Reviews in Cardiovascular Medicine

Rev. Cardiovasc. Med. **2025**; 26(12): 42395
https://doi.org/10.31083/RCM42395

Review

Right Ventricular Fibrosis With Pulmonary Arterial Hypertension

Xinrui Li[1,†], Peng Liu[1,†], Yongnan Li[2], Yang Liu[1], Wei Hao[1], Ping Jin[1], Rongzhi Zhang[1,*]

[1]Department of Anesthesiology, The Second Hospital & Clinical Medical School, Lanzhou University, 730000 Lanzhou, Gansu, China
[2]Department of Cardiac Surgery, The Second Hospital & Clinical Medical School, Lanzhou University, 730000 Lanzhou, Gansu, China
*Correspondence: ery_zhangrzery@lzu.edu.cn (Rongzhi Zhang)
[†]These authors contributed equally.

Academic Editor: Michael Dandel
Submitted: 24 May 2025 Revised: 15 August 2025 Accepted: 27 August 2025 Published: 19 December 2025

Abstract

Pulmonary hypertension (PH) is a progressive disease caused by structural and functional changes in the pulmonary vasculature resulting from diverse etiologies. PH ultimately leads to increased right ventricular (RV) afterload, RV hypertrophy, fibrosis, and right heart failure (RHF). Moreover, RV fibrosis initially serves as a protective mechanism against pressure overload-induced RV dilatation, but eventually progresses to excessive fibrosis, which impairs cardiac function. This review explores the relationship between RV fibrosis and RV function in PH patients, examines the clinical relevance of this relationship, evaluates techniques for quantifying RV fibrosis, and presents potential therapeutic strategies aimed at preserving right heart function in PH patients.

Keywords: pulmonary hypertension; right ventricular; fibrosis; clinical relevance; right heart failure

1. Introduction

Pulmonary hypertension (PH) is defined as a mean pulmonary artery pressure (mPAP) of $\geq$20 mmHg at rest, as measured by right heart catheterization (RHC). The World Health Organization (WHO) classifies PH into five groups based on etiology: pulmonary arterial hypertension (PAH), PH secondary to left heart disease, lung disease, pulmonary artery obstructions, and multifactorial mechanisms [1,2]. Among these, PAH is one of the most severe subtypes of PH.

The prevalence of PH is estimated to be approximately 1% worldwide, with a higher prevalence in individuals aged >65 years and those with cardiopulmonary complications [2]. PH is also more common in women, with a female to male prevalence of 4.3:1 [3]. The survival of adult patients with PH depends on age, severity of disease, underlying etiology, and the availability of evidence-based treatments [4]. PH is not easily curable and is therefore associated with a high mortality rate.

Right ventricular (RV) function is an important determinant of survival. Initially, the RV undergoes adaptive changes due to pressure overload. As the pulmonary artery pressure increases over time, maladaptive RV hypertrophy develops. This is manifested by reduced RV ejection fraction, pathological fibrosis, elevated end-diastolic pressure, and increased levels of brain natriuretic peptide (BNP) [2]. Early clinical manifestations are dyspnea, usually accompanied by fatigue, angina, dizziness, edema, and syncope. If left untreated, circulatory dysfunction is exacerbated, leading to organ ischemia, hypoxia, and a series of other complications. In severe cases, RV hypertrophy can lead to cardiac arrhythmias or even sudden death.

Pathological fibrosis of the RV is closely related to RV function, as evidenced by the accumulation of extracellular matrix (ECM) and pathological changes in the collagen network [5]. RV fibrosis is a hallmark of virtually all cardiac diseases, and is particularly common in idiopathic pulmonary hypertension and chronic thromboembolic pulmonary hypertension (CTEPH)-induced RV pressure overload [6]. This reactive fibrosis initially acts as a protective mechanism against RV dilatation. However, in the long term it leads to ventricular stiffness, diastolic dysfunction, and right heart failure (RHF), ultimately becoming the most common cause of death in patients with PH. Cardiac fibroblasts (CF), the primary collagen-producing cells, are activated by mechanical stress, neurohormonal stimuli, and inflammatory mediators. Excessive ECM deposition alters myocardial mechanical properties and increases ventricular stiffness, thereby contributing to RV dysfunction [5]. Although the degree of RV fibrosis correlates with disease severity and prognosis, its therapeutic significance is still under debate. Some studies have shown that RV fibrosis is reversible after mechanical unloading and is ameliorated by pharmacological inhibition, but others have shown that inhibition of pro-fibrotic factors does not improve RV function. In this article, we review the molecular mechanisms underlying the development of RV fibrosis and its clinical relevance in PH, as well as preclinical and clinical intervention studies of RV fibrosis in PH.

2. Literature Review

2.1 Normal Right Ventricle

RV function depends on the interaction between cardiomyocytes (CM) and mesenchymal stromal cells. The CM is the major functional cell, while mesenchymal stromal cells provide structural support and are involved in synthesis and regulation of the ECM. CF is the major collagen-producing cell, secreting type I and type III collagen to make up the ECM. Collagen synthesis and degradation are balanced by the actions of matrix metalloproteinases (MMPs) and tissue inhibitors of metalloproteinases (TIMPs) [6]. The ECM supports myocardial function by maintaining myocardial segment length, supporting CM alignment and ventricular morphology, transmitting mechanical forces, and promoting diastolic myocardial re-extension [6].

2.2 ECM Changes and Fibrosis in Pathological Conditions

Myocardial fibrosis is a common ECM remodeling process in various cardiac diseases. In patients with PH, a certain degree of pressure overload increases collagen formation, eventually leading to excessive collagen deposition. This is accompanied by a high rate of collagen renewal driven by the activation of MMPs and TIMPs, which leads to further imbalance in ECM homeostasis and exacerbates fibrosis [7]. RV diastolic stiffness in PAH was shown to coincide with increased RV contractility (Ees) and force-generating capacity of RV CM (active force). This may represent a compensatory response to increased afterload, but excessive contraction can also impair diastolic function. The elevated diastolic pressure stiffness in the RV results primarily from reduced titin protein phosphorylation, causing an approximately 3-fold increase in myofibrillar rigidity [8]. In patients with idiopathic PAH and CTEPH, RV afterload may increase by up to 5-fold, suggesting that RV pressure overload serves as a common triggering factor [5].

2.2.1 Changes in Collagen Type

PH induces significant shifts in collagen composition. Studies have shown that chronic pressure overload and hypoxia in PH lead to increased synthesis and deposition of type I collagen in both the pulmonary vasculature and RV myocardium, making it a dominant marker of fibrotic remodeling [9]. In contrast, type III collagen exhibits variable changes depending on the disease severity, with some reports indicating it shows a relative reduction in advanced PH, contributing to decreased myocardial elasticity [6].

While type I and type III collagen are the most studied in PH, emerging evidence suggests the potential involvement of other collagen subtypes. Type IV collagen for instance, which is typically associated with basement membranes, may also participate in vascular remodeling during PH progression. Additionally, fibrotic stimuli such as transforming growth factor-β (TGF-β), which is upregulated in PH, can modulate collagen cross-linking and alter the type I/III ratio, further impairing ventricular compliance [6].

2.2.2 Analysis of the Myocardial Remodeling Mechanism

Collagen fiber remodeling and loss of tissue anisotropy are key factors in the transition from adaptive to maladaptive remodeling [3]. Beyond collagen content, the microarchitectural reorganization of collagen fibers—particularly their crimping/slack state and reorientation—plays a pivotal role in determining myocardial mechanical behavior in both PH and heart failure with preserved ejection fraction (HFpEF) [3,10]. RV adaptation in PH involves myofiber and collagen fiber realignment to mitigate dilation. However, this can transition to maladaptive remodeling when the stiffness exceeds a critical threshold [3].

The pathological transformation in PH stems from a multilevel cascade involving firstly abnormal collagen deposition and increased fiber tautness which alter myocardial matrix properties. This is followed by myofiber realignment that modifies tissue anisotropy, ultimately leading to geometric remodeling [3]. The similar microstructural adaptation patterns observed in both PH-RV and HFpEF-left ventricular (LV) remodeling underscore the universal importance of evaluating collagen architecture, beyond simply measuring its content.

2.3 Triggers for RV Fibrosis in PH

RV fibrosis in PH patients is influenced by multiple factors, including mechanical stress, neurohormonal systems, ischemia, and inflammation. These factors are interrelated and may act simultaneously [5]. Prolonged stress overload leads to increased fibroblast proliferation and collagen production, dysregulation of integrin expression, release of TGF-β to activate myofibroblasts, upregulation of α-smooth muscle actin (α-SMA), and increased collagen production. CM also respond to mechanical stress by producing TGF-β and angiotensin-II (Ang-II). Increased levels of Galactose lectin-3 (Gal-3) promote TGF-β1-induced cardiac fibrosis by interacting with nicotinamide adenine dinucleotide phosphate oxidase 4 (NOX-4) and NOX-4-derived oxidative stress. Endothelin-1 (ET-1) can mediate RV fibrosis and dysfunction, stimulate fibroblast proliferation, and promote ECM protein synthesis [7]. The endothelial-to-mesenchymal transition (EndMT) is associated with myocardial fibrosis and diastolic dysfunction [7]. Aging is also associated with increased collagen production and decreased collagen degradation [11]. Moreover, gender is a critical variable in ventricular remodeling, with women showing a delayed RV functional decline in PH despite a similar fibrosis burden, possibly due to estrogen-mediated attenuation of collagen cross-linking [12,13] (Fig. 1).

Research has shown that diffuse RV fibrosis is prevalent among patients with PAH and PH-HFpEF. The RV extracellular volume fraction (ECV) in PAH is closely asso-

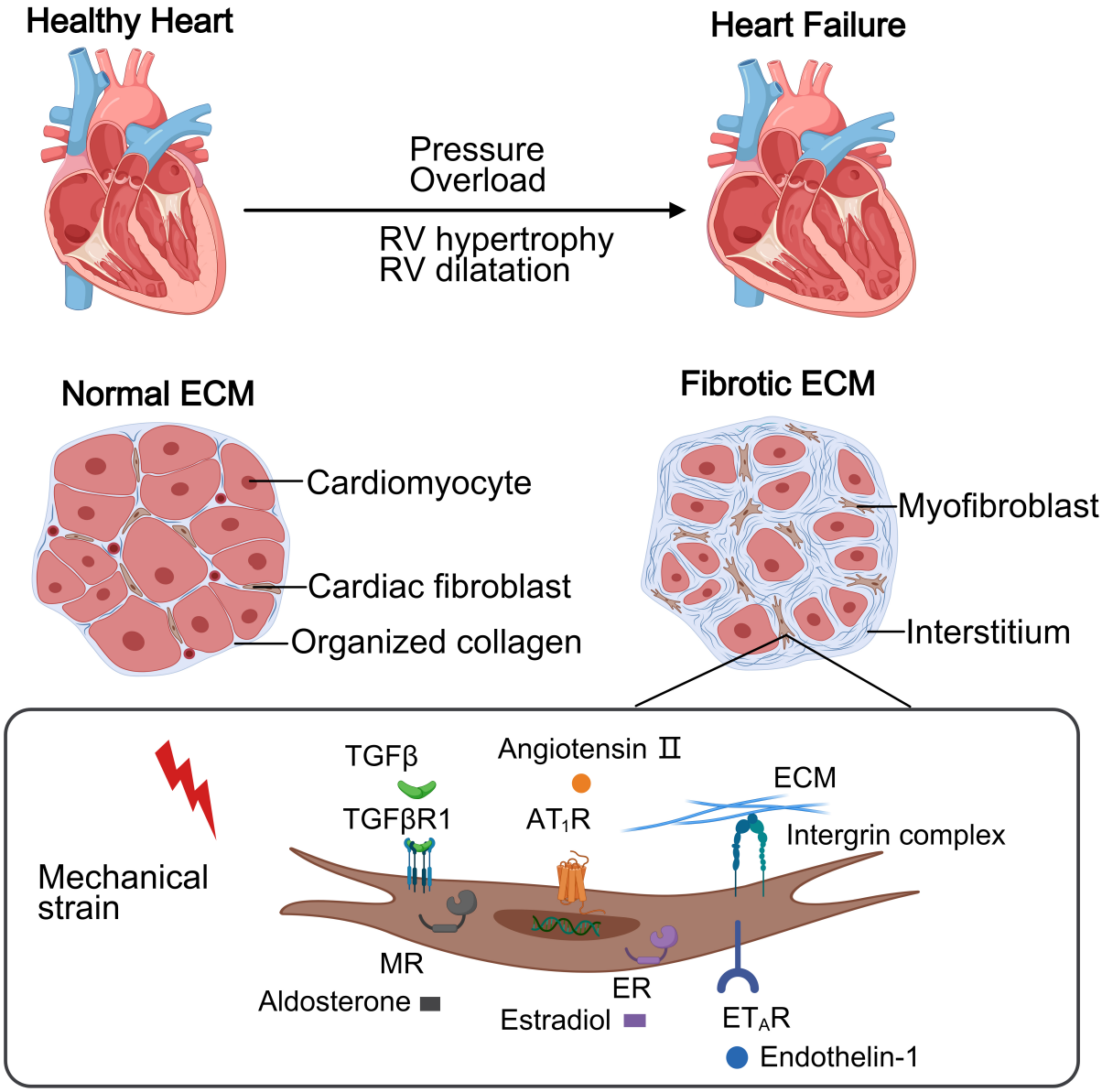

Fig. 1. This schematic contrasts a healthy heart and PH-induced right heart failure. The normal right ventricular (RV) maintains thin walls with organized collagen extracellular matrix (ECM) supporting cellular homeostasis. In PH, pressure overload causes RV hypertrophy and diffuse fibrosis via excessive collagen deposition. Mechanical stress activates cardiac fibroblasts through receptors, driving collagen production and progressive dysfunction. TGFβR1, transforming growth factor beta receptor 1; AT_1R, angiotensin II receptor type 1; MR, mineralocorticoid receptor; ER, estrogen receptor; ET_AR, endothelin-1 receptor type A. Created with MedPeer (www.medpeer.cn).

ciated with total pulmonary resistance (TPR), whereas RV fibrosis in PH-HFpEF shows no significant correlation with afterload. Intrinsic myocardial abnormalities such as LV, left atrial (LA) and RV chamber enlargement, increased RV myocardial stiffness, and reduced strain may play a dominant role in the RV ECV of PH-HFpEF. Although TPR was lower in the PH-HFpEF group than in the PAH group, both exhibited similar degrees of RV fibrosis [14].

2.4 Clinical Relevance

2.4.1 Assessment and Detection of RV Fibrosis

2.4.1.1 Histological Examination. Endocardial myocardial biopsies, surgically excised cardiac tissue, and autopsy specimens can be used to assess RV fibrosis. However, these methods are all invasive and it is therefore difficult to obtain samples in the early stages of disease. Most studies involve patients with end-stage PAH, and small sample sizes may not fully reflect fibrosis in PH patients with different etiologies and at different stages of disease [5]. His-

tological examination can assess interstitial and perivascular fibrosis, but may be unable to distinguish between different collagen subtypes, the degree of collagen cross-linking, and changes in the structural integrity of the ECM.

2.4.1.2 Imaging Techniques. Cardiac Magnetic Resonance (CMR) imaging is currently the gold standard and the main non-invasive method to assess RV fibrosis. CMR provides superior spatial resolution for accurate three-dimensional (3D) analysis of myocardial deformation. It is particularly valuable for detecting subtle regional functional abnormalities in patients with PH [1]. CMR-derived strain parameters in CTEPH show significant correlation with ECM remodeling, offering novel mechanistic insights into RV maladaptation [15]. The degree of RV fibrosis measured by CMR correlates with pulmonary hemodynamics, RV function and volume, and adverse clinical outcomes [16]. However, cardiac fibrosis cannot be detected in the early stages of heart failure (HF). Late gadolinium enhancement (LGE) magnetic resonance imaging (MRI) can detect focal fibrosis in the region of the ventricular insertion site, but the dynamic course of fibrosis is more difficult to ascertain. Longitudinal relaxation time (T1) mapping and ECV measurements provide a more comprehensive picture of diffuse fibrosis, which is closely related to RV dysfunction [5].

Diffusion tensor imaging allows the assessment of tissue composition and structure, while enhanced computed tomography (CT) scans, echocardiography, and circulating markers of collagen metabolism have also been used to assess fibrosis [17]. Speckle-tracking echocardiography (STE) has recently proven to be an effective method for assessing RV function. Reduced right ventricular free wall longitudinal strain (RVFWLS) is a predictor of poor prognosis in patients with PH, and has also been shown to correlate with the degree of RV myocardial fibrosis. Compared to pathological results, 3D-RVFWLS is a non-invasive method for the identification of severe myocardial fibrosis in patients with indicators of end-stage HF [18].

Novel molecular imaging techniques, such as enhanced MRI with collagen-targeted contrast agents, or positron emission tomography (PET) imaging with collagen type I -specific probes, are expected to overcome the limitations of existing techniques [5]. To image the heart and lungs, a bimolecular PET-MRI imaging protocol has been developed using a type I collagen-targeted PET probe (^{68}Ga-CBP8) and a lysine-targeted fibrogenesis MRI probe (Gd-1,4). This approach can assess cardiopulmonary fibrosis, allow staging and early diagnosis of the disease, as well as monitor the response to treatment. However, its feasibility and clinical value require further research [19]. Fibroblast activation protein inhibitor-42 (FAPI-42) can be detected by PET/CT imaging. A recent PET/CT imaging study reported a higher uptake of FAPI-42 in the RV of PH patients, as well as a progressive increase with the duration of pressure overload. PET/CT with [^{18}F]-FAPI-42 can thus be used as a noninvasive tool to accurately assess RV fibrosis and the development of RHF [20].

2.4.1.3 Biomarkers. Collagen triple helix repeat-containing protein 1 (CTHRC1) was reported to be a promising biomarker associated with RV functional impairment and fibrotic remodeling in PH, with particular relevance for monitoring therapeutic response to balloon pulmonary angioplasty in CTEPH [21]. Among the validated markers of ECM turnover, MMP-9 and TIMP-1 levels show robust correlations with disease severity in PAH, reflecting ongoing collagen dysregulation [11]. Advanced imaging biomarkers including ECV quantification and T1 mapping provide early detection of fibrotic changes, with elevated ECV and prolonged T1 relaxation times frequently preceding measurable contractile dysfunction, as evidenced by their dissociation from RV ejection fraction [5,14]. This temporal pattern suggests the above parameters may serve as sentinel markers of subclinical RV pathology.

Several novel circulating proteins show diagnostic and prognostic potential across the PH spectrum. An increased level of COL18A1/endostatin (ES) was observed early in RV disease progression and showed strong associations with histologically confirmed fibrosis [22]. Furthermore, cartilage intermediate layer protein 1 (CILP-1) appears to regulate myocardial fibrotic responses and may predict incident RV dysfunction in both PH and HF populations [23]. The pleiotropic effects of fibroblast growth factor 23 (FGF-23) extend to maladaptive RV remodeling processes [24]. They are paralleled by systemic indicators such as soluble ST2 and GDF-15 that show particular utility in stratifying the risk of impending RV failure [25].

2.4.1.4 Clinically Relevant Animal Models. Currently, the most commonly used animal models for PH research include the monocrotaline (MCT)-induced model, the Sugen hypoxia (SuHx)-induced model, and the pulmonary artery banding (PAB) model. The experimental animals used include rats, mice, pigs, and sheep. While the PAB model offers valuable insights into RV targeted therapies, it does not reflect changes in pulmonary vascular resistance (PVR) [6]. A dynamic PH with RHF model was developed in sheep. This was achieved by ligating the left pulmonary artery, progressively tightening the main pulmonary artery fascicle and implanting an RV pressure catheter, adjusting the rate of fascicle tightening to control the disease severity and RV phenotype, and assessing the effects of exercise in conjunction with exercise testing. The model successfully induced elevated RV pressures and ventricular remodeling and dysfunction. Moreover, it could induce varying degrees of RHF and fibrosis depending on the rate of fascicle tightening [26].

Table 1. Clinical trials targeting RV fibrosis.

Intervention	Target mechanism	NCT number	Results	Status	Phase
Eplerenone	RAAS	NCT00703352	N/A	Completed	Phase 4
Spironolactone	RAAS	NCT03593317	N/A	Not yet recruiting	Phase 2
		NCT03344159	N/A	Recruiting	Phase 4
Sacubitril/Valsartan	ARNI	NCT04197050	N/A	Not yet recruiting	Phase 4
Trimetazidine	FAO	NCT03273387	No significant reduction in RV fibrosis	Completed	Phase 2/3
Sotatercept	BMPR2/TGF-β	NCT06658522	No significant reduction in RV fibrosis	Not yet recruiting	Phase 4

RAAS, renin-angiotensin-aldosterone system; ARNI, angiotensin receptor-neprilysin inhibitor; FAO, fatty acid oxidation; BMPR, bone morphogenetic protein receptor; N/A, not applicable; NCT, national clinical trial.

Table 2. Preclinical trials targeting RV fibrosis (vasodilatory agents).

Target	Therapeutic drug	Animal model	Main result			Ref
			RV Function	RV Fibrosis	PVR	
Prostacyclin analogs	Iloprost	SuHx rat, PAB rat	↑	↓		[32]
sGC stimulation	Riociguat	SuHx rat, PAB rat	↑	↓		[33]
PDE-5 inhibition	Sildenafil	SuHx rat, PAB rat	↑	↓		[34,35]
AMPK activator	Metformin	MCT rat	↑	↓		[36]

sGC, soluble guanylate cyclase; PDE-5, phosphodiesterase type 5; AMPK, adenosine 5′-monophosphate (AMP)-activated protein kinase; MCT, monocrotaline; SuHx, sugen hypoxia; PAB, pulmonary artery banding; ↑, increased; ↓, decreased; PVR, pulmonary vascular resistance.

2.4.2 Relationship of RV Fibrosis to Prognosis

RV fibrosis is strongly associated with poor prognosis in patients with PAH. Decreased longitudinal strain serves as a significant predictor of poor prognosis in PH, with the pathophysiological basis primarily involving three key mechanisms: (1) Myofiber disarray—realignment of collagen and myofibers disrupts normal force transduction, substantially impairing contractile efficiency; (2) Microvascular dysfunction—hypoxia-induced capillary rarefaction exacerbates energy deficiency in longitudinally-oriented subendocardial fibers; and (3) Ventricular-arterial uncoupling—strain abnormalities directly reflect increased RV afterload secondary to elevated PVR, thus accelerating cardiac decompensation [27]. The combined assessment of strain parameters with CMR analysis may have superior predictive value for clinical outcomes compared to conventional RV functional indices [15].

Fibrosis at the ventricular insertion, mainly characterized by increased LGE, T1, and ECV, is an important indicator of poor prognosis. Increased T1 relaxation time and ECV may serve as early markers of PH disease progression. They suggest an early onset of septal shift, and are thus becoming important tools in the risk assessment of PH patients [5]. However, most existing studies are based on patients with end-stage PAH, and hence the prognostic value of these markers in the early stages of disease requires further investigation.

2.4.3 Reversibility of RV Fibrosis

RV fibrosis is a dynamic process, with partial reversibility observed in preclinical models. Reversal of RV hypertrophy, or "reverse remodeling" by targeted therapy, may improve the prognosis of PH. In severe PH, reverse RV remodeling is associated with reduced PVR [28]. RV function has been shown to improve after pulmonary endarterectomy, although RV fibrosis persists in some areas [29]. Mechanical unloading may also lead to partial reversal of RV fibrosis. Treatment with Iloprost can partially reverse established RV fibrosis by inducing collagen degradation and reducing neo-collagen synthesis [5]. A recent study employed 3D deep tissue imaging to compare the RV microvascular network between PAB mice and PH patients [30]. This work revealed complex microvascular remodeling in banded mice, with vessels stably wrapped around hypertrophied CM surfaces. Of note, these changes proved reversible upon the release of banding. In contrast, the microvascular-CM contact in fibrotic regions of the ECM remained impaired. Further investigation of the reversibility of RV fibrosis is therefore needed to optimize treatment strategies.

2.5 Treatment Strategy

In recent years, an increasing number of studies have focused on therapeutic strategies that target RV fibrosis to improve RV function and prognosis. However, only a few clinical trials have investigated RV fibrosis (Table 1). Sotatercept, which targets the Bone Morphogenetic Protein Receptor Type 2 (BMPR2)/TGF-β pathway, was found to reduce Right Ventricular End-Diastolic Volume (RVEDV)

Table 3. Preclinical trials targeting RV fibrosis (inhibition of RAAS and modulation of adrenergic signaling).

Target	Therapeutic drug	Animal model	Main result			Ref
			RV Function	RV Fibrosis	PVR	
ARNi	Sacubitril/Valsartan	SuHx rat, PAB mice	↑	↓	↓	[37,38]
Ang II	ACE2	PAB mice	↑	=		[39]
MR/RAAS	Spironolactone	MCT rat		=	↓	[40]
		Hx mice		↓	↓	[40]
α1A-adrenoceptor, agonism	A61603	Bleomycin mice	↑	↓	=	[41]
		PAB mice	↑	=		[42]
β-blockers	Bisoprolol, Carvedilol, Metoprolol	MCT rat	↑	↓	=	[43–45]
Reduction of heart rate	Ivabradine	SuHx, MCT, PAB rat	↑	↓	=	[46]
β3-adrenergic receptor agonists	CL316243	Hx mice, SuHx mice	↑	↓	↓	[47]

Ang, angiotensin; ACE, angiotensin-converting enzyme; ↑ , increased; ↓ , decreased; =, no effect.

Table 4. Preclinical trials targeting RV fibrosis (growth factors and metabolic modulation).

Target	Therapeutic drug	Animal model	Main result			Ref
			RV Function	RV Fibrosis	PVR	
Galectin-3 inhibition	N-acetyllactosamine	PAB mice	=	↓		[49]
	Pirfenidone	SuHx rat	↑	↓	↓	[50]
TGF-β inhibition	Pirfenidone	PAB mice	=	↓		[49]
	Nintedanib	SuHx rat	=	↓	=	[51]
Induction of BMP signaling	FK506	PAB mice, BMPR2 mutant mice	↑	↓		[52]
PDGFR inhibitor	Sorafenib, Sunitinib	MCT rat, PAB rat	↑	↓	↓	[53]
	Trimetazidine, Ranolazine	PAB rat	↑	↓		[54]
FAO inhibition	Ursolic acid	MCT rat	↑	↓		[55]
	Acetazolamide	SuHx rat	↑	↓	↓	[56]
PPARγ activation	Pioglitazone, chrysin	MCT rat, SuHx rats	↑	↓	↓	[57,58]

PDGFR, platelet-derived growth factor receptor; PPAR, peroxisome proliferator-activated receptor; FK506, tacrolimus; ↑ , increased; ↓ , decreased; =, no effect.

and RV mass, thus showing promise for reversing RV remodeling and improving fibrosis [31] (Table 2, Ref. [32–36]). Most drugs reduce pressure overload by targeting the pulmonary vasculature, and preclinical trials have shown that reducing RV fibrosis directly improves RV function. Preclinical therapies that target RV fibrosis are discussed below in the context of the molecular mechanisms that underlie the development of RV fibrosis.

2.5.1 Renin-Angiotensin-Aldosterone System (RAAS)

The RAAS system plays an important role in the pathogenesis of PAH. Dysregulation of RAAS affects the pulmonary vasculature, and this system is also directly involved in the development of cardiac fibrosis. Pressure overload induces ACE production to generate Ang II. The pro-fibrotic effects of Ang II are associated with activation of TGF-β signaling, while the binding of Ang II to the angiotensin type 1 receptor (AT1R) can also induce pro-fibrotic signaling independently of TGF-β. Activation of AT1R leads to phosphorylation of Smad2 and Smad3 via the extracellular signal-regulated kinase (ERK)/p38 mitogen-activated protein kinase (p38)/c-jun N-terminal ninase (JNK) pathway, which promotes CF activation and collagen synthesis [6]. Blocking of the Ang II receptor reduces cardiac fibrosis by attenuating EndMT [7]. Angiotensin signaling releases aldosterone, which induces activation of the salt-receptor and acts as a transcription factor to promote expression of pro-fibrotic genes. Clinical studies of the effects of RAAS inhibitors (Table 3, Ref. [37–47]) on RV fibrosis have generated great interest [6].

2.5.2 Adrenergic Signaling

Abnormalities in the adrenergic signaling pathway have also been reported in patients with PAH. *In vitro* experiments have shown that activation of the β-adrenergic receptor promotes fibroblastogenesis and induces fibrotic remodeling through the phosphoinositide 3-Kinase (PI3K), p38 and ERK pathways via the calcineurin-Nuclear Factor of Activated T-cell (NFAT) pathway. Prolonged β-adrenergic stimulation may lead to RV fibrosis [6]. The β3-adrenoceptor agonist CL316243 reduces RV systolic blood pressure to a similar extent as leucovorin and sildenafil. This agonist has been shown to reverse pulmonary vascular remodeling, reduce RV afterload, and decrease RV hypertrophy and fibrosis in hypoxic models [47] (Table 3, Ref. [37–47]).

2.5.3 Growth Factor Therapy

Growth factors play a key role in the development of RV fibrosis, with the TGF-β superfamily being the most widely studied pro-fibrotic factor. Increased levels of TGF-β are observed in pressure overloaded RV. The induction of BMP signaling may also have antifibrotic effects [6]. A recent study reported a novel, non-metallic nano-enzyme MMP that attenuates pulmonary vascular remodeling and RV fibrosis in MCT rats by inhibiting the TGF-β1 reactive oxygen species (ROS) signaling pathway and reducing the expression of TGF-β1 and its downstream signaling molecules Smad/3 [48]. It has an excellent *in vivo* safety profile, thus providing a new strategy for the treatment of RV fibrosis. Expression of the transcription factor Forkhead box O3 A (FOXO3A) in myocardial wall tissue gradually decreases with disease progression, whereas the expression of BNP and collagen types I and III increase. It has been suggested that reduced FOXO3A expression may be associated with RV dysfunction (Table 4, Ref. [49–58]), and is therefore a potential target for intervention in RV myocardial fibrosis [18].

2.5.4 Compensation of ECM Remodeling

Excessive deposition and abnormal cross-linking of ECM are important features of RV fibrosis. Lysyl oxidase (LOX) and lysyl oxidase homolog (LOXL2) catalyze collagen cross-linking, and their overexpression can exacerbate fibrosis. Inhibition of LOX/LOXL2 activity reduces collagen cross-linking and attenuates RV fibrosis [11]. The TGFβ1-Snail Family Transcriptional Repressor 1 (Snai1)-LOXL2 axis is central to the regulation of RV fibrosis, and targeting Snai1 inhibits fibrosis, thereby improving PH-RVF [59]. The non-antihypertensive metabolite of chlorosartan, EXP3179, reduces LOX overexpression and increases its activity, thereby preventing collagen cross-linking [11]. Activation of the adenosine A2B receptor (A2BAR) promotes CF proliferation and myofibroblast differentiation, thus exacerbating RV remodeling, but has a lesser effect on collagen production. Blocking A2BAR may be a potential strategy for the attenuation of RV remodeling and RHF [60]. Strategies that target ECM remodeling are still at an early stage and require further investigation.

2.5.5 Metabolic Regulation

2.5.5.1 Metabolic Characteristics of RV Fibrosis. Cardiometabolic abnormalities, particularly the Warburg effect of aerobic glycolysis, are a fundamental pathological feature in the development of RV fibrosis among PH patients [7]. Characteristic metabolic shifts include upregulated glycolysis and glucose oxidation, alongside impaired β-oxidation. These alterations lead to lipotoxicity when the fatty acid supply exceeds the mitochondrial oxidative capacity, with excessive mitochondrial fragmentation disrupting the fibroblast proliferation-apoptosis equilibrium and collectively promoting fibrotic remodeling. Systemic metabolic dysfunction has been identified as a modifiable risk factor for RV failure, with aberrant fatty acid oxidation (FAO) representing a key diagnostic hallmark [61].

2.5.5.2 Metabolic-Targeted Therapeutic Strategies. Excessive protein glycosylation exacerbates RV dysfunction in preclinical PAH models via the suppression of FAO [62]. Chrysin (CH) has multi-target effects in SU5416/hypoxia-induced PAH models. It ameliorates cardiac fibrosis, RV hypertrophy and PH through the coordinated regulation of mitochondrial biogenesis, energy metabolism, and gene expression [58]. Metformin is another pleiotropic agent, with phase II trial data (NCT01884051) indicating RV functional improvement and modulation of lipid metabolism in PH patients (Table 4, Ref. [49–58]). Mechanistic studies in MCT-treated rats demonstrate its capacity to activate adenosine 5′-monophosphate (AMP)-activated protein kinase (AMPK) signaling, enhance nitric oxide bioavailability, preserve contractile function, and prevent fibrotic remodeling [36].

2.5.6 Anti-inflammatory and Antioxidant Therapy

2.5.6.1 Pathological Mechanisms. The pathogenesis of RV fibrosis induced by pressure-overload involves synergistic interactions between chronic inflammatory activation and mechano-sensitive ROS generation [6,7]. Mechanical stretching triggers inflammatory cascades while simultaneously increasing oxidative stress, thereby creating a self-perpetuating cycle that drives fibrotic progression.

2.5.6.2 Therapeutic Intervention. Dihydromyricetin reduces inflammatory responses and ameliorates fibrosis and RV hypertrophy by inhibiting cellular pyroptosis mediated by the chemokine-like factor 1 (CKLF1)/C-C motif chemokine receptor 5 (CCR5) axis [63]. Lingguizhugan decoction [64] and notopterol from Qiang-Huo [65] may improve RV fibrosis and dysfunction by modulating multiple inflammatory pathways and immune cell activities [64]. Tripotassium hydroxycitrate hydrate reduces inflammation and oxidative stress levels and effectively attenuates RV fibrosis and pulmonary vascular remodeling [66]. Melatonin attenuates CM hypertrophy and mitochondrial oxidative stress and improves RV fibrosis in rats by activating the Mst1-Nrf2 signaling pathway [67] (Table 5, Ref. [63–84]).

Non-pharmacological interventions also show promise in attenuating disease progression. Diet-induced ketosis improves RV function, inhibits NOD-like receptor protein 3 (NLRP3) inflammatory vesicle activation, and counteracts RV fibrosis [85]. Swimming exercise has also been shown to improve RV structural remodeling and dysfunction, thereby reducing inflammation by improving systemic and RV insulin sensitivity [86].

Table 5. Preclinical trials targeting RV fibrosis (anti-inflammatory and antioxidant).

Target	Therapeutic drug	Animal model	Main result			Ref
			RV Function	RV Fibrosis	PVR	
Anti-inflammatory; AKT/ERK inhibition	Celastrol	MCT rat/Hx mouse/SuHx rat	↑	↓	↓	[68,69]
Anti-inflammatory, Nrf2	Sulforaphane	SuHx mice	↑	↓	↓	[70]
Nrf2 induction	Protandim	SuHx rat	↑	↓	=	[71]
Anti-inflammatory; ROCK inhibition	Tsantan Sumtang	Hx rat	↑	↓	↓	[72]
Anti-inflammatory, P38/MAPK	Magnesium lithospermate B; PH797804	PAB mice	↑	↓		[73,74]
Anti-inflammatory: TLR9/ NFκB	E6446/Pyrrolidinedithiocarbamate	PAB rat	↑	↓		[75]
ASK1/p38/JNK inhibition	GS-444217	MCT rats, SuHx rat, PAB mice	↑	↓		[76]
AKT inhibition	Nitrite	PAB mice	↑	↓		[77]
Anti-Inflammatory	Perillyl alcohol/quercetin/berberberine, Dihydromyricetinn, Lingguizhugan decoction, Notopterol	MCT rat	↑	↓		[63–65,78]
Anti-Inflammatory	Sevoflurane, 1,8-Cineole; Compound X	MCT rat	↑	↓	↓	[79–81]
Anti-inflammatory/antioxidant	EUK-134, Fluvoxamine	MCT rat	↑	↓	=	[82,83]
Anti-Inflammatory	hydroxycitric acid tripotassium hydrate	MCT rat, Hx rat	↑	↓		[66]
Antioxidant, activation of Mst1-Nrf2 pathway	Melatonin	MCT rat	↑	↓		[67]
Anti-Inflammatory	Vagal nerve stimulation	PAB rat	↑	↓		[84]

AKT, protein kinase B; ERK, extracellular regulated protein kinases; Nrf2, nuclear factor erythroid-derived 2-like; ROCK, rho-associated kinase; MAPK, mitogen-activated protein kinase; TLR, toll-like receptor; NFκB, nuclear factor kappa-B; ASK1, apoptosis signal-regulating kinase 1; JNK, c-Jun N-terminal kinase; Mst1, macrophage stimulating 1; ↑ , increased; ↓ , decreased; =, no effect.

Table 6. Preclinical trials targeting RV fibrosis (other treatments).

Target	Therapeutic drug	Animal model	Main result			Ref
			RV Function	RV Fibrosis	PVR	
Serotonin signaling antagonists	Terguride, SB204741	PAB mice	↑	↓		[87]
nAChR inhibition	Mecamylamine	SuHx rat	↑	↓	=	[88]
ER	17β-estradiol	MCT rat, SuHx rat	↑	↓	↓	[89,90]
ROCKs and STAT3 inhibition	Dehydroepiandrosterone	SuHx rat	↑	↓	↓	[91]
SGLT2 inhibition	Empagliflozin, Canagliflozin	MCT rat	↑	↓	↓	[92,93]
Genetics	H19 Gapmer	MCT rat, PAB rat	↑	↓	=	[94]
Stem cell therapy	Umbilical cord blood mononuclear cells	PAB mice	↑	↓		[95]
	pediatric cardiac progenitor cells	PAB rat	↑	↓		[96]
	Mesenchymal stem cells	PAB pig, SuHx rat	↑	↓		[97,98]
	Human induced pluripotent stem cells	PAB rat	↑	↓		[99]
CaSR	NPS2143	MCT rat, Hx mouse	↑	↓	↓	[100]
Genetics	siRNA AP-1	MCT rat	↑	↓		[101]
HMOX1/GSH inhibition	Ferrostatin-1	MCT rat	↑	↓		[102]

nAChR, nicotinic acetylcholine receptor; ER, estrogen receptor; STAT, signal transducer and activator of transcription; SGLT2, sodium-glucose cotransporter 2; CaSR, Ca^{2+}-sensing receptor; HMOX1, heme oxygenase 1; GSH, glutathione r-glutamyl cysteinyl +glycine; ↑, increased; ↓, decreased; =, no effect.

2.5.7 Other Treatments

The experimental field of non-coding RNAs in the treatment of RV fibrosis is still very limited (Table 6, Ref. [87–102]). Genes associated with the epithelial-mesenchymal transition and EndMT are significantly enriched in RHF [6], and stem cell administration may be an option for targeting RV fibrosis. Human induced pluripotent stem cell-derived myocardium patch transplantation improves RV function, inhibits ventricular fibrosis, and increases capillary density, thus warranting further clinical studies [99].

2.5.8 Indirect Treatments

Several interventions have been shown to indirectly reduce RV fibrosis by improving pulmonary vascular remodeling. A novel lysosomal autophagy inhibitor, ROC-325, was effective in preventing MCT- and Sugen5416/hypoxia-induced PH, vascular remodeling, and RV hypertrophy, fibrosis and dysfunction. The mechanism may be related to inhibition of autophagy, induction of endothelial nitric oxide synthase activity, reduction in the levels of Hypoxia-Inducible Factor 1 Alpha (HIF-1α) and Hypoxia-Inducible Factor 2 Alpha (HIF-2α), and increased NO production [103]. Pharmacological inhibition of Ang II signaling by diminazene reduced both PVR and RV fibrosis, with possible indirect cardioprotective effects [6].

A novel and highly selective inhibitor of platelet-derived growth factor receptor (PDGFR), WQ-C-401, was shown to decrease collagen I synthesis and increase α-SMA expression in pulmonary artery smooth muscle cells, inhibit pulmonary vascular remodeling by reducing muscle formation and fibrosis, and attenuate RV hypertrophy in MCT rats [104]. Salidroside reduced the mean pulmonary arterial pressure and ameliorated RV hypertrophy, collagen deposition, and fibrosis in PAH rats by modulating arginine metabolism, increasing NO synthesis, and improving pulmonary vascular remodeling [105]. Treatments involving vagus nerve stimulation [84] and noninvasive focused ultrasound of the spleen [106] were shown to significantly reduce RV systolic blood pressure and ameliorate RV fibrosis in a rat model of PAH. However, it is unclear whether this is a direct effect on the RV, or a secondary alteration after afterload reduction.

3. Conclusions

RV fibrosis due to PH is a complex process in which the clinical significance and therapeutic strategies remain to be thoroughly elucidated. Emerging evidence suggests that RV dysfunction and PH-like hemodynamics may persist in diverse clinical contexts [107]. Some patients with cardiopulmonary injury show characteristic symptoms such as fatigue and exertional palpitations, accompanied by mild PH and significant RV systolic dysfunction. Notably, symptom resolution often parallels RV functional recovery, suggesting a potentially reversible process. These observations highlight the fact that impairment of RV pulmonary circulation is a common pathological feature across multiple disease states.

RV fibrosis appears to have a dual role in PAH. In the early stages, it is an adaptive response of the RV to pressure overload and allows structural integrity to be maintained. However, as the disease progresses, excessive fibrosis leads to RV dysfunction and ultimately to RHF. The transition from an adaptive to a maladaptive response is dynamic, and some fibrosis may be reversible. Current studies have focused on the ventricular insertion site. Reduced longitudinal strain in the RV free wall has been shown to correlate with the degree of RV myocardial fibrosis and may serve as

a marker of poor prognosis in patients with PH [18]. Imaging techniques, particularly T1 mapping and ECV measurements, are valuable in assessing RV fibrosis and may be important indicators for early diagnosis and prognosis [5]. Novel molecular imaging techniques and biomarker studies are also being refined to provide new tools for staging and early diagnosis of the disease, as well as for monitoring treatment response.

Chronic mechanical stress-induced CF activation and chronic inflammation are key underlying factors in the mechanism of RV fibrosis. CF senses mechanical stress and initiates complex molecular signaling pathways that lead to ECM generation and remodeling. Chronic inflammation further promotes CF proliferation and activation and exacerbates collagen deposition [6]. Most of the current preclinical trials have failed to fully distinguish the effects of interventions on RV from those on PVR, posing a challenge in the interpretion of results. The timing of antifibrotic therapy is also critical, and a combination of noninvasive imaging and circulating biomarkers is needed to guide treatment and to monitor efficacy. Further studies are needed to better elucidate the molecular mechanisms of RV fibrosis and to develop more effective antifibrotic drugs. The timing of treatment needs to be optimized and new imaging techniques and biomarkers developed in order to better assess RV fibrosis and its relationship with clinical outcomes. Multidisciplinary collaboration will be essential for the advancement of RV fibrosis research.

Limitations

While this review synthesizes the current evidence on RV fibrosis mechanisms and therapies, several limitations should be acknowledged. First, translational challenges exist between preclinical animal models and human pathophysiology, particularly regarding cross-specific differences in collagen metabolism and drug responses. Second, long-term efficacy and safety data are lacking for many investigational agents. These gaps highlight the need for standardized large-animal models, longer-term randomized controlled trials, and dedicated studies on personalized therapeutic approaches.

Author Contributions

XRL and PL: Conceptualization, literature review, original draft preparation, and manuscript revision. YNL and RZZ: Supervision, conceptualization, critical review, editing, and administration. YL, WH, and PJ: Contributed to manuscript editing, conceptualization, resource collection, and technical support. All authors contributed to critical revision of the manuscript for important intellectual content. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

Not applicable.

Acknowledgment

Not applicable.

Funding

This research received funding from the Natural Science Foundation of Gansu Province [No. 23JRRA0964], Cuiying Scientific and Technological Innovation Program of Lanzhou University Second Hospital [No. CY2023–YB-B01], General Project of Joint Research Fund [25JRRA1275].

Conflict of Interest

The authors declare no conflict of interest.

Declaration of AI and AI-Assisted Technologies in the Writing Process

During the preparation of this work the authors used DeepSeek in order to check spell and grammar. After using this tool, the authors reviewed and edited the content as needed and takes full responsibility for the content of the publication.

References

[1] Working Group on Pulmonary Vascular Diseases of Chinese Society of Cardiology of Chinese Medical Association, Editorial Board of Chinese Journal of Cardiology. Chinese guidelines for the diagnosis and treatment of pulmonary hypertension 2018. Zhonghua Xin Xue Guan Bing Za Zhi. 2018; 46: 933–964. https://doi.org/10.3760/cma.j.issn.0253-3758.2018.12.006. (In Chinese)

[2] Humbert M, Kovacs G, Hoeper MM, Badagliacca R, Berger RMF, Brida M, *et al*. 2022 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension. The European Respiratory Journal. 2023; 61: 2200879. https://doi.org/10.1183/13993003.00879-2022.

[3] Neelakantan S, Vang A, Mehdi RR, Phelan H, Nicely P, Imran T, *et al*. Right Ventricular Stiffening and Anisotropy Alterations in Pulmonary Hypertension: Mechanisms and Relations to Right Heart Failure. Journal of the American Heart Association. 2025; 14: e037126. https://doi.org/10.1161/JAHA.124.037126.

[4] Mocumbi A, Humbert M, Saxena A, Jing ZC, Sliwa K, Thienemann F, *et al*. Pulmonary hypertension. Nature Reviews. Disease Primers. 2024; 10: 1. https://doi.org/10.1038/s41572-023-00486-7.

[5] Andersen S, Nielsen-Kudsk JE, Vonk Noordegraaf A, de Man FS. Right Ventricular Fibrosis. Circulation. 2019; 139: 269–285. https://doi.org/10.1161/CIRCULATIONAHA.118.035326.

[6] Bekedam FT, Goumans MJ, Bogaard HJ, de Man FS, Llucià-Valldeperas A. Molecular mechanisms and targets of right ventricular fibrosis in pulmonary hypertension. Pharmacology & Therapeutics. 2023; 244: 108389. https://doi.org/10.1016/j.pharmthera.2023.108389.

[7] Namazi M, Eftekhar SP, Mosaed R, Shiralizadeh Dini S, Hazrati E. Pulmonary Hypertension and Right Ventricle: A Pathophysiological Insight. Clinical Medicine Insights. Cardiology. 2024; 18: 11795468241274744. https://doi.org/10.1177/11795468241274744.

[8] Rain S, Handoko ML, Trip P, Gan CTJ, Westerhof N, Stienen GJ, *et al*. Right ventricular diastolic impairment in patients with pulmonary arterial hypertension. Circulation. 2013; 128: 2016–2025, 1–10. https://doi.org/10.1161/CIRCULATIONAHA.113.001873.

[9] Peixoto PDS, Deniset-Besseau A, Schanne-Klein MC, Mosser G. Quantitative assessment of collagen I liquid crystal organizations: role of ionic force and acidic solvent, and evidence of new phases†. Soft Matter. 2011; 23: 11203–11210. https://doi.org/10.1039/c1sm06076g.

[10] Torres WM, Barlow SC, Moore A, Freeburg LA, Hoenes A, Doviak H, *et al*. Changes in Myocardial Microstructure and Mechanics With Progressive Left Ventricular Pressure Overload. JACC. Basic to Translational Science. 2020; 5: 463–480. https://doi.org/10.1016/j.jacbts.2020.02.007.

[11] Schimmel K, Ichimura K, Reddy S, Haddad F, Spiekerkoetter E. Cardiac Fibrosis in the Pressure Overloaded Left and Right Ventricle as a Therapeutic Target. Frontiers in Cardiovascular Medicine. 2022; 9: 886553. https://doi.org/10.3389/fcvm.2022.886553.

[12] Kazmirczak F, Thenappan T, Prins KW, Prisco SZ. Sex differences in right ventricular function between Groups 1 and 3 pulmonary hypertension. Pulmonary Circulation. 2023; 13: e12288. https://doi.org/10.1002/pul2.12288.

[13] Chen YZ, Zhao XS, Yuan JS, Zhang Y, Liu W, Qiao SB. Sex-related differences in left ventricular remodeling and outcome after alcohol septal ablation in hypertrophic obstructive cardiomyopathy: insights from cardiovascular magnetic resonance imaging. Biology of Sex Differences. 2022; 13: 37. https://doi.org/10.1186/s13293-022-00447-x.

[14] Patel RB, Li E, Benefield BC, Swat SA, Polsinelli VB, Carr JC, *et al*. Diffuse right ventricular fibrosis in heart failure with preserved ejection fraction and pulmonary hypertension. ESC Heart Failure. 2020; 7: 253–263. https://doi.org/10.1002/ehf2.12565.

[15] Jafari L, Wiedenroth CB, Kriechbaum SD, Grün D, Chelladurai P, Guenther S, *et al*. Transcriptional changes of the extracellular matrix in chronic thromboembolic pulmonary hypertension govern right ventricle remodeling and recovery. Nature Cardiovascular Research. 2025; 4: 857–875. https://doi.org/10.1038/s44161-025-00672-8.

[16] Ginting Munte FA, Elen E, Lelya O, Rudiktyo E, Prakoso R, Lilyasari O. Right ventricular fibrosis in adults with uncorrected secundum atrial septal defect and pulmonary hypertension: a cardiovascular magnetic resonance study with late gadolinium enhancement, native T1 and extracellular volume. Frontiers in Cardiovascular Medicine. 2024; 11: 1395382. https://doi.org/10.3389/fcvm.2024.1395382.

[17] Barilli M, Tavera MC, Valente S, Palazzuoli A. Structural and Hemodynamic Changes of the Right Ventricle in PH-HFpEF. International Journal of Molecular Sciences. 2022; 23: 4554. https://doi.org/10.3390/ijms23094554.

[18] Song R, Wang P, Yang L, Liu J, Chen Z, Ding Y. Association of FOXO3A with right ventricular myocardial fibrosis and its detection by speckle-tracking echocardiography in pulmonary hypertension. Echocardiography (Mount Kisco, N.Y.). 2023; 40: 958–968. https://doi.org/10.1111/echo.15663.

[19] Moon BF, Zhou IY, Ning Y, Chen YCI, Le Fur M, Shuvaev S, *et al*. Simultaneous Positron Emission Tomography and Molecular Magnetic Resonance Imaging of Cardiopulmonary Fibrosis in a Mouse Model of Left Ventricular Dysfunction. Journal of the American Heart Association. 2024; 13: e034363. https://doi.org/10.1161/JAHA.124.034363.

[20] Zeng X, Zhao R, Wu Z, Ma Z, Cen C, Gao S, *et al*. [^{18} F] - FAPI-42 PET/CT assessment of Progressive right ventricle fibrosis under pressure overload. Respiratory Research. 2023; 24: 270. https://doi.org/10.1186/s12931-023-02565-5.

[21] Yokokawa T, Nishiura K, Katahira M, Sato Y, Miura S, Sato A, *et al*. Collagen Triple Helix Repeat-Containing Protein 1 Is a Novel Biomarker of Right Ventricular Involvement in Pulmonary Hypertension. The Canadian Journal of Cardiology. 2024; 40: 2281–2288. https://doi.org/10.1016/j.cjca.2024.04.016.

[22] Ambade AS, Naranjo M, Tuhy T, Yu R, Marimoutou M, Everett AD, *et al*. Collagen 18A1/Endostatin Expression in the Progression of Right Ventricular Remodeling and Dysfunction in Pulmonary Arterial Hypertension. American Journal of Respiratory Cell and Molecular Biology. 2024; 71: 343–355. https://doi.org/10.1165/rcmb.2024-0039OC.

[23] Weidenhammer A, Prausmüller S, Partsch C, Spinka G, Luckerbauer B, Larch M, *et al*. CILP-1 Is a Biomarker for Backward Failure and Right Ventricular Dysfunction in HFrEF. Cells. 2023; 12: 2832. https://doi.org/10.3390/cells12242832.

[24] Widmann L, Keranov S, Jafari L, Liebetrau C, Keller T, Troidl C, *et al*. Fibroblast growth factor 23 as a biomarker of right ventricular dysfunction in pulmonary hypertension. Clinical Research in Cardiology: Official Journal of the German Cardiac Society. 2023; 112: 1382–1393. https://doi.org/10.1007/s00392-023-02162-y.

[25] Keranov S, Widmann L, Jafari L, Liebetrau C, Keller T, Troidl C, *et al*. GDF-15 and soluble ST2 as biomarkers of right ventricular dysfunction in pulmonary hypertension. Biomarkers in Medicine. 2022; 16: 1193–1207. https://doi.org/10.2217/bmm-2022-0395.

[26] Johnson CA, Jr, Cortelli M, Jr, Glomp G, Cagnolatti C, Demarest CT, Ukita R, *et al*. A Dynamic Sheep Model to Induce Pulmonary Hypertension and Right Ventricular Failure. Methods in Molecular Biology (Clifton, N.J.). 2024; 2803: 239–258. https://doi.org/10.1007/978-1-0716-3846-0_18.

[27] Christou H, Khalil RA. Mechanisms of pulmonary vascular dysfunction in pulmonary hypertension and implications for novel therapies. American Journal of Physiology. Heart and Circulatory Physiology. 2022; 322: H702–H724. https://doi.org/10.1152/ajpheart.00021.2022.

[28] Tello K, Naeije R, de Man F, Guazzi M. Pathophysiology of the right ventricle in health and disease: an update. Cardiovascular Research. 2023; 119: 1891–1904. https://doi.org/10.1093/cvr/cvad108.

[29] Braams NJ, Kianzad A, van Wezenbeek J, Wessels JN, Jansen SMA, Andersen S, *et al*. Long-Term Effects of Pulmonary Endarterectomy on Right Ventricular Stiffness and Fibrosis in Chronic Thromboembolic Pulmonary Hypertension. Circulation. Heart Failure. 2023; 16: e010336. https://doi.org/10.1161/CIRCHEARTFAILURE.122.010336.

[30] Ichimura K, Boehm M, Andruska AM, Zhang F, Schimmel K, Bonham S, *et al*. 3D Imaging Reveals Complex Microvascular Remodeling in the Right Ventricle in Pulmonary Hypertension. Circulation Research. 2024; 135: 60–75. https://doi.org/10.1161/CIRCRESAHA.123.323546.

[31] Waxman AB, Systrom DM, Manimaran S, de Oliveira Pena J, Lu J, Rischard FP. SPECTRA Phase 2b Study: Impact of Sotatercept on Exercise Tolerance and Right Ventricular Function in Pulmonary Arterial Hypertension. Circulation. Heart Failure. 2024; 17: e011227. https://doi.org/10.1161/CIRCHEARTFAILURE.123.011227.

[32] Gomez-Arroyo J, Sakagami M, Syed AA, Farkas L, Van Tassell B, Kraskauskas D, *et al*. Iloprost reverses established fibrosis in experimental right ventricular failure. The European Respiratory Journal. 2015; 45: 449–462. https://doi.org/10.1183/09031936.00188013.

[33] Rai N, Veeroju S, Schymura Y, Janssen W, Wietelmann A, Kojonazarov B, *et al*. Effect of Riociguat and Sildenafil on Right Heart Remodeling and Function in Pressure Overload Induced Model of Pulmonary Arterial Banding. BioMed Research International. 2018; 2018: 3293584. https://doi.org/10.1155/2018/3293584.

[34] Corboz MR, Nguyen TL, Stautberg A, Cipolla D, Perkins WR, Chapman RW. Current Overview of the Biology and Pharmacology in Sugen/Hypoxia-Induced Pulmonary Hypertension in Rats. Journal of Aerosol Medicine and Pulmonary Drug Delivery. 2024; 37: 241–283. https://doi.org/10.1089/jamp.2024.0016.

[35] Borgdorff MA, Bartelds B, Dickinson MG, van Wiechen MPH, Steendijk P, de Vroomen M, *et al*. Sildenafil treatment in established right ventricular dysfunction improves diastolic function and attenuates interstitial fibrosis independent from afterload. American Journal of Physiology. Heart and Circulatory Physiology. 2014; 307: H361–H369. https://doi.org/10.1152/ajpheart.00843.2013.

[36] Abdelazeem H, Tu L, Thuillet R, Ottaviani M, Boulfrad A, Beck T, *et al*. AMPK activation by metformin protects against pulmonary hypertension in rats and relaxes isolated human pulmonary artery. European Journal of Pharmacology. 2023; 946: 175579. https://doi.org/10.1016/j.ejphar.2023.175579.

[37] Clements RT, Vang A, Fernandez-Nicolas A, Kue NR, Mancini TJ, Morrison AR, *et al*. Treatment of Pulmonary Hypertension With Angiotensin II Receptor Blocker and Neprilysin Inhibitor Sacubitril/Valsartan. Circulation. Heart Failure. 2019; 12: e005819. https://doi.org/10.1161/CIRCHEARTFAILURE.119.005819.

[38] Shen M, Zheng C, Chen L, Li M, Huang X, He M, *et al*. LCZ696 (sacubitril/valsartan) inhibits pulmonary hypertension induced right ventricular remodeling by targeting pyruvate dehydrogenase kinase 4. Biomedicine & Pharmacotherapy. 2023; 162: 114569. https://doi.org/10.1016/j.biopha.2023.114569.

[39] Johnson JA, West J, Maynard KB, Hemnes AR. ACE2 improves right ventricular function in a pressure overload model. PloS One. 2011; 6: e20828. https://doi.org/10.1371/journal.pone.0020828.

[40] Preston IR, Sagliani KD, Warburton RR, Hill NS, Fanburg BL, Jaffe IZ. Mineralocorticoid receptor antagonism attenuates experimental pulmonary hypertension. American Journal of Physiology. Lung Cellular and Molecular Physiology. 2013; 304: L678–L688. https://doi.org/10.1152/ajplung.00300.2012.

[41] Cowley PM, Wang G, Joshi S, Swigart PM, Lovett DH, Simpson PC, *et al*. α_{1A}-Subtype adrenergic agonist therapy for the failing right ventricle. American Journal of Physiology. Heart and Circulatory Physiology. 2017; 313: H1109–H1118. https://doi.org/10.1152/ajpheart.00153.2017.

[42] Cowley PM, Wang G, Swigart PM, Raghunathan A, Reddy N, Dulam P, *et al*. Reversal of right ventricular failure by chronic α_{1A}-subtype adrenergic agonist therapy. American Journal of Physiology. Heart and Circulatory Physiology. 2019; 316: H224–H232. https://doi.org/10.1152/ajpheart.00507.2018.

[43] de Man FS, Handoko ML, van Ballegoij JJM, Schalij I, Bogaards SJP, Postmus PE, *et al*. Bisoprolol delays progression towards right heart failure in experimental pulmonary hypertension. Circulation. Heart Failure. 2012; 5: 97–105. https://doi.org/10.1161/CIRCHEARTFAILURE.111.964494.

[44] Okumura K, Kato H, Honjo O, Breitling S, Kuebler WM, Sun M, *et al*. Carvedilol improves biventricular fibrosis and function in experimental pulmonary hypertension. Journal of Molecular Medicine (Berlin, Germany). 2015; 93: 663–674. https://doi.org/10.1007/s00109-015-1251-9.

[45] Bogaard HJ, Natarajan R, Mizuno S, Abbate A, Chang PJ, Chau VQ, *et al*. Adrenergic receptor blockade reverses right heart remodeling and dysfunction in pulmonary hypertensive rats. American Journal of Respiratory and Critical Care Medicine. 2010; 182: 652–660. https://doi.org/10.1164/rccm.201003-0335OC.

[46] Ishii R, Okumura K, Akazawa Y, Malhi M, Ebata R, Sun M, *et al*. Heart Rate Reduction Improves Right Ventricular Function and Fibrosis in Pulmonary Hypertension. American Journal of Respiratory Cell and Molecular Biology. 2020; 63: 843–855. https://doi.org/10.1165/rcmb.2019-0317OC.

[47] Karimi Galougahi K, Zhang Y, Kienzle V, Liu CC, Quek LE, Patel S, *et al*. β3 adrenergic agonism: A novel pathway which improves right ventricular-pulmonary arterial hemodynamics in pulmonary arterial hypertension. Physiological Reports. 2023; 11: e15549. https://doi.org/10.14814/phy2.15549.

[48] Liu R, Zhou T, Li X, Zou Q, Yu J, Ye J, *et al*. A Non-Metallic Nanozyme Ameliorates Pulmonary Hypertension Through Inhibiting ROS/TGF-β1 Signaling. Advanced Healthcare Materials. 2024; 13: e2401909. https://doi.org/10.1002/adhm.202401909.

[49] Crnkovic S, Egemnazarov B, Damico R, Marsh LM, Nagy BM, Douschan P, *et al*. Disconnect between Fibrotic Response and Right Ventricular Dysfunction. American Journal of Respiratory and Critical Care Medicine. 2019; 199: 1550–1560. https://doi.org/10.1164/rccm.201809-1737OC.

[50] Poble PB, Phan C, Quatremare T, Bordenave J, Thuillet R, Cumont A, *et al*. Therapeutic effect of pirfenidone in the sugen/hypoxia rat model of severe pulmonary hypertension. FASEB Journal: Official Publication of the Federation of American Societies for Experimental Biology. 2019; 33: 3670–3679. https://doi.org/10.1096/fj.201801659R.

[51] Rol N, de Raaf MA, Sun XQ, Kuiper VP, da Silva Gonçalves Bos D, Happé C, *et al*. Nintedanib improves cardiac fibrosis but leaves pulmonary vascular remodelling unaltered in experimental pulmonary hypertension. Cardiovascular Research. 2019; 115: 432–439. https://doi.org/10.1093/cvr/cvy186.

[52] Boehm M, Tian X, Ali MK, Mao Y, Ichimura K, Zhao M, *et al*. Improving Right Ventricular Function by Increasing BMP Signaling with FK506. American Journal of Respiratory Cell and Molecular Biology. 2021; 65: 272–287. https://doi.org/10.1165/rcmb.2020-0528OC.

[53] Kojonazarov B, Sydykov A, Pullamsetti SS, Luitel H, Dahal BK, Kosanovic D, *et al*. Effects of multikinase inhibitors on pressure overload-induced right ventricular remodeling. International Journal of Cardiology. 2013; 167: 2630–2637. https://doi.org/10.1016/j.ijcard.2012.06.129.

[54] Fang YH, Piao L, Hong Z, Toth PT, Marsboom G, Bache-Wiig P, *et al*. Therapeutic inhibition of fatty acid oxidation in right ventricular hypertrophy: exploiting Randle's cycle. Journal of Molecular Medicine (Berlin, Germany). 2012; 90: 31–43. https://doi.org/10.1007/s00109-011-0804-9.

[55] Gao X, Zhang Z, Li X, Wei Q, Li H, Li C, *et al*. Ursolic Acid Improves Monocrotaline-Induced Right Ventricular Remodeling by Regulating Metabolism. Journal of Cardiovascular Pharmacology. 2020; 75: 545–555. https://doi.org/10.1097/FJC.0000000000000815.

[56] Spyropoulos F, Michael Z, Finander B, Vitali S, Kosmas K, Zymaris P, *et al*. Acetazolamide Improves Right Ventricular Function and Metabolic Gene Dysregulation in Experimental Pulmonary Arterial Hypertension. Frontiers in Cardiovascular Medicine. 2021; 8: 662870. https://doi.org/10.3389/fcvm.2021.662870.

[57] Behringer A, Trappiel M, Berghausen EM, Ten Freyhaus H, Wellnhofer E, Odenthal M, *et al*. Pioglitazone alleviates cardiac and vascular remodelling and improves survival in monocrotaline induced pulmonary arterial hypertension. Naunyn-Schmiedeberg's Archives of Pharmacology. 2016; 389: 369–379. https://doi.org/10.1007/s00210-015-1205-3.

[58] Kobayashi T, Kim JD, Naito A, Yanagisawa A, Jujo-Sanada T, Kasuya Y, *et al*. Multi omics analysis of right ventricles in rat models of pulmonary arterial hypertension: Consideration of mitochondrial biogenesis by chrysin. International Journal of Molecular Medicine. 2022; 49: 69. https://doi.org/10.3892/ijmm.2022.5124.

[59] Banerjee S, Onwunyi VRC, Hong J, Martineau S, Fishbein GA, Bonnet SB, *et al*. RV-specific Targeting of Snai1 Res-

cues Pulmonary Hypertension-induced Right Ventricular Failure by Inhibiting EndMT and Fibrosis via LOXL2 Mediated Mechanism. bioRxiv. 2024. https://doi.org/10.1101/2024.04.30.591766. (preprint)

[60] Bessa-Gonçalves M, Bragança B, Martins-Dias E, Vinhas A, Certal M, Rodrigues T, *et al*. Blockage of the adenosine A_{2B} receptor prevents cardiac fibroblasts overgrowth in rats with pulmonary arterial hypertension. Purinergic Signalling. 2024; 20: 163–179. https://doi.org/10.1007/s11302-023-09952-z.

[61] Houston BA, Brittain EL, Tedford RJ. Right Ventricular Failure. The New England Journal of Medicine. 2023; 388: 1111–1125. https://doi.org/10.1056/NEJMra2207410.

[62] Prisco SZ, Hartweck L, Keen JL, Vogel N, Kazmirczak F, Eklund M, *et al*. Glyoxylase-1 combats dicarbonyl stress and right ventricular dysfunction in rodent pulmonary arterial hypertension. Frontiers in Cardiovascular Medicine. 2022; 9: 940932. https://doi.org/10.3389/fcvm.2022.940932.

[63] Yan Q, Li P, Liu S, Sun Y, Chen C, Long J, *et al*. Dihydromyricetin treats pulmonary hypertension by modulating CKLF1/CCR5 axis-induced pulmonary vascular cell pyroptosis. Biomedicine & Pharmacotherapy. 2024; 180: 117614. https://doi.org/10.1016/j.biopha.2024.117614.

[64] Lv J, Shi S, Fu Z, Wang Y, Duan C, Hu S, *et al*. Exploring the inflammation-related mechanisms of Lingguizhugan decoction on right ventricular remodeling secondary to pulmonary arterial hypertension based on integrated strategy using UPLC-HRMS, systems biology approach, and experimental validation. Phytomedicine: International Journal of Phytotherapy and Phytopharmacology. 2024; 132: 155879. https://doi.org/10.1016/j.phymed.2024.155879.

[65] Huang L, Li H, Huang S, Wang S, Liu Q, Luo L, *et al*. Notopterol Attenuates Monocrotaline-Induced Pulmonary Arterial Hypertension in Rat. Frontiers in Cardiovascular Medicine. 2022; 9: 859422. https://doi.org/10.3389/fcvm.2022.859422.

[66] Wang S, Li H, Liu Q, Ma H, Huang L, Yu L, *et al*. Hydroxycitric Acid Tripotassium Hydrate Attenuates Monocrotaline and Hypoxia-Induced Pulmonary Hypertension in Rats. International Heart Journal. 2024; 65: 318–328. https://doi.org/10.1536/ihj.23-350.

[67] Chen S, Sun P, Li Y, Shen W, Wang C, Zhao P, *et al*. Melatonin activates the Mst1-Nrf2 signaling to alleviate cardiac hypertrophy in pulmonary arterial hypertension. European Journal of Pharmacology. 2022; 933: 175262. https://doi.org/10.1016/j.ejphar.2022.175262.

[68] Li H, Liu Q, Yue Y, Wang S, Huang S, Huang L, *et al*. Celastrol attenuates the remodeling of pulmonary vascular and right ventricular in monocrotaline-induced pulmonary arterial hypertension in rats. Cardiovascular Diagnosis and Therapy. 2022; 12: 88–102. https://doi.org/10.21037/cdt-21-360.

[69] Kurosawa R, Satoh K, Nakata T, Shindo T, Kikuchi N, Satoh T, *et al*. Identification of Celastrol as a Novel Therapeutic Agent for Pulmonary Arterial Hypertension and Right Ventricular Failure Through Suppression of Bsg (Basigin)/CyPA (Cyclophilin A). Arteriosclerosis, Thrombosis, and Vascular Biology. 2021; 41: 1205–1217. https://doi.org/10.1161/ATVBAHA.120.315731.

[70] Kang Y, Zhang G, Huang EC, Huang J, Cai J, Cai L, *et al*. Sulforaphane prevents right ventricular injury and reduces pulmonary vascular remodeling in pulmonary arterial hypertension. American Journal of Physiology. Heart and Circulatory Physiology. 2020; 318: H853–H866. https://doi.org/10.1152/ajpheart.00321.2019.

[71] Bogaard HJ, Natarajan R, Henderson SC, Long CS, Kraskauskas D, Smithson L, *et al*. Chronic pulmonary artery pressure elevation is insufficient to explain right heart failure. Circulation. 2009; 120: 1951–1960. https://doi.org/10.1161/CIRCULATIONAHA.109.883843.

[72] Yang Z, Sun H, Su S, Nan X, Li K, Jin X, *et al*. Tsantan Sumtang Restored Right Ventricular Function in Chronic Hypoxia-Induced Pulmonary Hypertension Rats. Frontiers in Pharmacology. 2021; 11: 607384. https://doi.org/10.3389/fphar.2020.607384.

[73] Qu C, Xu Y, Yang X, Lu X. Magnesium lithospermate B improves pulmonary artery banding induced right ventricular dysfunction by alleviating inflammation via p38MAPK pathway. Pulmonary Pharmacology & Therapeutics. 2020; 63: 101935. https://doi.org/10.1016/j.pupt.2020.101935.

[74] Kojonazarov B, Novoyatleva T, Boehm M, Happe C, Sibinska Z, Tian X, *et al*. p38 MAPK Inhibition Improves Heart Function in Pressure-Loaded Right Ventricular Hypertrophy. American Journal of Respiratory Cell and Molecular Biology. 2017; 57: 603–614. https://doi.org/10.1165/rcmb.2016-0374OC.

[75] Yoshida K, Abe K, Ishikawa M, Saku K, Shinoda-Sakamoto M, Ishikawa T, *et al*. Inhibition of TLR9-NF-κB-mediated sterile inflammation improves pressure overload-induced right ventricular dysfunction in rats. Cardiovascular Research. 2019; 115: 658–668. https://doi.org/10.1093/cvr/cvy209.

[76] Budas GR, Boehm M, Kojonazarov B, Viswanathan G, Tian X, Veeroju S, *et al*. ASK1 Inhibition Halts Disease Progression in Preclinical Models of Pulmonary Arterial Hypertension. American Journal of Respiratory and Critical Care Medicine. 2018; 197: 373–385. https://doi.org/10.1164/rccm.201703-0502OC.

[77] Hu J, Sharifi-Sanjani M, Tofovic SP. Nitrite Prevents Right Ventricular Failure and Remodeling Induced by Pulmonary Artery Banding. Journal of Cardiovascular Pharmacology. 2017; 69: 93–100. https://doi.org/10.1097/FJC.0000000000000446.

[78] Rajabi S, Najafipour H, Jafarinejad-Farsangi S, Joukar S, Beik A, Askaripour M, *et al*. Quercetin, Perillyl Alcohol, and Berberine Ameliorate Right Ventricular Disorders in Experimental Pulmonary Arterial Hypertension: Effects on miR-204, miR-27a, Fibrotic, Apoptotic, and Inflammatory Factors. Journal of Cardiovascular Pharmacology. 2021; 77: 777–786. https://doi.org/10.1097/FJC.0000000000001015.

[79] Zhai W, Li Y, Luo Y, Gao W, Liu S, Han J, *et al*. Sevoflurane prevents pulmonary vascular remodeling and right ventricular dysfunction in pulmonary arterial hypertension in rats. American Journal of Translational Research. 2021; 13: 11302–11315.

[80] Ferraz AP, Seara FAC, Baptista EF, Barenco TS, Sottani TBB, Souza NSC, *et al*. BK_{Ca} Channel Activation Attenuates the Pathophysiological Progression of Monocrotaline-Induced Pulmonary Arterial Hypertension in Wistar Rats. Cardiovascular Drugs and Therapy. 2021; 35: 719–732. https://doi.org/10.1007/s10557-020-07115-5.

[81] Alves-Silva JM, Zuzarte M, Marques C, Viana S, Preguiça I, Baptista R, *et al*. 1,8-Cineole ameliorates right ventricle dysfunction associated with pulmonary arterial hypertension by restoring connexin43 and mitochondrial homeostasis. Pharmacological Research. 2022; 180: 106151. https://doi.org/10.1016/j.phrs.2022.106151.

[82] Redout EM, van der Toorn A, Zuidwijk MJ, van de Kolk CWA, van Echteld CJA, Musters RJP, *et al*. Antioxidant treatment attenuates pulmonary arterial hypertension-induced heart failure. American Journal of Physiology. Heart and Circulatory Physiology. 2010; 298: H1038–H1047. https://doi.org/10.1152/ajpheart.00097.2009.

[83] Sun Y, Wan W, Zhao X, Han X, Ye T, Chen X, *et al*. Chronic Sigma 1 receptor activation alleviates right ventricular dysfunction secondary to pulmonary arterial hypertension. Bioengineered. 2022; 13: 10843–10856. https://doi.org/10.1080/21655979.2022.2065953.

[84] Yoshida K, Saku K, Jan Bogaard H, Abe K, Sunagawa K, Tsutsui H. Vagal nerve stimulation preserves right ventricular function in a rat model of right ventricular pressure overload. Pulmonary Circulation. 2022; 12: e12154. https://doi.org/10.1002/pul2.12154.

[85] Blake M, Puchalska P, Kazmirczak F, Blake J, Moon R, Thenap-

pan T, *et al*. Ketone bodies in right ventricular failure: A unique therapeutic opportunity. Heliyon. 2023; 9: e22227. https://doi.org/10.1016/j.heliyon.2023.e22227.

[86] Chen Z, Wang J, Qin X, Di N, Deng H, Li X. Long-term swimming exercise attenuates right ventricular hypertrophy via modulating meta-inflammation in monocrotaline-induced pulmonary hypertensive rats. Biochemical and Biophysical Research Communications. 2024; 733: 150710. https://doi.org/10.1016/j.bbrc.2024.150710.

[87] Janssen W, Schymura Y, Novoyatleva T, Kojonazarov B, Boehm M, Wietelmann A, *et al*. 5-HT2B receptor antagonists inhibit fibrosis and protect from RV heart failure. BioMed Research International. 2015; 2015: 438403. https://doi.org/10.1155/2015/438403.

[88] Vang A, da Silva Gonçalves Bos D, Fernandez-Nicolas A, Zhang P, Morrison AR, Mancini TJ, *et al*. α7 Nicotinic acetylcholine receptor mediates right ventricular fibrosis and diastolic dysfunction in pulmonary hypertension. JCI Insight. 2021; 6: e142945. https://doi.org/10.1172/jci.insight.142945.

[89] Wang YD, Li YD, Ding XY, Wu XP, Li C, Guo DC, *et al*. 17β-estradiol preserves right ventricular function in rats with pulmonary arterial hypertension: an echocardiographic and histochemical study. The International Journal of Cardiovascular Imaging. 2019; 35: 441–450. https://doi.org/10.1007/s10554-018-1468-0.

[90] Lahm T, Frump AL, Albrecht ME, Fisher AJ, Cook TG, Jones TJ, *et al*. 17β-Estradiol mediates superior adaptation of right ventricular function to acute strenuous exercise in female rats with severe pulmonary hypertension. American Journal of Physiology. Lung Cellular and Molecular Physiology. 2016; 311: L375–L388. https://doi.org/10.1152/ajplung.00132.2016.

[91] Alzoubi A, Toba M, Abe K, O'Neill KD, Rocic P, Fagan KA, *et al*. Dehydroepiandrosterone restores right ventricular structure and function in rats with severe pulmonary arterial hypertension. American Journal of Physiology. Heart and Circulatory Physiology. 2013; 304: H1708–H1718. https://doi.org/10.1152/ajpheart.00746.2012.

[92] Chen X, Yu X, Lian G, Tang H, Yan Y, Gao G, *et al*. Canagliflozin inhibits PASMCs proliferation via regulating SGLT1/AMPK signaling and attenuates artery remodeling in MCT-induced pulmonary arterial hypertension. Biomedicine & Pharmacotherapy. 2024; 174: 116505. https://doi.org/10.1016/j.biopha.2024.116505.

[93] Chowdhury B, Luu AZ, Luu VZ, Kabir MG, Pan Y, Teoh H, *et al*. The SGLT2 inhibitor empagliflozin reduces mortality and prevents progression in experimental pulmonary hypertension. Biochemical and Biophysical Research Communications. 2020; 524: 50–56. https://doi.org/10.1016/j.bbrc.2020.01.015.

[94] Omura J, Habbout K, Shimauchi T, Wu WH, Breuils-Bonnet S, Tremblay E, *et al*. Identification of Long Noncoding RNA H19 as a New Biomarker and Therapeutic Target in Right Ventricular Failure in Pulmonary Arterial Hypertension. Circulation. 2020; 142: 1464–1484. https://doi.org/10.1161/CIRCULATIONAHA.120.047626.

[95] Oommen S, Yamada S, Cantero Peral S, Campbell KA, Bruinsma ES, Terzic A, *et al*. Human umbilical cord blood-derived mononuclear cells improve murine ventricular function upon intramyocardial delivery in right ventricular chronic pressure overload. Stem Cell Research & Therapy. 2015; 6: 50. https://doi.org/10.1186/s13287-015-0044-y.

[96] Agarwal U, Smith AW, French KM, Boopathy AV, George A, Trac D, *et al*. Age-Dependent Effect of Pediatric Cardiac Progenitor Cells After Juvenile Heart Failure. Stem Cells Translational Medicine. 2016; 5: 883–892. https://doi.org/10.5966/sctm.2015-0241.

[97] Wehman B, Sharma S, Pietris N, Mishra R, Siddiqui OT, Bigham G, *et al*. Mesenchymal stem cells preserve neonatal right ventricular function in a porcine model of pressure overload. American Journal of Physiology. Heart and Circulatory Physiology. 2016; 310: H1816–H1826. https://doi.org/10.1152/ajpheart.00955.2015.

[98] Schmuck EG, Hacker TA, Schreier DA, Chesler NC, Wang Z. Beneficial effects of mesenchymal stem cell delivery via a novel cardiac bioscaffold on right ventricles of pulmonary arterial hypertensive rats. American Journal of Physiology. Heart and Circulatory Physiology. 2019; 316: H1005–H1013. https://doi.org/10.1152/ajpheart.00091.2018.

[99] Watanabe T, Kawamura T, Harada A, Taira M, Yoshioka D, Shimamura K, *et al*. Human induced pluripotent stem cell-derived cardiomyocyte patches ameliorate right ventricular function in a rat pressure-overloaded right ventricle model. Journal of Artificial Organs: the Official Journal of the Japanese Society for Artificial Organs. 2025; 28: 234–243. https://doi.org/10.1007/s10047-024-01479-3.

[100] Guo Q, Huang JA, Yamamura A, Yamamura H, Zimnicka AM, Fernandez R, *et al*. Inhibition of the Ca(2+)-sensing receptor rescues pulmonary hypertension in rats and mice. Hypertension Research: Official Journal of the Japanese Society of Hypertension. 2014; 37: 116–124. https://doi.org/10.1038/hr.2013.129.

[101] Comarița IK, Tanko G, Anghelache IL, Georgescu A. The siRNA-mediated knockdown of AP-1 restores the function of the pulmonary artery and the right ventricle by reducing perivascular and interstitial fibrosis and key molecular players in cardiopulmonary disease. Journal of Translational Medicine. 2024; 22: 137. https://doi.org/10.1186/s12967-024-04933-1.

[102] Song J, Chen Y, Chen Y, Wang S, Dong Z, Liu X, *et al*. Ferrostatin-1 Blunts Right Ventricular Hypertrophy and Dysfunction in Pulmonary Arterial Hypertension by Suppressing the HMOX1/GSH Signaling. Journal of Cardiovascular Translational Research. 2024; 17: 183–196. https://doi.org/10.1007/s12265-023-10423-4.

[103] Bao C, Liang S, Han Y, Yang Z, Liu S, Sun Y, *et al*. The Novel Lysosomal Autophagy Inhibitor (ROC-325) Ameliorates Experimental Pulmonary Hypertension. Hypertension (Dallas, Tex.: 1979). 2023; 80: 70–83. https://doi.org/10.1161/HYPERTENSIONAHA.122.19397.

[104] Huang W, Zhou H, He Y, Wang A, Wang B, Chen Y, *et al*. A novel PDGFR inhibitor WQ-C-401 prevents pulmonary vascular remodeling in rats with monocrotaline-induced pulmonary arterial hypertension. Experimental Cell Research. 2024; 441: 114154. https://doi.org/10.1016/j.yexcr.2024.114154.

[105] Li J, Zhang Z, Zhu C, Zheng X, Wang C, Jiang J, *et al*. Salidroside enhances NO bioavailability and modulates arginine metabolism to alleviate pulmonary arterial hypertension. European Journal of Medical Research. 2024; 29: 423. https://doi.org/10.1186/s40001-024-02016-x.

[106] Zafeiropoulos S, Ahmed U, Bekiaridou A, Jayaprakash N, Mughrabi IT, Saleknezhad N, *et al*. Ultrasound Neuromodulation of an Anti-Inflammatory Pathway at the Spleen Improves Experimental Pulmonary Hypertension. Circulation Research. 2024; 135: 41–56. https://doi.org/10.1161/CIRCRESAHA.123.323679.

[107] Rossi R, Coppi F, Monopoli DE, Sgura FA, Arrotti S, Boriani G. Pulmonary arterial hypertension and right ventricular systolic dysfunction in COVID-19 survivors. Cardiology Journal. 2022; 29: 163–165. https://doi.org/10.5603/CJ.a2021.0159.