Adaptation and Maladaptation of the Right Ventricle in Pulmonary Vascular Diseases

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KEYWORDS

• Right ventricle • Right heart failure • Pulmonary vascular diseases • Adaptive remodeling • Maladaptive remodeling • Right ventricular hypertrophy • Right ventricular dilation

KEY POINTS

- Right ventricle adaptive remodeling to increased afterload is characterized by preserved right ventricle function due to increased contractility and right ventricular hypertrophy.
- Right ventricle maladaptive remodeling to chronic increased afterload is defined by decreased right ventricle function because of an enlarged right ventricle.
- Right heart failure is the result of ventriculoarterial uncoupling.

INTRODUCTION

Pulmonary vascular diseases (PVDs) have significant morbidity and mortality. Patients present with either acute or chronic symptoms resulting from damage to the pulmonary vasculature (eg, hypoxia, hemoptysis) or from the development of right heart failure (eg, exercise intolerance, fluid retention, syncope).[1,2] PVDs embrace a wide and diverse group of underlying pathologies, but this article focuses on right ventricular (RV) adaptation in pulmonary hypertension (PH).

Pulmonary arterial hypertension (PAH) is a vasculopathy that exhibits abnormalities mostly in small pulmonary arteries and arterioles. Excessive pulmonary vascular remodeling and arterial obstruction lead to elevated pulmonary vascular resistance and mean pulmonary artery pressure (mPAP), and consequently increase the RV afterload. Thin walled and crescentic in shape, the RV is highly sensitive to changes in pressure.[3] In PAH, the RV has to adapt to an up to fivefold increase in afterload. Right heart failure (RHF) develops when the RV is unable to cope with the increased demand.[4] As described by the International Right Heart Failure Foundation Scientific Working Group, RHF is *a clinical syndrome due to an alteration of structure and/or function of the right heart circulatory system that leads to suboptimal delivery of blood flow (high or low) to the pulmonary circulation and/or elevated venous pressures—at rest or with exercise*.[5]

In this article, we investigate the changes that the RV undergoes to adapt to the increased afterload and progress to RHF. These changes are comprised in RV (mal)adaptation, and may also be referred as RV remodeling. Thus, cardiac remodeling is an imprecise term that encompasses hypertrophy, fibrosis, and a shape change of the cardiac chambers, depending on the subject. The mechanisms behind cardiac remodeling have been explored extensively in the left ventricle (LV), but not in the RV. There is a thin line between the adaptive and maladaptive phenotypes, as they

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are not 2 different responses, but rather a sequence of states of cardiac adaptability.[6] Unfortunately, the mechanisms behind the transition toward RHF remain poorly understood. This article summarizes the current knowledge of both adaptive and maladaptive RV phenotypes linked to PVD, more especially associated to PAH.

THE RIGHT VENTRICLE

To better understand the plasticity of the RV under pathologic conditions, a brief review of its physiologic anatomy and function is necessary.

Right Ventricular Development and Anatomy

The heart is the first organ to develop in the human embryo and starts beating at approximately day 21. All subsequent events depend on the heart's ability to match its output with the demands of oxygen and nutrients; thus, differences among ventricles depend on both the embryologic origin and the hemodynamic environment from the very beginning, even though hemodynamic differences are not present until birth.[7]

The heart is assembled in modules, for instance the LV originates first from the heart tube, whereas the RV arises next from the extracardiac mesoderm within the second heart field.[8] Moreover, each compartment is governed by unique genetic programs; thus, the LV and the RV develop independently. Indeed, several genes have been identified in the development of the RV: *ISL1*, *HAND2, GATA4, NKX2.5, MEF2C, BOP*, and *FGF10*.[9–15] Some of the previously mentioned genes are present in both ventricles; however, few are chamber-restricted, as HAND1 and HAND2 are limited to the LV and RV, respectively.[10] Nonetheless, adult human cardiomyocytes from both ventricles show a great overlap in gene and protein expression.

After birth, the foramen ovale closes and the RV free wall thins in response to the low resistance and low pressure of the pulmonary circulation; thus, under physiologic conditions, the interventricular septum is concave toward the LV. Hence, both ventricles are morphologically and functionally different. The RV is the most anterior cardiac chamber, has a nonspherical crescentic shape, larger volume, smaller mass and fewer cardiomyocytes, higher collagen content, multiple papillary muscles, and uniformly coarse trabeculations, compared with the ellipsoid and stronger LV.[16] In addition, in the myocardial layer of the RV, it is possible to distinguish 2 myofiber orientations:

1. On the epicardial surface mainly circumferential aggregated myofibers are observed, which are components of myofiber tracts that are shared with the LV.
2. A subendocardial layer with predominantly longitudinal aggregates.

In contrast to the LV, the third mid-layer containing circumferential fibers is absent in physiologic conditions in the RV.[17,18] However, congenital and acquired modifications have been described in which the mid-layer was also observed in the RV.

Right Ventricular Function

The function of the RV depends on multiple factors: the preload, the contractility of the RV free wall and interventricular septum, the afterload, and the pericardial compliance.[19]

The RV contracts in a peristalticlike pattern starting from the inlet portion and finishing at the infundibulum in 3 steps:

1. Longitudinal shortening with traction of the tricuspid annulus toward the apex
2. Inward radial motion of the RV free wall (also known as "bellows effect")
3. Anteroposterior shortening of the chamber by stretching the free wall over the septum during LV contraction.[18]

In PAH, for example, longitudinal function is relatively preserved, while radial and anteroposterior shortening are decreased (**Fig. 1**).[18] Thus, RV radial motion can be used as a prognostic value in PH patients.[20]

The RV and LV are anatomically interconnected through the septum, the epicardium, and the pericardium. Ventricular interdependence occurs when forces are transmitted between ventricles via common myofibers, perivalvular fibrous annulus, and pericardium; and it is independent of neural, humoral, or circulatory systems. In the healthy situation, the influence of the RV on LV function is insignificant. However, during sustained pressure overload, such as observed in PH, there is a significant influence of RV function on the LV through 3 interrelated events:

1. Leftward septal bowing caused by a prolonged RV free wall peak contraction compared with the septum or LV free wall[16] hampering early diastolic LV filling
2. Decreasing LV filling due to low RV stroke volume (SV)[21,22]
3. Diastolic ventricular interaction because both ventricles compete for space within the nondistensible pericardial sac[23]

Due to the underfilling of the LV, atrophy and reduced contractile function of the LV

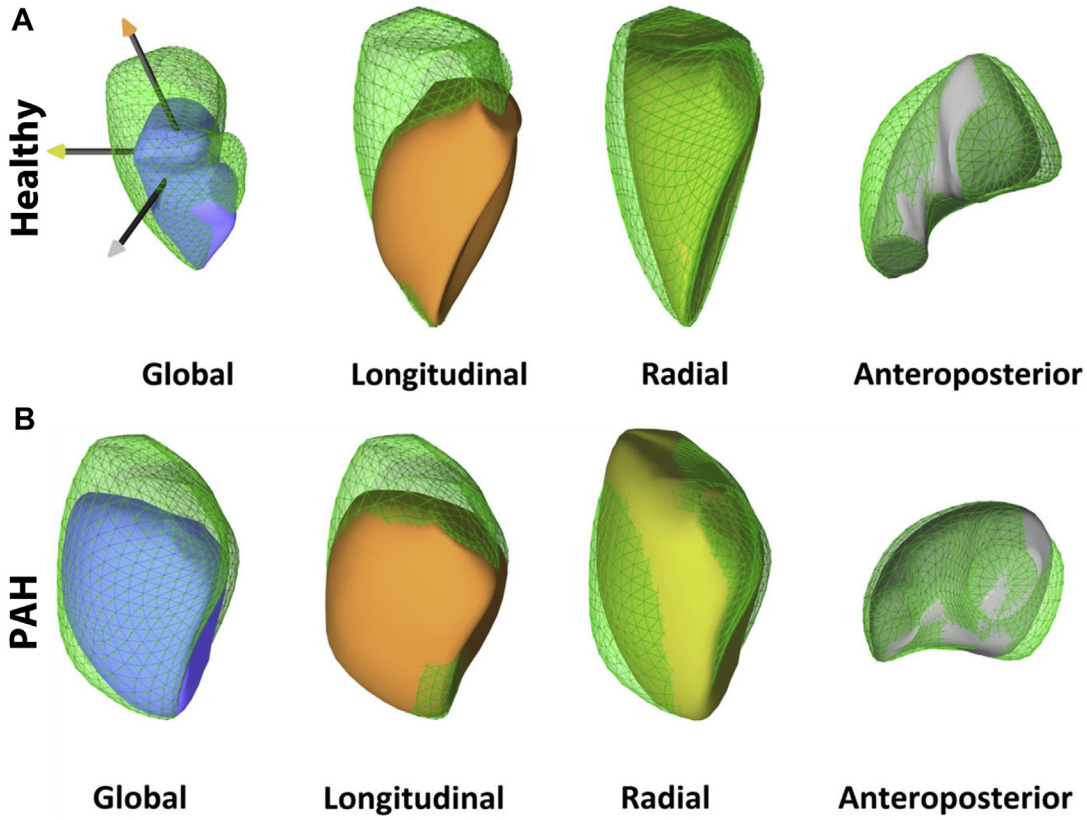

Fig. 1. Global function and decomposed motions of the RV in a healthy subject (*A*) and in a representative patient with PAH (*B*). The green mesh represents end-diastolic RV volume, and the blue surface is the end-systolic RV volume with all motion directions enabled. By decomposing the mechanical pattern of the 3-dimensional RV model, the different anatomically relevant wall motion components can be quantified individually. Each surface represents the volume loss at end systole generated by only the longitudinal (*orange*), radial (*yellow*), or anteroposterior (*gray*) motions, respectively. In (*A*), the relative contribution of each component is approximately 24%. In (*B*), longitudinal function is 17%, whereas radial and anteroposterior shortening decreased to approximately 7%. (*From* Kovacs *et al*[18]; with permission under the Creative Commons Attribution 4.0 International License (http://creativecommons.org/licenses/by/4.0/).)

cardiomyocytes has been observed in patients with end-stage RHF.[24]

To assess RV function, noninvasive and invasive techniques can be used. Two-dimensional (2D) echocardiography is the most common, and relatively low-cost technique to evaluate RV mechanics and morphology in suspected PH.[25] However, because of the complex anatomy of the RV, RV function cannot be fully explored with 2D echocardiography. Therefore, cardiac MRI is commonly used to assess global RV function (RV volume, mass, and ejection fraction), monitor RV dilatation, estimate transvalvular flow, and detect RV remodeling (myocardial fibrosis and inflammation) in healthy subjects and patients with PVD. Systolic and diastolic RV function can be measured through RV ejection fraction (RVEF) and right atrial pressure, respectively. Recently developed techniques, such as feature tracking, enable precise strain analyses to assess regional changes in wall motion and contraction patterns.[26] A major advantage of cardiac MRI is that it can provide information on pulmonary vascular dimensions. However, the technique is expensive, requires technical expertise, and is less widely available than echocardiography. In addition, both imaging modalities are highly load-dependent and become less accurate in a pathologic scenario. Thus, to understand ventriculoarterial coupling of the cardiopulmonary unit under physiologic or pathologic conditions, in a load-independent manner, pressure volume (P-V) loops can be used.[27] The main parameters to study RV systolic and diastolic function, as well as the arterial load by P-V loops are as follows:

- End-systolic elastance (E_{es}) to study RV systolic function. E_{es} is given by the slope of the end-systolic pressure versus the end-systolic volume of multiple P-V loops.
- Arterial elastance (E_a) to measure RV afterload. E_a is calculated as the product of the Total Pulmonary Resistance (TPR) and heart rate (HR),[28] Alternatively, E_a can be calculated as the ratio of RV end-systolic pressure (P_{es}) to SV (E_a = TPR · HR = P_{es}/SV). As such, P_{es} is considered to be approximately equal to mPAP, which assumption does not hold completely in RHF.
- Ventriculoarterial coupling is the ratio between end-systolic elastance and arterial elastance (E_{es}/E_a).
- End-diastolic elastance (E_{ed}) to assess RV diastolic function and stiffness. E_{ed} is the slope of the P-V relation at end-diastole.

In the healthy RV, optimal coupling occurs when there is maximal transference of potential energy from the ventricle to the pulmonary circulation at a minimal cost. In the adaptive RV, the increased afterload (E_a) causes RV hypertrophy, which augments contractility (E_{es}) and, as a consequence, ventriculoarterial coupling is maintained (preserved E_{es}/E_a). By contrast, with the progression toward a maladaptive RV, the HR increases (higher E_a) in an attempt to maintain cardiac output and ventriculoarterial uncoupling occurs (decreased E_{es}/E_a)[27,29] (**Fig. 2**). In addition, RV diastolic stiffness (E_{ed}) is related to worse clinical progression in PAH. In patients surviving more than 5 years, the increase in E_{ed} is explained by hypertrophy. However, in patients with poor survival (<5 years), E_{ed} values are not just higher than in controls due to hypertrophy. In fact, in end-stage PAH, other factors (eg, myofibril stiffness, fibrosis) contribute to the increase in RV diastolic stiffness.[30]

As a summary, the RV is coupled to the low pressure and highly compliant pulmonary circulation, which determines its anatomic features and also the energetically efficient way to pump the blood into the pulmonary arteries. During chronic pressure overload, such as in PH, enhancing RV contractility is essential to preserve RV adaptation. Afterward, the gain in ventricular pressures augments the stretch on the RV wall, leading to adaptive hypertrophy. Prolonged increase of RV pressure overload results in RV dilation, maladaptive remodeling, and ventriculoarterial uncoupling.[4] RV dilation may result in tricuspid regurgitation and functional decline. This functional deterioration is characterized by ventricular asynchrony and reduced RV SV, which links to underfilling of the LV.[21]

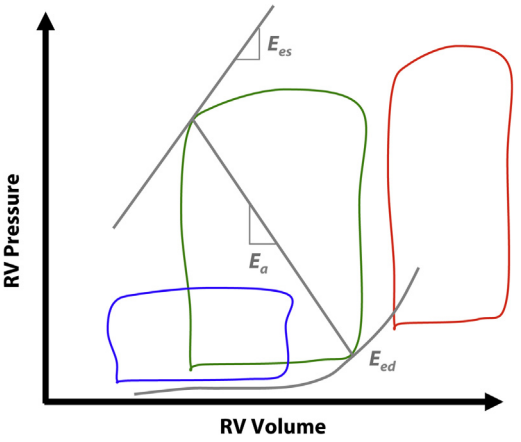

Fig. 2. Representative P-V loops of healthy, adaptive and maladaptive RVs. The ventriculoarterial coupling and RV wall stress are maintained in both healthy (*blue*) and adaptive (*green*) RVs. In the maladaptive RV (*red*), the volume and the wall stress are increased, and the RV is uncoupled from the pulmonary circulation. E_{es} (RV contractility) is the slope of the end-systolic pressure volume relation, E_a (arterial load) is a measure of the TPR and HR, and E_{ed} (ventricular elastance) is the slope of the end-diastolic pressure volume relation.

Several processes have been associated with either adaptive or maladaptive RV phenotypes, such as capillary rarefaction, metabolic shift from oxidative metabolism toward glycolysis, sympathetic hyperactivity, and fibrosis, among others.

In the following sections, we highlight the principal mechanisms involved in RV remodeling to increased pressure overload, from early until late stages of the disease. The progression from initial stages into the uncoupled failing stage is a continuum in which the remodeling events will, eventually, overlap and smoothly transit throughout the stages; it is not a switch on/off process. Notably, the progression from an adaptive to a maladaptive RV with functional loss may take place while the patient is in a stable clinical condition.[31]

EARLY ADAPTIVE MECHANISMS OF THE RIGHT VENTRICLE

RV adaptation to pressure overload is quite variable among patients, and the progression to RHF cannot be predicted currently. Top research priorities are the identification of novel ways to predict and assess RHF, such as new plasma or imaging

biomarkers, the generation and optimization of cell/animal models, and the development of innovative therapies. Briefly, the RV adaptive response (homeometric adaptation) is characterized by augmented RV contractility to match the afterload.[32] RV adaptation is illustrated by normal cardiac output, RVEF, and exercise capacity. RV function is maintained through concentric RV hypertrophy (increased mass to volume ratio to reduce wall tension) with minimal dilation and fibrosis. Intracellular mechanisms involved in the RV adaptive phenotype are rarely studied on human samples because of limited availability. Thus, most of the information is obtained from research on the LV and preclinical models such as in vitro cell culture or in vivo animal models. Nevertheless, different mechanisms involved in the adaptive RV remodeling have been proposed, like the regression into a fetal phenotype, increased neurohormonal stimulation, and the hypertrophied RV, all of which are detailed next.

Fetal Phenotype

One of the first mechanisms triggered by pressure overload is a regression toward the fetal phenotype by an upregulation of fetal isogenes and a downregulation of adult isogenes, which remains until end-stage PAH. This fetal regression is described by an altered expression of genes involved in cell metabolism, cardiac contractility, and calcium handling, which may affect the electromechanical conduction system.[7,33]

Cardiac metabolism is determined by energy demand, oxygen delivery, and the availability of substrates. Under physiologic conditions, high glycolytic metabolism occurs in the fetus, whereas oxidative metabolism is predominant in the adult heart.[34] The hypertrophic fetal RV prefers glycolytic metabolism, which maintains ATP production when less oxygen is available.[35] In adult life, hypertrophic cardiomyocytes use a similar transition from oxidative toward glycolytic metabolism. Characteristic of this glycolytic switch is the fact that glucose and not fatty acids become the main substrate for energy production.[36] Increased expression of c-Myc, glycolytic (ie, aldolase, hexokinase, pyruvate kinase, pyruvate dehydrogenase kinase, glucose transporter 1, and glucose-6-phosphate dehydrogenase) and structural (ie, myosin) genes were observed in experimental PH models.[37–40] A shift toward increased glycolysis is observed in the RV of patients with PAH who underwent PET imaging, and the increased glucose uptake correlated with dysfunction and pressure overload.[35,41] Even though the glycolytic adaptation is beneficial in the short-term to decrease the oxygen demand, it is insufficient to fulfill the demands of the RV and preserve RV function, leading to an energy-starved state and contributing to RHF.[42]

Furthermore, in the RV of subjects with moderate PAH-induced RHF, increased expression of natriuretic peptides and a shift toward the β-myosin heavy chain (β-MHC) isoform is observed. This slower/less active and more efficient β-MHC isoform reduces the ATP demand by cardiomyocytes.[43] The downregulation of α-MHC linked to the upregulation of β-MHC accounts for a reduced shortening velocity and contributes to myocardial dysfunction in PAH.[43] In addition, patients with PAH and patients with chronic thromboembolic PH (CTEPH) present with increased levels of both atrial and brain natriuretic peptides, which are associated with RV hypertrophy and RV dysfunction.[44]

Neurohormonal Activity

The neurohormonal system is involved in cardiovascular homeostasis through the sympathetic nervous system (SNS) and the renin-angiotensin-aldosterone system (RAAS). Pulmonary vascular cells and RV cardiomyocytes express the adrenoceptors β_1 and β_2, evidencing an RV-pulmonary vascular regulation by neurohormonal mechanisms. Patients with PAH present with increased neurohormonal activation. Increased systemic and pulmonary RAAS contributes to pulmonary vascular remodeling.[45] In addition, RV remodeling is regulated by both SNS and RAAS, whereas activation of both systems leads to increased stiffness of the RV and the consequent RV hypertrophy, as well as other molecular changes within the cardiomyocytes.[46,47]

Pressure overload is detected by cardiomyocytes through neurohormonal stimulation and mechanotransduction, which will contribute to RV hypertrophy.[48] Research on the LV showed that circulating and locally produced neurohormones, such as angiotensin II, endothelin-1, and norepinephrine, induce cardiomyocyte hypertrophy through the activation of janus kinase 2 (JAK2) and extracellular signal-regulated kinase, and the subsequent nuclear translocation of NFAT and GATA-4 transcription factors.[49,50] Interestingly, endothelin-1 and its receptor are upregulated in the human hypertrophied RV myocardium in patients with PAH, which might act as an early adaptive mechanism to trigger hypertrophy and maintain RV contractility in the setting of increased RV afterload.[51]

In addition, cardiomyocytes directly sense mechanical stimuli through integrin conformational

changes, stretch-activated ion-channels, and sarcomeres[52] (Fig. 3). Integrins are transmembrane receptors that connect the extracellular matrix (ECM) to the intracellular cytoskeleton (ie, α-actinin and titin) via downstream effectors (ie, focal adhesion kinases) and small GTPases. Titin is a giant sarcomeric protein responsible for the muscle passive stiffness and for keeping myosin molecules in place, and so defining the elastic properties of the cardiomyocytes. Actually, mechanical stretch leads to the extension of the unique N2B region in the cardiac titin, thereby revealing new binding places for signaling molecules, such as the Four and a Half LIM domains 2 (FHL2), which modulates titin elasticity and is crucial for cardiac development and hypertrophy signaling.[53]

Right Ventricular Hypertrophy

Pathologic hypertrophy is the consequence of a stressful stimulus on the heart, like an increased hemodynamic load. The hypertrophic growth of the RV in response to hemodynamic stress is a compensatory mechanism to reduce both the stress on the RV wall and oxygen consumption, but also to increase the force-generating capacity of the RV up to fivefold to remain coupled to the pulmonary unit.[54]

Adaptive hypertrophy is characterized by an increase in cardiomyocyte size through protein synthesis. This results in the addition of sarcomeres in parallel and lateral growth of individual myocytes. Cardiomyocyte hypertrophy occurs in the RV free wall, in muscular bands, and in trabeculations.[55] Altered myocardial fiber orientation was also described in adaptive hypertrophy. There are different morphologic patterns to describe the hypertrophic phenotype, and the one described in this section matches concentric hypertrophy with increased relative wall thickness and cardiac mass with little or no change in chamber volume.[6]

The hypertrophied RV has increased hypoxia inducible factor-1α (HIF-1α) stabilization, which leads to augmented vascular endothelial growth factor (VEGF) expression and activity as well as enhanced angiogenesis.[56] The hypertrophic response is associated with a proportional increase in the number of capillaries to ensure tissue perfusion and preserve RV function. In contrast, incoordinated myofiber growth and vascularization may lead to RHF. The angiogenic response is regulated by molecular cross-talk between cardiomyocytes and endothelial cells.[57] For example, in the chronic pressure-overload piglet model,

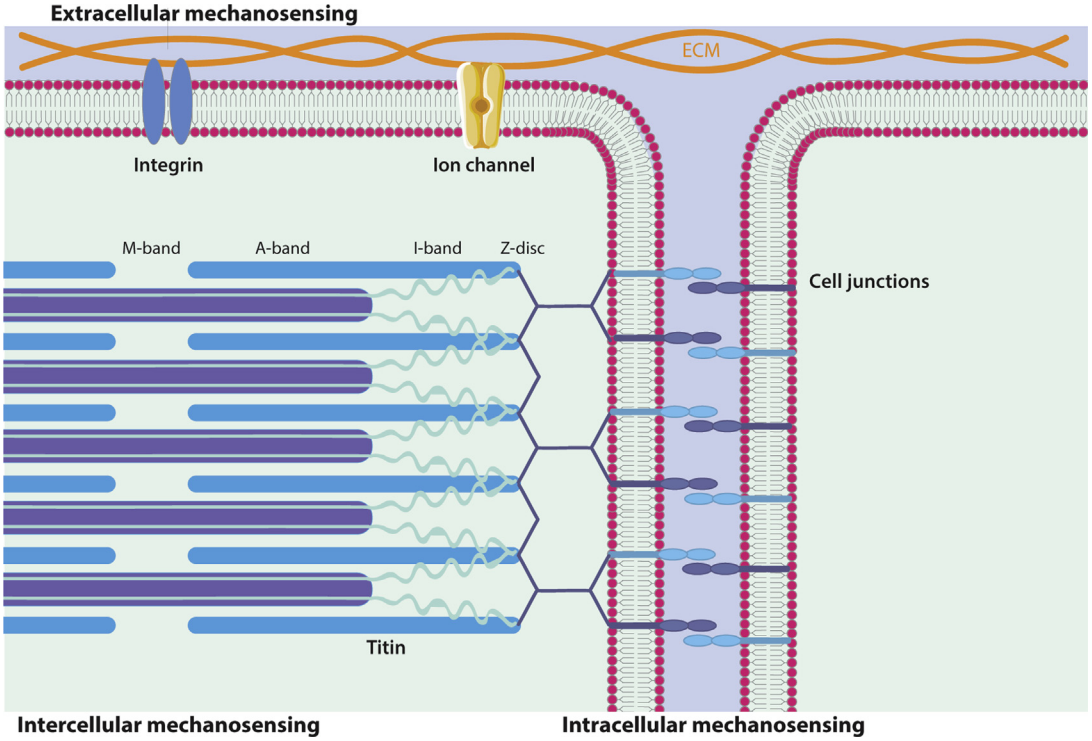

Fig. 3. Cardiomyocyte mechanosensing mechanisms in PH. Increased pressure overload is sensed by the cardiomyocytes throughout integrin conformational changes, stretch-activated ion-channels, cell junctions, and the sarcomeric titin.

adaptive RV remodeling is associated with an increased capillary density and low degree of fibrosis.[58] Along the same line, in the chronic hypoxia-induced PH murine model, RV angiogenesis is an early adaptive response to ensure a perfect coordination between myocardial capillary growth and cardiomyocyte growth, thereby preserving cardiac function. However, after continued exposure to chronic hypoxia, progressive RV hypertrophy without additional angiogenesis led to the activation of hypoxia-dependent gene expression and RV hypoxia.[59] Insufficient RV angiogenesis is suggested to be a consequence of the VEGF/HIF-1α dysregulation and Akt1 activation, as observed in the Sugen hypoxia model.[60] From the LV of Akt1–transgenic mice, it has been hypothesized that adaptive hypertrophy and appropriate angiogenesis is the result of short-term Akt1 activation; whereas long-term Akt1 activation is linked to maladaptive dilation and capillary rarefaction.[61] A recent study of mice with hypoxia-induced PH demonstrated that Akt signaling is involved in RV remodeling.[62] Therefore, PH experimental models suggest that the maladaptive RV phenotype is the result of a mismatch among RV hypertrophy, metabolism, and angiogenesis that induces myocardial ischemia and subsequent RHF.[60,63]

As Hill and Olson[6] pointed out, the adaptive phenotype observed in patients with PVD is an example of pathologic hypertrophy that, under persistent stress, may lead to heart failure and arrhythmias.

PROLONGED ADAPTATION RESULTS IN THE MALADAPTIVE RIGHT VENTRICLE

The mechanisms behind the transition from RV adaptation to maladaptation and RHF remain elusive. Nevertheless, RHF is characterized by RV dilation, reduced oxygen supply, RV cardiomyocyte growth arrest, RV diastolic stiffness, mitochondrial dysfunction, increased RV inflammation, and pronounced RV fibrosis.

The maladaptive phenotype (heterometric adaptation) appears when the RV experiences irreversible decompensation after a period of immense adaptation. The RV expands to maintain flow output, at the expense of rising filling pressures and systemic congestion.[32] In slowly advancing pressure overload, RV contractility can increase up to fivefold, mitigating RV dilation and the decrease in SV. When RV dilatation becomes inevitable, the septum bows toward the LV, worsening the function of both ventricles. At this time, the RV has progressed into the uncoupled failing stage, characterized by increased tissue stiffness and high metabolic demand.

Interestingly, animal in vivo experimentation supports the idea that chronic pressure overload is responsible for RV hypertrophy, but requires other events, such as myocardial apoptosis, fibrosis, and capillary rarefaction, to promote RV failure.[60]

Right Ventricular Dilation

Sustained and progressive pressure overload during the disease progression will, eventually, limit RV hypertrophy. As an escape mechanism, the RV may dilate to preserve the SV and cardiac output, by means of the Frank-Starling mechanism "increase in SV associated with increased preload." Nevertheless, excessive dilation and overstretching of the RV cardiomyocytes will limit myocardial contractility and ultimately lead to the RV uncoupling from its pulmonary circulation.[27]

RV dilation is associated with (ECM)remodeling and increased collagen turnover.[64] In addition, RV dilation changes the shape of the chamber into a more spherical one, which is associated with functional tricuspid valve regurgitation and elevated right atrial pressure.[65] In fact, significant backward flow into the vena cava during right atrial contraction is associated with RV diastolic stiffness and impaired RV filling in patients with PAH, whereas backward flow due to tricuspid regurgitation was minimal. Consequently, RV SV is reduced because venous return was restricted, and RV volumes may also influence the amount of backflow.[66]

Oxygen Supply-Demand Mismatch

Under physiologic conditions, RV coronary flow is highest in systole; by contrast, LV coronary flow predominantly occurs during diastole. RV perfusion is altered under pathologic conditions, that is, increased in the hypertrophied RV as previously explained, and reduced in maladaptive remodeling. Therefore, progressive blood flow through the coronary system is reduced in advanced PAH, but it is still unclear if it is because of reduced global perfusion due to a lower driving pressure and/or to capillary rarefaction. Regardless, we can appreciate a mismatch at the level of the cardiomyocyte between decreased oxygen supply and increased demand, which could contribute to the development of RHF in PAH.

Reduced coronary flow and capillary rarefaction

The coronary circulation encompasses the blood vessels supplying oxygen and nutrients to the

heart muscle. Perfusion abnormalities in the RV were detected in patients with severe PAH with normal coronary angiography.[67,68] Patients with PH with maladaptive RV remodeling have decreased RV systolic coronary flow that is proportional to RV mass and pressure,[68] with reduced myocardial oxygenation.[68,69] An adenosine stress perfusion cardiac MRI study on patients with PAH demonstrated diminished perfusion, which was inversely correlated with RV workload and RVEF.[70] Decreased myocardial perfusion and expression of angiogenic and protective genes and microRNAs may contribute to RV ischemia and RHF, as observed in experimental models of PH.[63,71,72] In addition, higher concentrations of mitochondrial reactive oxygen species (ROS) will, ultimately, suppress angiogenesis, as described in the monocrotaline-induced PAH model.[63]

Capillary rarefaction is characterized by impaired angiogenesis and reduced microvascular density, due to underproliferation of endothelial cells rather than vessel loss, as no apoptosis was observed in RV sections in the Sugen hypoxia rat model.[71] Patients with maladaptive PAH show a decreased capillary density and reduced myoglobin content and activity in the RV.[73] In addition, capillary rarefaction has been described for patients with PAH and linked to RV glutaminolysis.[40] Interestingly, RV capillary density was decreased and morphologically heterogeneous in the Sugen hypoxia rat model, but not significantly altered in the pulmonary artery banding (PAB) model, suggesting that different alterations in the pulmonary vasculature may affect the RV microcirculation.[60]

Mitochondrial dysfunction

The glycolytic shift in the long run induces mitochondrial dysfunction and excessive ROS production, which has been linked to NFAT activation.[74] Both ventricles have similar mitochondrial protein profiles under physiologic conditions; however, under pathologic conditions, the antioxidant response is lower in the RV.[75] In fact, in the monocrotaline rat model, it was shown that antioxidant enzymes were not activated at an early phase, which predisposed the hypertrophied RV to ROS-induced damage (ie, extensive apoptosis) and contributed to RHF.[76] Likewise, in the PAB murine model, earlier downregulation of antioxidant enzymes and increased ROS production was also observed.[42] It has been hypothesized that increased NADPH oxidase and mitochondrial complex II activity leads to enhanced mitochondrial ROS generation.[77]

Interestingly, genes involved in mitochondrial biogenesis and metabolism are altered in the monocrotaline rat model with severe PAH and decompensated RHF, and also in patients with PAH with mutations in the gene encoding for the bone morphogenetic protein receptor type 2 (BMPR2).[78] Excessive ROS production was demonstrated in human PAH-patient derived cells[79] and PH animal models.[75,77,79,80] Indeed, mitochondrial dysfunction is observed in patients with PAH and preliminary results with mitochondria-targeting drugs show hemodynamic improvement in genetically susceptible patients.[81] A recent study with a rat cardiomyocyte cell line carrying common BMPR2 mutations demonstrated reduced mitochondrial respiration with increased mitochondrial superoxide production.[82] Decompensated PAH rats presented with elevated mitochondria-derived ROS levels, reduced HIF-1α and VEGF expression, and capillary rarefaction due to ROS-mediated activation of the pro-oncogenic factor p53.[63] Although little is known about the role of oxidative stress in RV remodeling, in PAH experimental models, oxidative stress has been associated with increased RV apoptosis, fibrosis, and worse RV function.[60,76,78,80]

Neurohormonal Overactivation

The maladaptive phenotype also has been associated with increased chronic sympathetic activation, decreased parasympathetic activity, RV diastolic stiffness, oxidative and nitrosative stress, changes in the β-adrenergic pathway, and decreased activity of the catalytic subunit of adenylate cyclase.[30,83–88]

Increased sympathetic activity, and the subsequent activation of the RAAS, is considered beneficial at early stages of RHF because it offers inotropic support, peripheral vasoconstriction, and salt and water retention to maintain cardiac output and systemic perfusion pressure. However, chronic sympathetic activation is detrimental because it desensitizes β-adrenergic receptors, reduces the chronotropic response, leads to pathologic RV remodeling, impairs the inotropic reserve of the RV, shifts energy metabolism, enhances cardiomyocyte apoptosis, delays HR recovery, and increases mortality.[83,89]

The maladaptive RV in PAH is characterized by increased expression levels of β_2-adrenergic receptors and downregulation of β_1-adrenergic receptors, both associated with systolic dysfunction.[43,83,90,91] β_1-adrenoreceptor downregulation impairs protein kinase A (PKA) activation and subsequent phosphorylation of important proteins involved in calcium handling and sarcomeric function,[92] as explained in the next section.

Diastolic stiffness

Early in the progression of PAH, the RV increases its contractility as a mechanism of adaptation to the augmented afterload. Nevertheless, in advanced stages of the disease, systolic function cannot satisfy the demand and the RV progressively dilates; and diastolic dysfunction becomes impaired. Increased RV diastolic stiffness in patients with PAH is attributed to interstitial and perivascular fibrosis as well as RV cardiomyocyte stiffening.[84] Hypertrophy, fibrosis and sarcomeric disorganization affect cardiomyocyte contractility and increase ventricular stiffness.[93] Myocardial fibrosis and sarcomeric stiffening were reported in patients with PAH and were directly related to increased passive tension of isolated RV cardiomyocytes at different sarcomere lengths. In fact, cardiomyocyte stiffening was associated with decreased titin phosphorylation in the RV, and not to titin isoform composition.[84] Furthermore, 3 main protein modifications contributed to RV diastolic stiffness in PAH. First, decreased PKA-mediated titin phosphorylation increased RV cardiomyocyte stiffness. Second, reduced cardiac troponin I phosphorylation increased calcium sensitivity. And third, altered expression and phosphorylation of calcium-handling proteins, as Sarco/Endoplasmic Reticulum Ca^{2+}-ATPase 2a and phospholamban impaired calcium clearance during diastole.[92]

Fibrosis

Tissue stiffness is directly related to RV fibrosis and cardiomyocyte performance. A recent review from Andersen and colleagues[94] proposed a dual role for RV fibrosis in PVD: (1) an early adaptive response to prevent cardiomyocyte overstretch and ventricular dilatation for optimal function; and (2) a late maladaptive response that augments myocardial stiffness, disturbs cardiomyocyte excitation-contraction coupling, and perturbs the cardiac contraction coordination. Adaptive fibrosis is a compensatory mechanism to support ventricular shape. Ultimately, fibrosis becomes maladaptive because of excessive collagen accumulation and altered collagen structure and organization, damaging the ECM integrity and contributing to cardiac dysfunction.[95]

Cardiac function depends on the contraction and relaxation of the myocardium, which, at the same time, relies on the collagen content in the ECM. Cardiac fibrosis is the result of mechanical stress on both RV interstitium (fibroblasts) and cardiomyocytes. Interstitial fibrosis is characterized by collagen synthesis and deposition by differentiated myofibroblasts, which leads to an increased collagen I/III ratio and augments myocardial stiffness, which has been described in patients with more severe RHF.[84] Little is known of an association between the ECM and the cardiac systole. During systole, the force is transferred throughout the collagen network; thus, fibrosis disrupts the cardiac electromechanical coupling and, subsequently, the synchronized myocardial contraction. A reduced number of gap junctions has been observed in fibrotic tissue, which alters the coordination of the heart contraction because of both deteriorated intercellular coupling and decreased conduction velocity as observed in the PAB rat model.[96] On the other hand, several reports described the contribution of myocardial fibrosis to diastolic dysfunction.[30,97,98] A stiffer myocardium, caused by fibrosis and cardiomyocyte stiffness, is associated with impaired early diastolic filling.[97]

Unfortunately, histologic assessment of RV interstitial fibrosis and collagen composition has been limited to postmortem histomorphometric analyses. Thus, to reveal the importance of RV fibrosis during the progression toward RHF and the eligibility for lung transplantation, new techniques and biomarkers are needed that are sensitive enough to detect interstitial fibrosis. Currently, interstitial fibrosis is also estimated by delayed gadolinium enhancement and T1 mapping cardiac MRI, with limited resolution.[99]

Accordingly, the reversibility of interstitial fibrosis after decreasing the RV afterload has not been studied, even though it has been proposed, opposite to the irreversible replacement fibrosis following cardiomyocyte loss. The RV is able to decrease RV wall thickness and improve RV function after lung transplantation in patients with PAH, and also in patients with CTEPH undergoing pulmonary arterial endarterectomy or balloon angioplasty.[100–104] Despite an immediate reduction in RV size and pulmonary artery pressures, and a normalization of the septal geometry, the functional improvement remains variable and is associated with prior hemodynamics and the duration of disease before lung transplantation.[105]

In summary, regression into a fetal phenotype, the inefficient metabolism and contractility, the altered neurohormonal stimulation, myocardial fibrosis, and the insufficient tissue vascularization, contribute to the deterioration of the RV. Therefore, accumulative and interrelated cell and molecular changes within the RV that start as beneficial adaptations, lead to impaired cardiac function in the long-term, and the consequent maladaptive RV phenotype, as illustrated in **Fig. 4**.

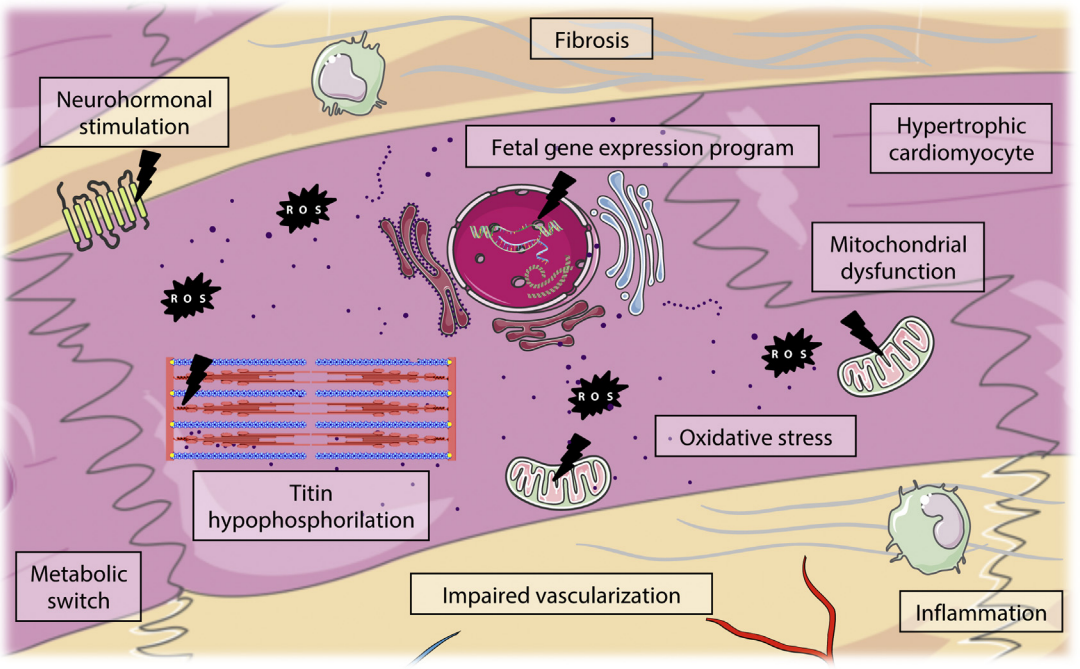

Fig. 4. Pathomechanisms that trigger RV maladaptation. Molecular, cellular, and tissular mechanisms in the cardiomyocyte promote the transition from adaptive to maladaptive RV remodeling in the long run. Image created using Servier Medical Art database under a Creative Commons Attribution 3.0 Unported License.

DISCUSSION

The RHF-specialized research carried out during the past decade evidenced an important role for the RV, and substantial differences between both ventricles regarding their structure, embryologic origin, anatomy, function, and remodeling in response to increased afterload. In the clinical setting, it is easy to observe heterogeneity in the RV response to a given increased afterload, which indicates that some genetic and environmental factors are key and still need to be elucidated. Patients with similar RV afterload can show completely different responses. We speculate in this article that there is a continuum of events of cardiac remodeling. Chronic adaptation processes such as neurohormonal activation, hypertrophy, and reactivation of the fetal gene program will eventually exhaust and result in maladaptation and induce RHF; in some patients, probably at earlier time-points than others.

Another interesting aspect is the role of inflammation in the context of RHF. Except from its contribution to RV fibrosis as previously explained, this subject has been largely ignored. It is well-known that inflammation is involved in pulmonary vascular remodeling.[106] Moreover, patients with PAH have high circulating levels of inflammatory chemokines and cytokines.[107] Whether a high inflammatory milieu contributes to maladaptive RV remodeling has not been studied. The presence of inflammatory cells and the expression of proinflammatory cytokines and adhesion molecules within the RV have been shown in acute RHF, but not so much in chronic RHF.[108] An original hypothesis to explain the inflammatory role in RV dysfunction is gaining momentum: "a sick pulmonary circulation promotes RV maladaptation." It suggests that proinflammatory mediators released by the altered pulmonary circulation are transported into the coronary circulation and, once there, negatively affect RV function, already challenged by the increased mechanical stress. The harmful influence of the lungs is mediated by immune cells activated within the pulmonary vascular wall, which progressively infiltrate the heart and release chemokines, antibodies, and hormones (ie, angiotensin II and endothelin-1).[108]

Currently, there are no specific therapies to treat RHF, and our knowledge on the mechanisms underlying the adaptive and maladaptive responses of the RV is still under construction. Human tissue is scant and limited to end-stage PAH, and the knowledge on the pathophysiological mechanisms behind PAH and RHF progression are mostly based on studies with animal models. Unfortunately, humans and animals have different physiology and disease progression, and there is no animal model that fully recapitulates the clinical

features of PAH. Thus, to move the field forward and to develop RHF-specific therapies, there is a clear need to develop novel strategies to investigate the progression of RV adaptation to RV failure within patients. Advanced imaging techniques and software, interdisciplinary approaches to evaluate multiorgan affectation, as well as development of human cell models are essential.

In conclusion, PVDs result in an excessive increase in RV pressure. To preserve ventriculoarterial coupling, the contractility of the RV increases and RV hypertrophy is induced. Neurohormonal activation and mechanosensing play key roles in this process. In addition, to enhance myocardial efficiency, the fetal gene program is reactivated; however, prolonged activation of these adaptive mechanisms eventually leads to RV diastolic stiffness, ischemia, and mitochondrial dysfunction.

The key questions still under investigation today are as follows: Which mechanisms control RV adaptation in PVD? Can we predict disease progression at early stages? What is the best treatment for both RV and lungs? Unfortunately, research is hampered by limited availability of human samples and the not always successful translation from animal models. Therefore, new strategies and human cell models are fundamental. More information will help to explain disease progression and the succession of RV changes, and will hopefully result in the development of specific treatments to prevent the development of RHF.

CLINICAL CARE POINTS

- Right ventricular function is the major determinant of prognosis in Pulmonary Hypertension.
- Cardiac MRI is the superior method to assess right ventricular adaptation.
- Neurohormonal activation, reduced oxygen delivery and metabolic remodeling are key components of progressive right ventricular dysfunction.
- Given the lack of proven therapies directly improving right ventricular function, symptomatic treatment of right ventricular failure consists of management of preload and afterload.

DISCLOSURE

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