systolic excursion) / PASP (PA systolic pressure) ratio, which reflects the balance between RV contractile function and afterload and mirrors the invasive Ees/Ea ratio. A preserved ratio indicates adequate coupling, whereas a declining ratio signals loss of contractile reserve and progressive uncoupling. As a noninvasive surrogate, a TAPSE/PASP ratio < 0.31 mm/mmHg has been associated with this uncoupling and is prognostic of RV failure and adverse outcomes [20]. Progressive RV-PA uncoupling leads to compromised forward flow, as reflected in a reduced RV outflow tract velocity integral. Uncoupling is suggested in right heart catheterization by elevated RA pressure, reduced stroke volume, and disproportionate RV failure relative to afterload. Other echocardiographic parameters include shortened pulmonary acceleration time (< 90 ms), mid-systolic notching, and septal flattening (systolic pressure overload and diastolic volume overload), which together produce a D-shaped LV. CMR reveals reduced myocardial perfusion reserve, particularly in the RV, resulting in coronary flow dysregulation and causing RV ischemia, dysfunction, and failure [21].

Additionally, pulmonary vascular remodeling in PAH is driven by progressive perivascular cellular accumulation and immune dysregulation within the arterial wall. Endothelial cells, smooth muscle cells, fibroblasts, and inflammatory cells interact in the context of disrupted TGF-β/BMP signaling, promoting endothelial-to-mesenchymal transition, cellular hyperproliferation, and extracellular matrix deposition. Vascular rarefaction and the formation of complex vascular lesions further increase PVR, progressively increase RV afterload, and contribute to functional decline. This evolving molecular environment perpetuates disease progression even when hemodynamic parameters initially appear compensated [14].

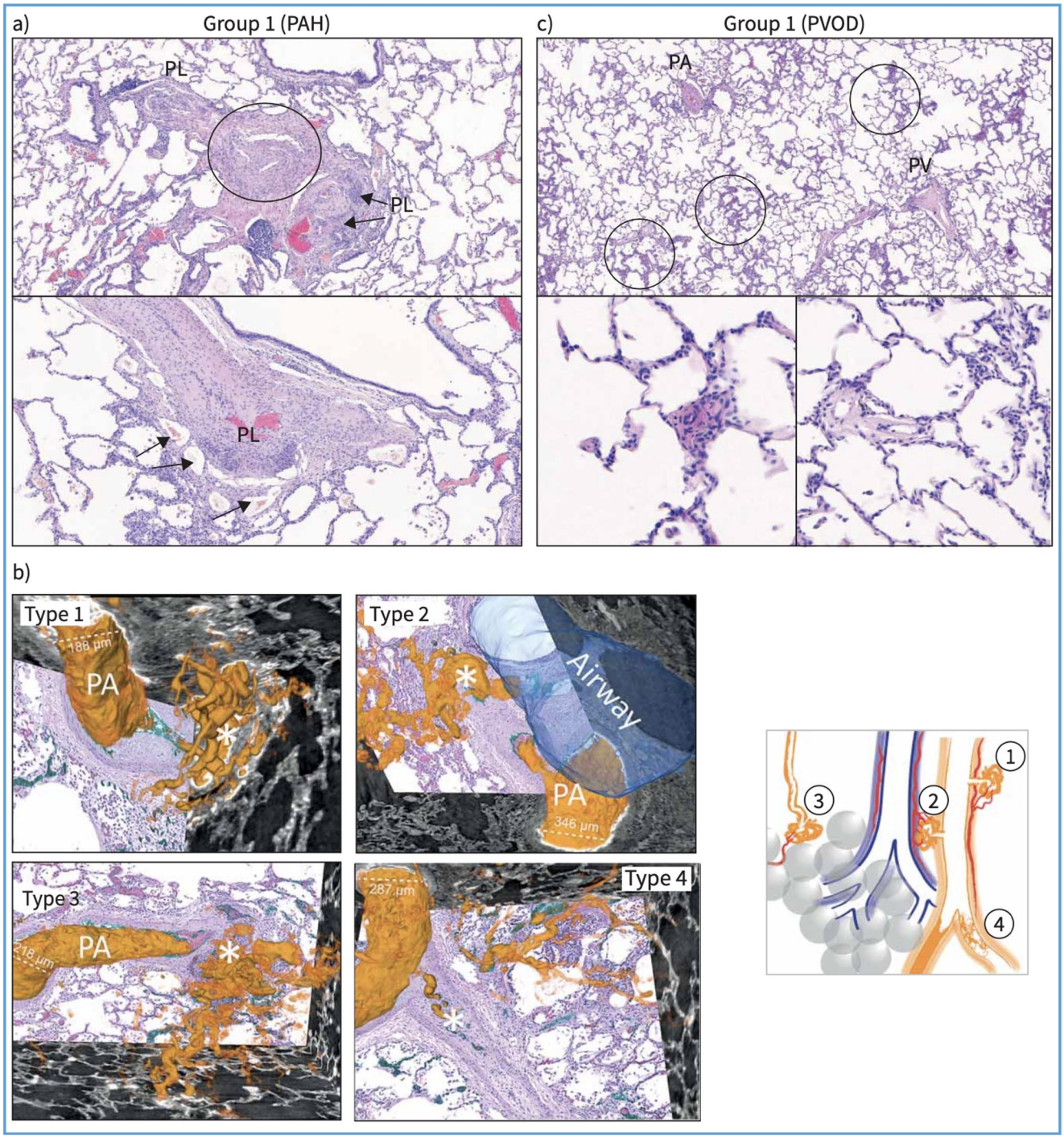


Fig. 1 Spectrum of pulmonary vascular diseases in PH. Reproduced from Guignabert C et al. Pathology and pathobiology of pulmonary hypertension: current insights and future directions. Eur Respir J. 2024; 64:2401095. doi:https://doi.org/10.1183/13993003.01095-2024. © The authors 2024. Distributed under the terms of the Creative Commons Attribution Non-Commercial 4.0 License (CC BY-NC 4.0)

Impaired RV function and cardiac remodeling

As PVR increases and the proximal PAs stiffen, reflected pressure waves return earlier. This increases the late-systolic RV load, according to Pascal's law. This phenomenon is evident in invasive hemodynamics as a late-systolic pressure rise. It correlates with echocardiographic signs, such as shortened PA acceleration time, RV outflow tract notching, and impaired strain or TAPSE [22, 23]. Once the contractile reserve is exhausted, RV-PA uncoupling occurs [20]. The RV, a thin-walled, compliant chamber suited for high-volume, low-pressure flow, is poorly equipped to

handle the elevated afterload resulting from a stiffened pulmonary vasculature. Initially, the RV compensates through concentric hypertrophy and increased contractility, referring to the intrinsic myocardium force-generating capacity and systolic elastance, facilitated by autoregulation and the Frank-Starling mechanism. As the PVR increases 5 to 10-fold, the RV is subjected to higher afterload, and remodeling becomes maladaptive. The following characteristics define this phase: reduced RVEF, dilation, wall thinning, fibrosis, elevated RV end-diastolic pressure despite reduced RV filling and effective preload, impaired RV-PA coupling, and tricuspid regurgitation [24, 25]. CMR reveals this through reduced RV volumes, reduced RVEF, and late gadolinium enhancement at septal hinge points and in shear-stress-related fibrotic regions, all of which correlate with RV dysfunction and outcomes [21]. Functionally, RV strain, especially in the free wall, declines early, before systolic dysfunction [26]. However, persistent overload lowers the RVEF below 35%, inducing systemic hypoperfusion.

Reduced myocardial perfusion reserve in PAH may contribute to impaired myocardial oxygen supply-demand balance and ventricular mechanical dysfunction [27]. The RA enlarges as RV compliance declines; an RA volume index > 74 mL/m² predicts a worse prognosis [28]. Systemic conditions, such as systemic sclerosis, can cause early RV dysfunction even with a modest hemodynamic burden [29, 30]. As PA pressures rise, right coronary perfusion decreases, and RV ischemia becomes a major contributor. Additionally, microvascular rarefaction, metabolic shifts, reduced oxidative phosphorylation, increased glycolysis, and fatty acid oxidation further impair RV contractility [13]. This progressive transition from adaptive RV hypertrophy to maladaptive remodeling and eventual RV–PA uncoupling is paralleled by worsening hemodynamics, rising PVR, and declining CO. Ultimately, RV failure is a key determinant of clinical outcome in patients with PAH. Figure 2 shows the stepwise pathophysiological cascade integrating vascular, ventricular, and hemodynamic changes.

The left heart and its coupling with the pulmonary circulation

Although normal filling pressures define PAH, previous reports suggest that LV mechanics may be altered [31]. As the PVR and RV function deteriorate, LV filling is limited by reduced preload and interventricular septal shift. This phenomenon further contributes to LV dysfunction [32]. Even mild PAH can reduce LV output during stress, and targeted RV volume reduction (e.g., via inferior vena cava occlusion) enhances LV preload, demonstrating the systemic ripple effect of RV strain [33–35]. Other contributors to cardiac workload, including decreased LV torsion, increased RV stress dysfunction, ventricular desynchrony, pericardial constraint, and heart rate, are also likely to contribute to PAH-associated LV changes [31, 36].

Left atrial dysfunction

Reduced pulmonary capillary blood return due to increased PVR and RV dysfunction in advanced PAH leads to decreased LA preload, resulting in diminished LA volume and reduced LV volume [37]. Reports suggest potential atrial remodeling secondary to hemodynamic changes, such as reduced pulmonary venous return; however, strong evidence on LA fibrosis remains limited. A cohort of 326 patients with PAH was analyzed to assess the relationship between RA remodeling and the risk of atrial fibrillation. The LA volume index remained within the RA limits, indirectly suggesting an absence of significant hemodynamic alterations involving the LA [38]. The current evidence suggests that chronic underfilling predominantly drives functional impairment [1, 36], while structural remodeling remains insufficiently characterized.

In a cross-sectional CMR study by Leong et al., the LA volume index and peak LA strain distinguished pre- and post-capillary PH, with patients with idiopathic PAH having normal LA volumes. Nevertheless, they found a reduced LA strain relative to healthy controls, suggesting that functional LA impairment may occur independently of volumetric changes, possibly secondary to reduced preload due to RV failure [38]. Left atrial reservoir strain (LARS), assessed by speckle-tracking echocardiography, has emerged as a sensitive marker of impaired LA compliance and reduced pulmonary venous return in PAH [18, 37]. The LA strain may be a more sensitive and earlier marker of LA dysfunction than volume alone, potentially aiding in risk stratification and early detection of left-sided heart involvement [35, 39]. Recent evidence from Guo et al. [1], demonstrated a modest inverse relationship between LA global strain and the transpulmonary gradient in pre-capillary PH. Another possible explanation is subclinical diastolic dysfunction without LA enlargement [1]. However, more research is needed to explore this observation.

Left ventricular underfilling

RV enlargement directly affects LV diastolic filling through ventricular interdependence, LV end-diastolic volume (LVEDV), and stroke volume. Joong-Gan et al. [39] reported echocardiographic findings that support this hypothesis, demonstrating: (1) early diastolic filling rate is closely linked to interventricular septum curvature at the time of maximal curvature, (2) this filling rate correlates with LVEDV, and

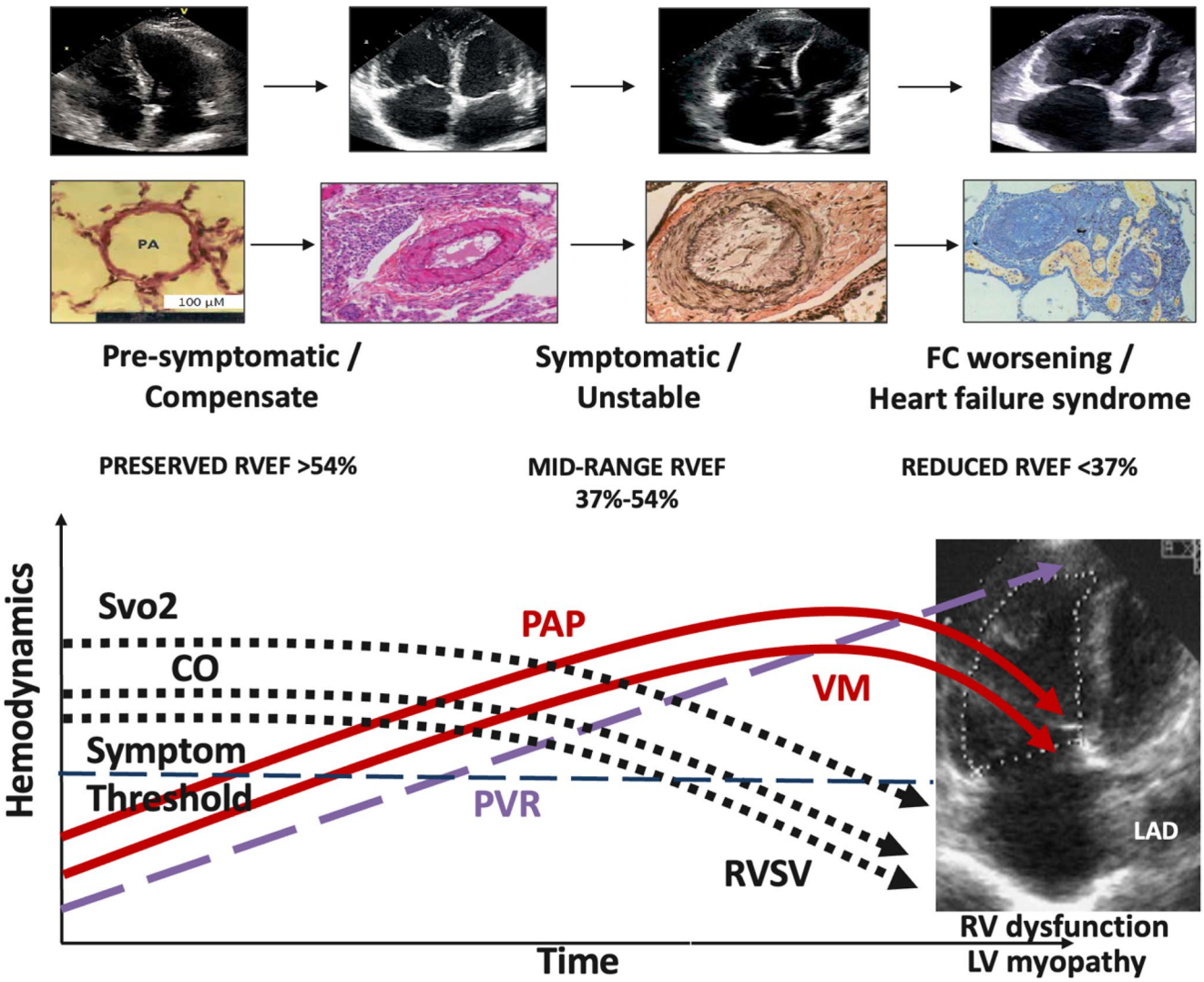


Fig. 2 Progression of PAH from adaptive RV remodeling to RV failure. Schematic representation of PAH progression integrating echocardiographic changes (upper panels), vascular remodeling (lower panels), and hemodynamic changes (central graph). The stages of development are illustrated across three stages: 1) a compensated phase (RVEF >54%) with adaptive RV hypertrophy and preserved CO; (2) a symptomatic/unstable phase (RVEF 37–54%) marked by progressive RV–pulmonary arterial uncoupling; and (3) an advanced right heart failure phase (RVEF <37%) characterized by RV dilation, severe tricuspid regurgitation, reduced forward flow, and LV underfilling. In the central hemodynamic graph, red solid curves represent PAP and VM, both progressively increasing; the purple dashed curve represents PVR, which rises steadily; and black dotted curves represent SvO_2, CO, and RVSV, which decline following RV–PA uncoupling. The horizontal dashed line indicates the clinical symptom threshold. Advanced stages demonstrate interventricular septal shift and reduced LV cavity size, reflecting ventricular interdependence and late biventricular involvement.
Abbreviations: CO: Cardiac output; LA: Left atrium; LV: Left ventricle; PA: Pulmonary artery; PAH: Pulmonary arterial hypertension; PAP: Pulmonary arterial pressure; PVR: Pulmonary vascular resistance; RV: Right ventricle; RVEF: Right ventricular ejection fraction; RVSV: Right ventricular stroke volume; SvO_2: Mixed venous oxygen saturation; VM: Ventricular mass.

(3) LA filling was standard, and with no relation to LVEDV, suggesting LV underfilling is predominantly driven by mechanical septal displacement rather being purely a consequence of LA volume depletion. Advanced PAH compromises LV filling through two parallel mechanisms: serial interaction and direct ventricular interaction. While chronically increased PVR and RV dysfunction reduce pulmonary capillary blood return, thereby reducing baseline LA preload and volume (serial interaction), the dynamic underfilling of the LV during early diastole is largely dictated by direct ventricular interaction. Specifically, right-to-left interventricular septal displacement mechanically restricts the LV cavity in early diastole, an impairment that operates independently of changes in LA volume (Fig. 3)

A mechanistic approach using PV area and flow has been proposed to assess LV underfilling. A recent CMR imaging study demonstrated reduced LV size and end-diastolic volume compared with healthy controls [37]. Notably, PV area

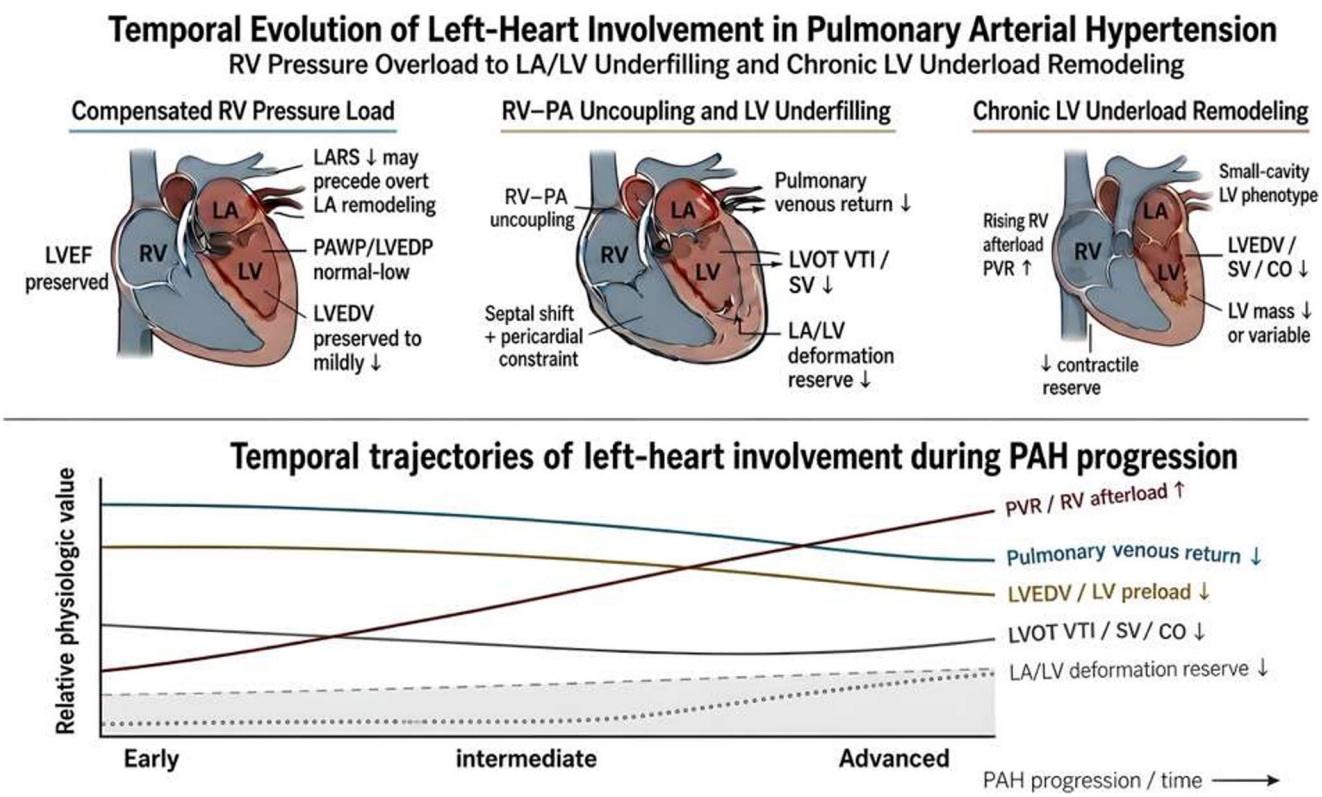


Fig. 3 Temporal Evolution of Left Heart Involvement in PAH. Schematic representation of the temporal evolution of left-heart involvement during PAH. The upper panels illustrate progression from compensated RV pressure overload to RV–PA uncoupling and ultimately chronic LV underload remodeling. Early disease is characterized by preserved LV filling and output despite rising PVR. As RV–PA uncoupling develops, reduced transpulmonary forward flow, septal shift, and pericardial constraint impair pulmonary venous return, progressively lowering LV preload, LVOT-VTI, SV, and CO. Advanced disease is associated with a small-cavity LV phenotype, reduced contractile reserve, diminished LVEDV, and impaired LA/LV deformation reserve.The lower panel schematically depicts the temporal trajectories of these physiologic changes during PAH progression, demonstrating rising RV afterload/PVR alongside progressive reductions in pulmonary venous return, LV preload, LVOT-VTI, SV/CO, and LA/LV deformation reserve.
Abbreviations: CO: Cardiac output; LA: Left atrium; LV: Left ventricle; LVEDV: Left ventricular end-diastolic volume; LVOT-VTI: Left ventricular outflow tract velocity-time integral; PAH: Pulmonary arterial hypertension; PVR: Pulmonary vascular resistance; RV: Right ventricle; RV–PA: Right ventricular–pulmonary arterial; SV: Stroke volume.

was not associated with LV global longitudinal strain (LV-GLS), suggesting that LV dysfunction in PAH is primarily driven by underfilling rather than by an intrinsic myocardial defect. Greater RV dysfunction, abnormal septal configuration, and reduced LV preload are other mechanisms of LV-GLS impairment [39]. These findings underscore the potential value of LV underfilling and PV area measurement as prognostic markers of LV dysfunction in patients with PAH. LV underfilling has been independently associated with adverse clinical outcomes and correlated with more advanced disease [3].

LV underfilling and underload lead to remodeling over time. CMR studies by Simpson et al. [2] and Sjögren et al. [3] have shown that predicted LV mass values are lower in idiopathic and connective-tissue disease PAH subgroups [2], suggesting atrophy secondary to LV underfilling. Normal fluctuations in LV filling are reduced in a sheltered and unchallenged LV, thus eliminating a myocardial growth factor [36]. Chronic underutilization provides the most plausible explanation for LV atrophy. In other settings where the LV is underutilized, such as mitral stenosis, bed rest, zero-gravity conditions, or certain congenital heart diseases, a decrease in its mass has also been reported [36]. However, Guo et al. [1] found that in patients with PAH, the LV undergoes cavity shrinkage and elevated filling pressures. However, no reduction in myocardial mass was observed, resulting in LV underfilling without LV atrophy. Whether chronic LV underfilling leads to LV atrophy in PAH remains controversial. In this context, it is important to distinguish LV preload from LV filling pressure. Although these terms are often used interchangeably in clinical practice, preload more accurately refers to LV end-diastolic myocardial stretch or chamber filling volume. In contrast, filling pressure reflects the pressure measured within the ventricle at end diastole. In PAH, LV preload is typically reduced because of chronic

LV underfilling, septal displacement, and impaired pulmonary venous return. However, LV filling pressures or LV end-diastolic pressure may be normal or even elevated due to altered ventricular compliance, pericardial constraint, and geometric distortion related to ventricular interdependence. Accordingly, elevated LV end-diastolic pressure does not necessarily indicate increased effective LV preload in PAH.

Left ventricular atrophy and dysfunction

Several complementary mechanisms have been proposed to explain LV dysfunction in PAH, including chronic LV underfilling secondary to ventricular interdependence, structural remodeling related to reduced LV workload and atrophy, and secondary intrinsic myocardial alterations involving sarcomeric and molecular remodeling. The following section discusses the available evidence supporting each of these proposed mechanisms. Chronic LV underfilling leads to LV preload deficiency and hypovolemia. Although LVEF may remain within normal limits, global intrinsic LV force-generating capacity may remain relatively preserved despite evidence of molecular, sarcomeric, and ultrastructural remodeling described in advanced PAH. An adaptive atrophic change opposite to RV hypertrophy could explain this phenomenon [36]. The combination of low flow and small left-sided chambers will reduce the need for high contractile force on the left side due to decreased myocardial stretch [4], resulting in an unchallenged LV that becomes deconditioned to higher workloads. Evidence has shown reduced LV contractility and strain, as well as lower LV mass, in patients with PAH compared with healthy controls [31, 40]. Additionally, another study shows that patients with PAH had significantly elevated myocardial fibrosis markers and increased LV T1, which may induce atrophy-related extracellular changes, such as fibrosis and collagen deposition [40]. Importantly, several experimental studies have failed to demonstrate significant LV fibrosis or major collagen remodeling in PAH models despite evidence of altered LV geometry and function. Ishikawa et al. reported no significant increase in LV collagen content in monocrotaline-treated rats. At the same time, Fowler et al. similarly found no increase in myocardial fibrosis despite evidence of ventricular dysfunction [41–43]. Nevertheless, some studies have demonstrated molecular, neurohumoral, and electrophysiologic alterations in the LV despite the absence of overt fibrosis or hypertrophy. Lourenço et al. demonstrated impaired LV contractility and relaxation associated with neurohumoral activation without structural remodeling. At the same time, Hardziyenka et al. identified electrophysiologic remodeling and connexin alterations in the atrophic LV of pressure-overloaded RV failure models [44, 45]. These observations suggest that secondary myocardial adaptation may occur in advanced disease, although the extent to which these changes represent intrinsic irreversible myocardial dysfunction remains uncertain. The LV-GLS and left atrioventricular plane displacement have also been shown to be markedly reduced in patients with PAH, further suggesting impaired LV contractility [4]. Molecular analysis of PAH myocardial biopsies by Manders et al. [4] revealed significant reductions in LV cardiomyocytes' cross-sectional area and maximal force-generating capacity. Contractile weakness is attributed to a reduction in the number of available myosin-based cross-bridges and a decrease in the phosphorylation level of sarcomeric proteins. Moreover, increased LV calcium sensitivity may represent a compensatory mechanism but may also drive LV diastolic dysfunction [46]. The demonstrated atrophy, decreased contractility, and increased calcium sensitivity may explain LV dysfunction in severe PAH. Reduced CO may lead to reduced coronary blood flow, inducing ischemia and adding cause for subclinical LV dysfunction [32]. In addition to altered loading conditions, several experimental studies have demonstrated remodeling at the ultrastructural and protein levels within the LV myocardium in PAH models. Reported abnormalities include reduced t-tubule periodicity, disruption of normal sarcomeric organization, and disorganized ryanodine receptor distribution, suggesting altered excitation-contraction coupling and subcellular remodeling despite the absence of overt fibrosis or severe structural myocardial injury. These findings indicate that chronic RV pressure overload and LV underfilling may induce secondary molecular and ultrastructural adaptations within the LV myocardium. Nevertheless, the functional significance and reversibility of these alterations remain incompletely understood, particularly given the preserved force generation observed in isolated LV trabeculae and the rapid recovery of LV function following relief of RV pressure overload [47].

Although some experimental and translational studies suggest sarcomeric and molecular remodeling in advanced PAH, evidence regarding intrinsic LV contractile dysfunction remains conflicting. Experimental studies using isolated LV muscle strips and trabeculae have demonstrated preserved intrinsic LV mechanical performance despite impaired in vivo LV systolic function. Kögler et al. showed normal contractile function, preserved relaxation, and largely unchanged calcium-handling protein expression in isolated LV trabeculae from monocrotaline-treated rats. In contrast, abnormalities were predominantly confined to the pressure-overloaded RV [48]. Similarly, Han et al. demonstrated that, once RV pressure overload was experimentally removed, the LV recovered normal systolic pressure and stress generation ex vivo and in vitro despite persistent LV atrophic remodeling [49]. These findings support

the concept that LV dysfunction in PAH is predominantly mediated by ventricular interdependence, altered loading conditions, and chronic underfilling rather than by primary intrinsic LV myocardial failure.

Beyond the hemodynamic alterations observed clinically, a constellation of ionic, electrical, and biochemical changes within the LV myocardium has also been described in PAH. Experimental studies have reported prolonged action potential duration, reduced outward potassium currents, increased cardiomyocyte apoptosis, and shifts in myosin heavy chain isoform expression, suggesting secondary myocardial remodeling at the cellular level [50, 51]. These findings suggest that LV remodeling in PAH may extend beyond hemodynamic alterations alone. However, the precise contribution of these alterations to LV mechanical dysfunction and disease progression remains unclear.

Patients with end-stage PAH who undergo lung transplantation may experience transient heart failure secondary to acute LV dysfunction, likely resulting from the sudden re-exposure of an atrophic LV to increased workload despite its anatomic return to normal geometry [46, 52, 53]. However, most patients recover LV function within days to months, suggesting remodeling. In chronic thromboembolic PH, the reduction of LV free wall mass, muscular atrophy, and myocyte shrinkage is reversible after pulmonary endarterectomy, and patients with severe mitral stenosis after mitral valvuloplasty or pulmonary emphysema following lung transplantation have a similar outcome [54]. These findings suggest that prolonged underfilling and chronic ventricular remodeling may eventually induce secondary intrinsic myocardial alterations in advanced PAH. However, the available evidence remains conflicting, and several experimental studies demonstrate that intrinsic LV contractile function is preserved once abnormal loading conditions are removed [4].

LV dysfunction phenotyping and prognostic relevance

The functional interdependence between the RV and LV is increasingly clinically relevant in PAH, especially because left-sided parameters may provide prognostic insights. CMR enables accurate quantification of RVEF and stroke volume index (SVI), both of which are integral to current risk stratification models [55]. Beyond right-sided metrics, LV-GLS assessed by CMR or echocardiography has emerged as a sensitive marker of subclinical LV dysfunction. In a prospective cohort with pre-capillary PH, a reduced LV-GLS was associated with worse survival, and a threshold of < 14.2% identified patients at significantly higher mortality risk [56]. Similarly, echocardiographic studies have shown that impaired LV-GLS (> -15%) is associated with adverse outcomes, even when LVEF remains preserved. Kishiki et al. [30] identified three echocardiographic parameters independently associated with mortality in patients with PAH: RV-free wall strain > -12%, right atrial volume index (RAVi) > 46 mL/m², and LV-GLS > -15% [32]. LV end-diastolic volume index, though not LV mass, also showed prognostic importance in patients with PAH in a meta-analysis.

LA metrics also provide insight into left-sided hemodynamics. Gerges et al. [56] demonstrated that elevated LA volumes and LV filling pressures were independently associated with poorer long-term survival. Another emerging marker identified is LV underfilling. Guo et al. [1] categorized patients with PAH by indexed LV mass/volume ratio (≥ 0.7 g/mL in men and ≥ 0.6 g/mL in women) and found that those with low LV filling and high RV mass had significantly elevated N-terminal-pro-B-type natriuretic peptide measurements, reduced RVEF, and a 2.7-fold increase in all-cause mortality compared with their counterparts. The time-velocity integral of the LV outflow tract (TVI-LVOT) has also demonstrated prognostic utility. In a multicenter study, a baseline TVI-LVOT < 17.1 cm was associated with significantly reduced survival and was an independent predictor of cardiovascular mortality in patients with PAH (HR 0.856, $P = 0.001$) [57]. Collectively, these findings suggest that LV metrics may function as downstream integrators of RV failure severity, rather than independent pathological drivers [1, 4]. In this context, incorporating parameters such as LV-GLS, LA volume, LV underfilling, and TVI-LVOT into routine evaluation may enable more precise risk stratification and earlier identification of patients who may benefit from intensified therapy or closer monitoring. Figure 4 illustrates the interaction between a maladaptive right ventricle and its resulting structural and hemodynamic repercussions on the left ventricle.

Final considerations

Emerging evidence suggests that LV dysfunction in PAH may be at least partially reversible following relief of RV pressure overload. Experimental studies demonstrate normalization of LV systolic pressure and stress generation once abnormal RV loading conditions are removed, while clinical studies have reported rapid recovery of LV performance after pulmonary endarterectomy or relief of pulmonary outflow obstruction. These observations support the concept that many LV abnormalities in PAH predominantly reflect ventricular interdependence and chronic underfilling rather than irreversible intrinsic myocardial injury.

The reversibility of LV dysfunction after relief of RV pressure overload further supports a predominantly load-dependent mechanism of LV impairment in PAH. Experimental studies have shown restoration of normal LV systolic pressure generation ex vivo after removal of RV

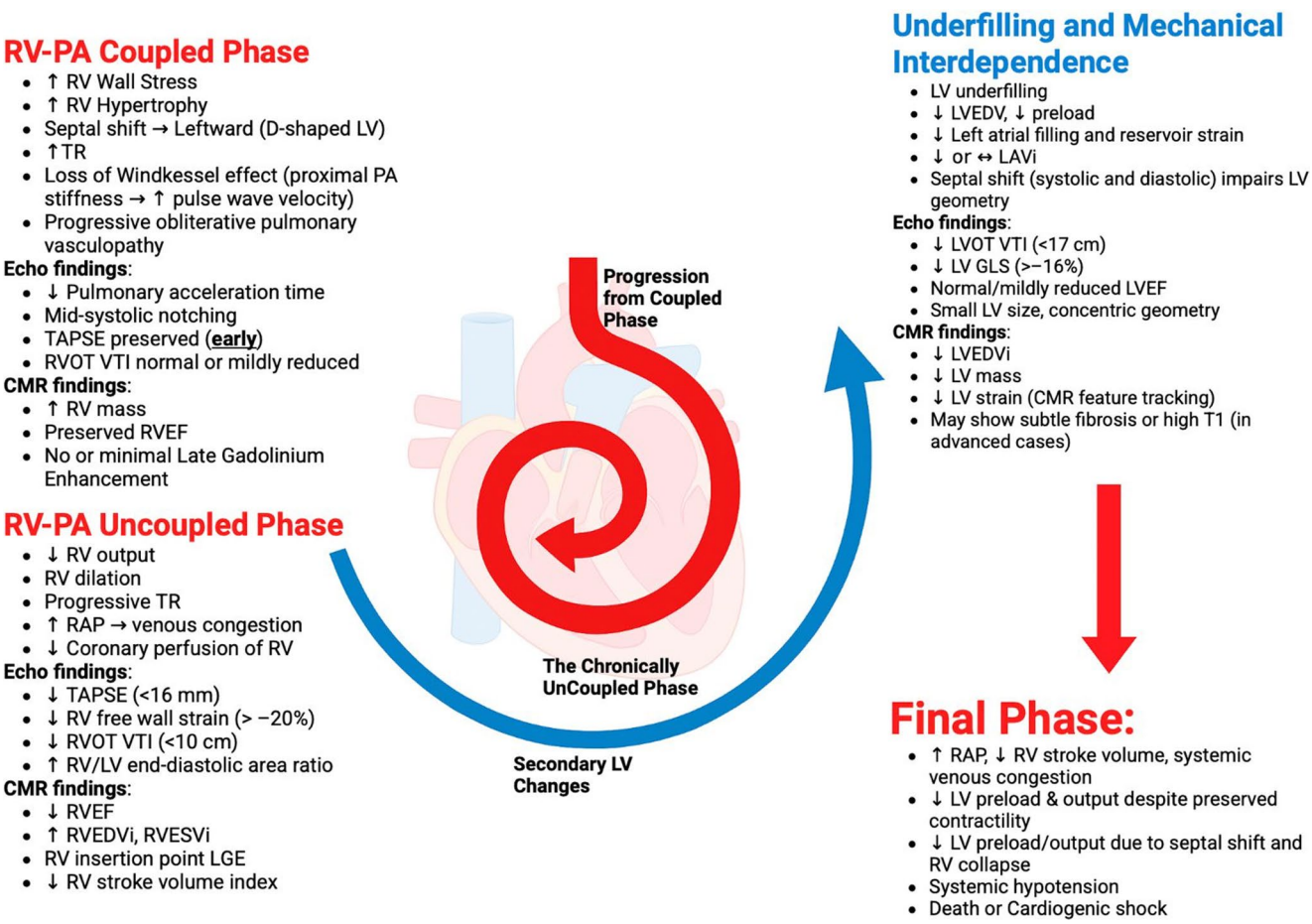


Fig. 4 Pathophysiological cascade of progressive right ventricular dysfunction and left ventricular involvement in pulmonary arterial hypertension. Schematic depiction of progressive RV–PA uncoupling and its impact on left heart structure and function in PAH. The red spiral arrow represents increasing RV afterload and disease burden, while the blue arc indicates transient compensatory adaptation. In the RV–PA coupled phase, adaptive RV hypertrophy preserves systolic function despite rising PVR, with early echocardiographic signs of pressure overload. In the RV–PA uncoupled phase, loss of contractile reserve leads to RV dilation, reduced RVEF, worsening tricuspid regurgitation, and impaired forward flow, accompanied by adverse CMR features including increased RV volumes and late gadolinium enhancement. Chronic RV dysfunction results in interventricular septal displacement and LV underfilling, reflected by reduced LV preload (reduced LV filling volume), impaired LV strain, and decreased LVOT VTI despite preserved or mildly reduced LVEF. In the final stage, advanced biventricular failure culminates in systemic hypoperfusion and multi-organ dysfunction.
Abbreviations: CMR: Cardiac magnetic resonance; LAVi: Left atrial volume index; LGE: Late gadolinium enhancement; LV: Left ventricle; LV-GLS: Left ventricular global longitudinal strain; LVEDV: Left ventricular end-diastolic volume; LVEDVi: Left ventricular end-diastolic volume index; LVEF: Left ventricular ejection fraction; LVOT VTI: Left ventricular outflow tract time-velocity integral; PA: Pulmonary artery; RAP: Right atrial pressure; RV: Right ventricle; RV-PA: Right ventricular–pulmonary arterial; RVEDVi: Right ventricular end-diastolic volume index; RVEF: Right ventricular ejection fraction; RVESVi: Right ventricular end-systolic volume index; RVOT VTI: Right ventricular outflow tract time-velocity integral; TAPSE: Tricuspid annular plane systolic excursion; TR: Tricuspid regurgitation.

pressure overload, despite persistent LV atrophic remodeling. Consistent with these findings, clinical studies in patients undergoing pulmonary endarterectomy or relief of pulmonary outflow obstruction demonstrated rapid normalization of LV systolic and diastolic performance, in some cases within days to weeks after intervention. These observations argue against irreversible primary LV myocardial failure as the dominant mechanism underlying LV dysfunction in PAH and instead support ventricular interdependence and chronic underfilling as central pathophysiological drivers [58].

Future directions and conclusions

This review highlights the increasingly recognized role of the left heart in PAH and underscores the complex interdependence between the right and left ventricles. Progressive RV pressure overload, interventricular septal displacement, pericardial constraint, and chronic LV underfilling contribute to significant alterations in left-sided structure and function, even in the absence of overt left heart disease. Emerging imaging markers such as LV-GLS, LVOT VTI, and LA strain may provide incremental prognostic

information beyond traditional right-sided parameters and may help refine risk stratification in PAH. The evidence suggests that many LV abnormalities observed in PAH primarily reflect altered loading conditions and ventricular interdependence rather than primary intrinsic LV myocardial failure. Experimental studies demonstrating preserved contractile function in isolated LV preparations further support this concept. Nevertheless, whether chronic underfilling and prolonged ventricular remodeling may ultimately induce intrinsic myocardial alterations in advanced disease remains incompletely understood. Accordingly, PAH may be better conceptualized as a dynamic cardiopulmonary syndrome with progressive biventricular interaction rather than an isolated right-sided disorder.

Author contributions M.J.C.G., J.R.R., P.G.F., and C.J.S. conceived the study. M.J.C.G., J.R.R., A.L.M.R., and C.J.S. contributed to the methodology. Investigation was performed by M.J.C.G., J.R.R., J.P., S.A.L., A.L.M.R., E.P.G., H.D.L.G., R.M.A., J.A.M.M., and M.J.S. Data curation was carried out by M.J.C.G., J.R.R., and J.P., while formal analysis was conducted by M.J.C.G. and J.R.R. Validation was performed by C.J.S.R., A.R.R., and C.J.S. Visualization, creation and review of figures was carried out by J.P., A.G.P.B., and C.J.S. The original draft of the manuscript was written by M.J.C.G., J.R.R., J.P., A.L.M.R., E.P.G., H.D.L.G., R.M.A., A.T., D.A., M.J.S., and C.J.S. Review and editing were performed by H.D.L.G., S.A.L., A.G.P.B., and C.J.S.R. Supervision and project administration were provided by C.J.S. All authors reviewed and approved the final version of the manuscript.

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Declarations

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AI disclosure During the preparation of this work, the authors used an AI-based image enhancement tool (Figure-Labs AI Image Enhancer) solely to improve the visual quality and resolution of the central figure. The figure was fully conceptualized and created by the authors using BioRender. No generative AI was used to create or modify the scientific content of the figure. The authors reviewed and edited the final image and take full responsibility for its content.

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