

Right Heart Adaptation to Pulmonary Arterial Hypertension

Physiology and Pathobiology

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Survival in patients with pulmonary arterial hypertension (PAH) is closely related to right ventricular (RV) function. Although pulmonary load is an important determinant of RV systolic function in PAH, there remains a significant variability in RV adaptation to pulmonary hypertension. In this report, the authors discuss the emerging concepts of right heart pathobiology in PAH. More specifically, the discussion focuses on the following questions. 1) How is right heart failure syndrome best defined? 2) What are the underlying molecular mechanisms of the failing right ventricle in PAH? 3) How are RV contractility and function and their prognostic implications best assessed? 4) What is the role of targeted RV therapy? Throughout the report, the authors highlight differences between right and left heart failure and outline key areas of future investigation. (J Am Coll Cardiol 2013;62:D22–33) © 2013 by the American College of Cardiology Foundation

Pulmonary arterial hypertension (PAH) is a progressive disorder that affects both the pulmonary vasculature and the heart (1–6). Although the initial insult in PAH involves the pulmonary vasculature, survival of patients with PAH is closely related to right ventricular (RV) function (7–19). The right ventricle adapts to the increased afterload by increasing its wall thickness and contractility. In the vast majority of

patients, however, these compensatory mechanisms are insufficient, and RV dysfunction occurs. In this report, we highlight current understanding of RV pathobiology in PAH and briefly outline the evidence underlying the management of right heart failure (RHF) in PAH. Future directions and priorities of research in RV research in PAH are also discussed. Although the majority of the report

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focuses on RHF in the setting of PAH, the committee also wants to emphasize that RV function is also a strong predictor of outcomes in patients with left heart failure, advanced lung disease, and congenital heart disease (20).

Definition of the Right Heart Failure Syndrome

RHF in patients with PAH can be defined as a complex clinical syndrome due to suboptimal delivery of blood and/or elevated systemic venous pressure at rest or exercise as a consequence of elevated RV afterload.

The cardinal clinical manifestations of RHF are exercise limitation and fluid retention. Exercise limitation is the earliest symptom of RHF and is a strong predictor of survival in patients with PAH (8,14,21). Exercise limitation is related to a decrease in flow reserve during exercise (decreased peak cardiac index) (22–24). In addition, a reduction in peripheral blood flow can increase lactate production, further contributing to muscle fatigue and exercise limitation. Supraventricular tachycardia, which can occur in approximately 12% of patients with PAH or inoperable thromboembolic pulmonary hypertension, can also lead to clinical deterioration and reduced exercise capacity (25). Syncope, a less common symptom of PAH, often indicates severe limitations in flow reserve. As in left-sided heart failure, RHF can also lead to chronic kidney disease and hyponatremia (26). Shah *et al.* (27) showed that chronic kidney disease in patients with PAH is associated with increased right atrial pressure and a higher likelihood of death or transplantation. Similarly, acute kidney injury has also been associated with worse outcomes after acute RHF (28). Although congestive hepatopathy is often observed in patients with RHF and PAH, cirrhosis is a late complication of severe RHF. In patients with worsening hypoxemia and PAH, right-to-left shunting through a patent foramen ovale must be considered.

Patients with PAH may also present with acute heart failure. Recent studies have shown that the short-term mortality in patients with PAH and acute RHF may be as high as 40% in patients who require admission to the hospital (29–32). Although the majority of patients with acute RHF are admitted with congestive symptoms requiring diuretic therapy, a smaller proportion of patients will have low-cardiac output syndrome requiring inotropic or vasopressor support (29,30). Although the most common cause of death in patients with PAH is progressive RHF, sudden and unexpected death may also occur (33). In a study by Hoepfer *et al.* (33), sudden death explained 17% of cardiopulmonary arrest for which resuscitation was attempted. Among all patients who had cardiopulmonary arrest (not just those with sudden death), the initial electrocardiogram at the time of cardiopulmonary resuscitation showed bradycardia in 45%, electromechanical dissociation in 28%, asystole in 15%, ventricular fibrillation in 8%, and other rhythms in 4% (33).

In patients with chronic left heart failure, heart failure is usually classified into 4 stages of development: at risk for heart

failure (stage A), “asymptomatic” heart dysfunction (stage B), symptomatic heart failure (stage C), and end-stage heart failure (stage D) (34). This classification could potentially be applied to patients with RHF, with the caveat that the majority of patients with advanced RHF (stage D) have the ability to reverse remodel after lung transplantation. Also importantly, although we often consider the right ventricle and the left ventricle as separate entities, this distinction is somewhat artificial, because both ventricles are interconnected through the interventricular septum, shared myofibers, and the pericardium. Because of ventricular interdependence, patients with RHF will often have relaxation abnormalities of the left ventricle and, in severe cases, even left ventricular systolic dysfunction (2,20,35). Recent studies have also emphasized electrophysiological remodeling in the left ventricle in patients with PAH (36).

Abbreviations and Acronyms

BNP = B type natriuretic peptide
CO = cardiac output
Ea = arterial elastance
Ees = ventricular elastance
LV = left ventricular
MHC = myosin heavy chain
MPAP = mean pulmonary arterial pressure
PAC = pulmonary arterial compliance
PAH = pulmonary arterial hypertension
PH = pulmonary hypertension
PVR = pulmonary vascular resistance
RAP = right atrial pressure
RHF = right heart failure
RNA = ribonucleic acid
RV = right ventricular
RVEF = right ventricular ejection fraction

Pathobiology of Right Heart Failure Syndrome in Pulmonary Arterial Hypertension

The continuum of RV remodeling in PAH. RV adaptation and ventricular remodeling in PAH is a complex process that depends not only on the severity of pulmonary vascular disease but also on the interplay between neurohormonal activation, coronary perfusion, and myocardial metabolism (Fig. 1) (6,20,37–45). Other factors that may influence RV adaptation include the rate and time of onset of pulmonary hypertension, its underlying etiology, and, although not yet well defined, genetic and epigenetic factors.

Although ventricular remodeling in PAH represents a continuum, experimental studies often differentiate 2 patterns of ventricular remodeling on the basis of morphometric and molecular characteristics: adaptive and maladaptive remodeling (Table 1). Adaptive remodeling is characterized by more concentric remodeling (higher mass-to-volume ratio) and preserved systolic and diastolic function (e.g., ventricular remodeling observed in patients with Eisenmenger syndrome), whereas maladaptive remodeling is associated with more eccentric hypertrophy and worse systolic and diastolic function (e.g., remodeling observed in patients with PAH associated with connective tissue disease or idiopathic PAH) (9,46). Tricuspid regurgitation, which is

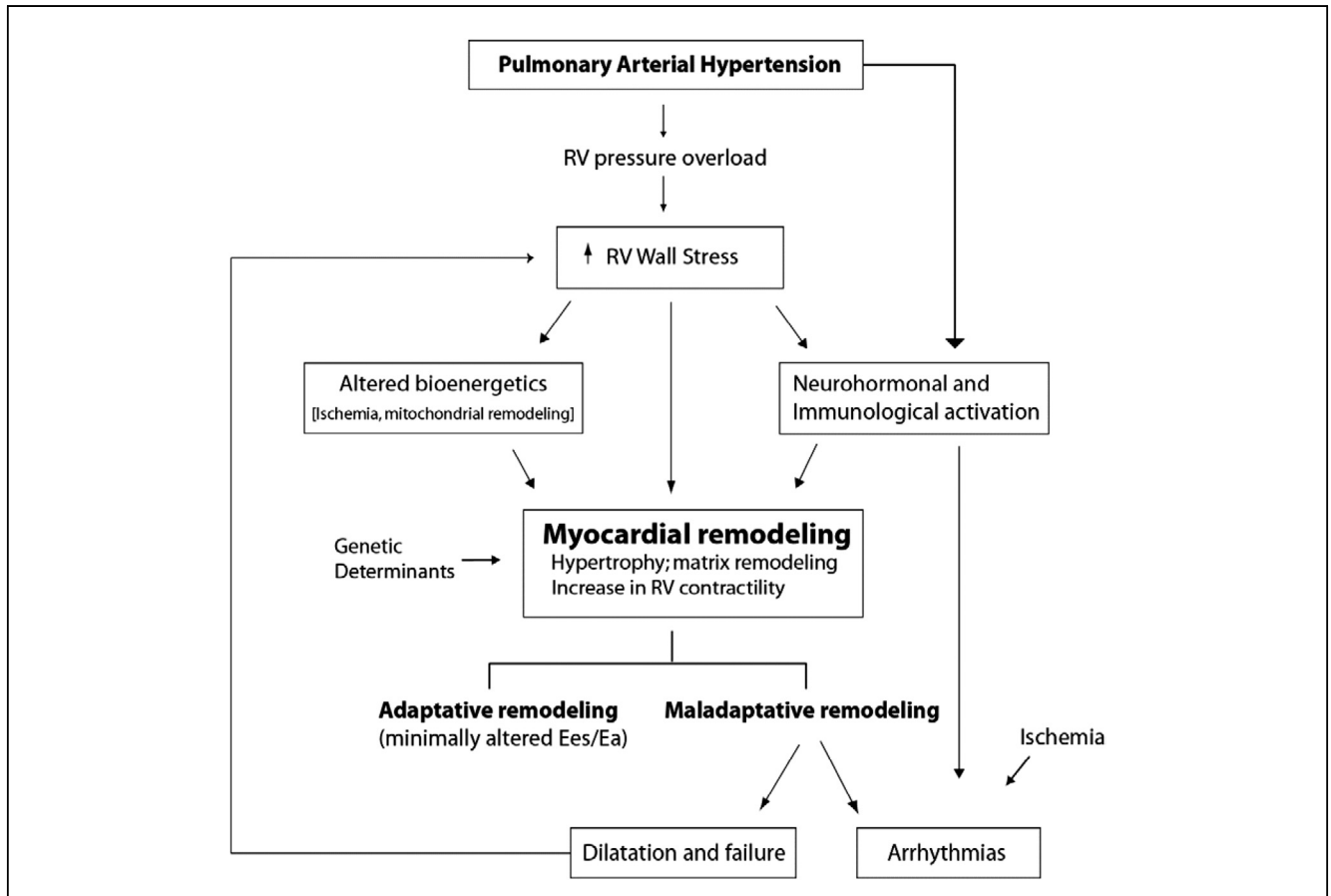


Figure 1 Pathophysiology of RV Dysfunction in PAH

Increased right ventricular (RV) wall stress, neurohormonal activation, inflammation, and altered bioenergetics contribute to RV remodeling in pulmonary arterial hypertension (PAH). Adaptive remodeling is associated with minimally altered ventriculoarterial coupling. Progressive RV dilation with maladaptive remodeling further contributes to RV stress. Adapted, with permission, from Champion et al. (5), Benza et al. (8), and Rudski et al. (99).

often secondary to annular dilation, may also lead to adverse ventricular remodeling and decreased flow reserve. Right-to-left shunting through a patent foramen ovale is also observed more frequently in patients with maladaptive remodeling and more severe RHF (47). Recent studies also suggest that RV dyssynchrony is a marker of maladaptive remodeling and more severe dysfunction (48–54). In PAH, the RV free wall is still contracting while the left ventricle is already in its early diastolic phase, leading to late systolic leftward septal movement (55). Because myocytes under mechanical stress prolong their contraction time and action potential duration, right-to-left ventricular dyssynchrony will increase in the failing right ventricle with increased wall stress, explaining why measures of dyssynchrony are associated with prognosis.

When comparing ventricular remodeling with pressure overload, several differences emerge between the right and left ventricles. First, ventricular enlargement occurs much earlier in the course of PAH compared with the pressure-overloaded left ventricle (e.g., in systemic hypertension or aortic stenosis). Mechanically, this can be partially explained by the fact that

RV wall stress is greater for a comparable pressure increase because of the smaller thickness of the right ventricle. Second, fibrosis is much less extensive in patients with RV pressure overload (often <10% of ventricular volume) and often limited to the RV-septal insertion points compared with myocardial fibrosis observed in patients with aortic stenosis or severe systemic hypertension (56–59). This explains why the majority of patients with severe RHF recover their ventricular function after lung transplantation, even if right ventricular ejection fraction (RVEF) is severely reduced at the time of transplantation (60–63). Identifying which patients would not recover right heart function after lung transplantation alone and therefore would benefit from heart-lung transplantation remains a subject of ongoing investigation (64).

The concept of ventriculoarterial coupling and the cardiopulmonary unit in PAH. Recent focus in PAH research has shifted from looking at the pulmonary vasculature and the right heart as separate entities to analyzing the cardiopulmonary unit as a system (5). This is valid not only from the physiological perspective but also from a therapeutic aspect. Several studies have shown that RV adaptation

Characteristic	Adaptive Remodeling	Maladaptive Remodeling
Remodeling		
RV size	Normal size to mild dilation	RV enlargement
Mass/volume ratio	Higher	Lower
Function		
VA coupling	Usually preserved or mildly decreased	Lower
RVEF at rest	Normal to mildly decreased	Decreased
CPET	Usually better preserved exercise capacity and ventilatory efficiency	Decreased exercise capacity and increased ventilatory inefficiency
Ventricular/flow reserve	Probably decreased early	Decreased
BNP or NT-BNP	Normal	Elevated
Perfusion	Normal or mildly impaired	Decreased
Metabolism	Normal glucose uptake	Increased glucose uptake
Molecular (selected)		
Micro-RNA 133a	Normal	Decreased
Apelin	Increased	Severely reduced
Insulin-like growth factor-1	Increased	No increase
Vascular endothelial growth factor	Increased	Normal/reduced
Hexokinase-1	Decreased	Increased
Alcohol dehydrogenase-7	Normal	Decreased

Most of the molecular data are based on experimental studies. Ventricular reserve refers to either the contractile response of the right ventricle or the dynamic change in diastolic RV end-diastolic pressures during exercise or pharmacological stress.
 BNP = B-type natriuretic peptide; CPET = cardiopulmonary exercise testing; NT-BNP = N-terminal B-type natriuretic peptide; RNA = ribonucleic acid; RV = right ventricular; RVEF = right ventricular ejection fraction; VA = ventriculoarterial.

to PAH depends on the right ventricle’s ability to increase its contractility in response to the increased afterload (43,65). “Ventriculoarterial coupling” specifically refers to the relationship between ventricular contractility and afterload (Fig. 2). Its most objective metric is the ratio between ventricular elastance and arterial elastance. Although the idea is based mainly on research involving the left ventricle, it is assumed that the normal ratio of ventricular to arterial elastance for the right ventricle is also between 1.5 and 2.0,

corresponding to an optimal balance between RV mechanical work and oxygen consumption (5,43,66). Kuehne et al. previously showed that chronic RV pressure overload in PAH was associated with reduced RV pump function despite enhanced RV myocardial contractility. Using ventriculoarterial measures, recent studies have also confirmed worse ventriculoarterial coupling in patients with scleroderma-associated PAH compared with those with afterload-matched idiopathic PAH (67).

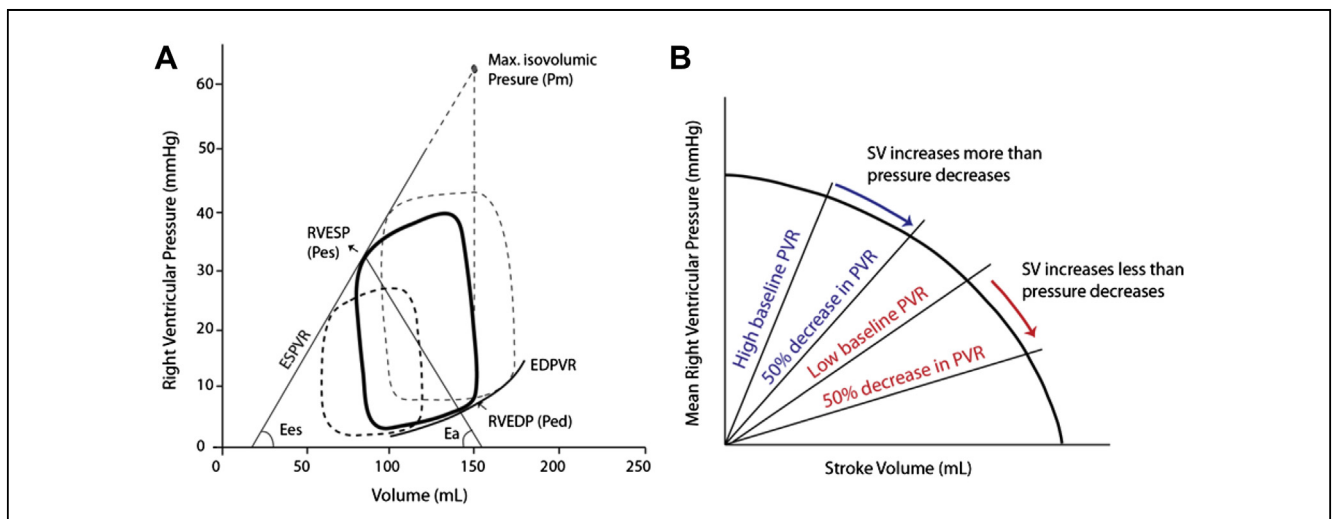


Figure 2 Describing Right Ventricular Function

(A) Pressure-volume relation, illustrating the concepts of ventricular elastance (Ees), arterial elastance (Ea), and the maximal isovolumic pressure used to estimate single-beat Ees. (B) Pump function graph, illustrating that when baseline pulmonary vascular resistance (PVR) is high, a decrease in PVR mainly causes an increase in stroke volume, while at lower baseline PVR, pressure is more affected.

Table 2 Measures of Ventricular and Pulmonary Load

Component of Load	Equation or Definition	Comment
PVR	$PVR = TPG/CO$	Most commonly used clinical measure of resistive load
PAC	$PAC = SV/PP$	Most commonly used clinical measure of pulsatile load
Ea	$Ea = RVESP/SV$	Common measure of load used in pressure-volume loop analysis
Pulmonary impedance	Fourier transformation yields impedance and phase according to harmonics	Used in experimental and research settings; cannot be summarized by a single number
DPPG	$DPPG = DPAP - \text{mean PCWP}$	New markers to assess out-of-proportion heart failure with left heart disease
Mean pulmonary arterial distensibility	$(\text{Area}_{\text{systole}} - \text{Area}_{\text{diastole}})/\text{Area}_{\text{systole}}$	Assessed with MRI; may be useful in detecting early PH
Mean PAP-CO slope	Slope of mean PAP to CO relationship or main slope of TPG-CO relationship	The slope represents a more dynamic concept of resistance to flow; may be a more physiological way to define exercise-induced PH
RV afterload	Estimated by RV wall stress: $RVESWS = (0.5 \times RVSP \times r_{RVES})/RVES \text{ wall thickness}$	Simplified formula, as RV geometry is more difficult to assess

PVR can be indexed to BSA. Usually PAC is not indexed, because it represents a measure of flow and pressure.

CO = cardiac output; DPAP = diastolic pulmonary arterial pressure; DPPG = diastolic pulmonary pressure gradient; Ea = pulmonary arterial elastance; MRI = magnetic resonance imaging; PAC = pulmonary arterial capacitance; PAP = pulmonary arterial pressure; PCWP = pulmonary capillary wedge pressure; PH = pulmonary hypertension; PP = pulmonary pressure; PVR = pulmonary vascular resistance; r_{RVES} = right ventricular end-systolic radius; RV = right ventricular; RVES = right ventricular end-systolic; RVESP = right ventricular end-systolic pressure; RVESWS = right ventricular end-systolic wall stress; RVSP = right ventricular systolic pressure; SV = stroke volume; TPG = transpulmonary gradient.

Clinically, RV afterload is estimated using simple measures of load such as arterial elastance, pulmonary vascular resistance, and pulmonary arterial compliance (Table 2). Arterial elastance is the metric of afterload used during pressure-volume loop analysis, while pulmonary vascular resistance and pulmonary arterial compliance are used to describe the resistive and pulsatile load of the pulmonary circulation. The resistive and pulsatile components of pulmonary load are also useful to describe the work of the right ventricle. Recent studies have found that the

steady or resistive component accounts for approximately 77% of total hydraulic RV power and that the remaining 23% is used for the pulsatile component (68). This relatively constant distribution follows from the unique properties of the pulmonary circulation compared with the systemic circulation. In contrast to the systemic circulation, in the pulmonary circulation, resistance and compliance are inversely related to each other over time and after therapy (Fig. 3) (69,70). This is because the resistive vessels in the pulmonary circulation also contribute to the compliance of

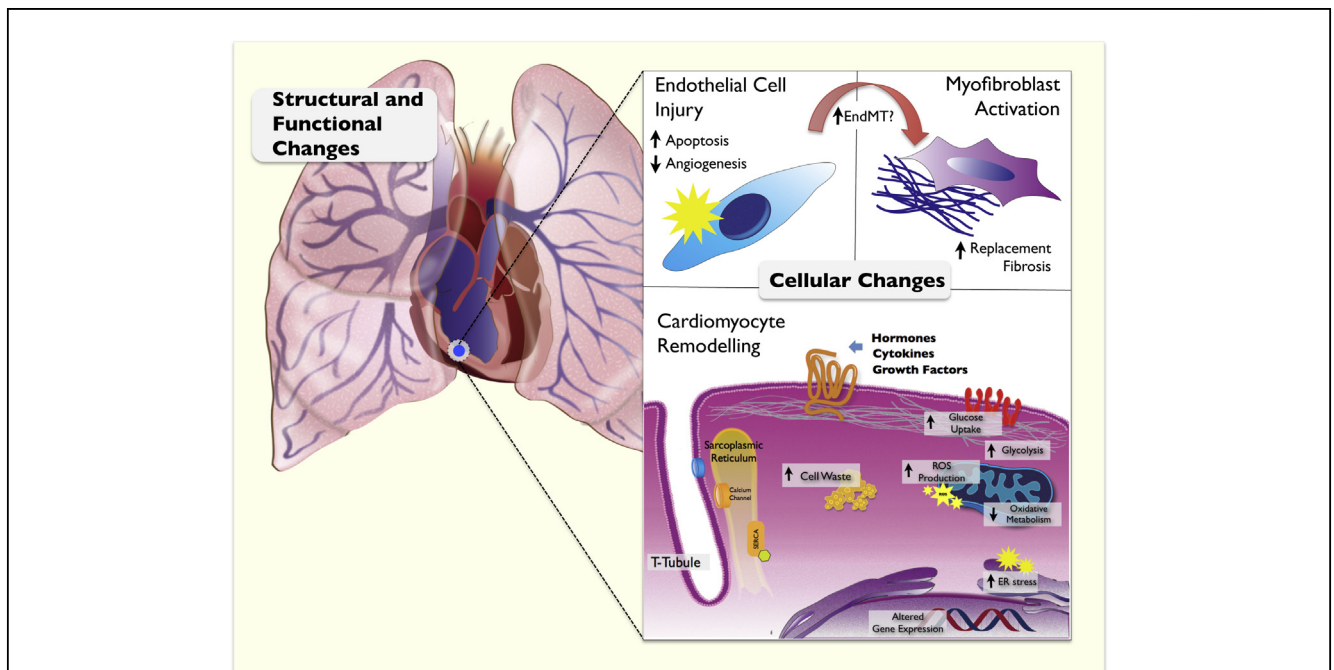


Figure 3 Molecular Pathways Involved in RV Remodeling in PAH

The figure outlines the importance of cardiomyocyte remodeling involving altered metabolism, increased reactive oxygen species (ROS) production, decreased oxidative metabolism, and endothelial reticulum stress. PAH = pulmonary arterial hypertension; RV = right ventricular.

the system (71). Recent studies have showed, however, that elevated pulmonary capillary wedge pressure can decrease the resistance-compliance time constant in the pulmonary system, thus enhancing net RV afterload by elevating pulsatile, relative to resistive, load (72).

Although the previously mentioned indexes of afterload are clinically useful, a more physiological definition of RV afterload would need to take into account all factors that contribute to total myocardial wall stress (or tension) during systole, such as ventricular pressure, chamber enlargement, wall thickness, and ventricular geometry. Moreover, tricuspid regurgitation and right-to-left shunting (i.e., through a patent foramen ovale, septal defect, or atrial septostomy) can also decrease afterload by offering an alternative, less resistive path (73–75). More comprehensive models of afterload may better predict the course of RHF. Research groups are currently working on developing biophysical models linking local cardiac myofiber mechanics to global cardiovascular system dynamics and adaptation are currently being developed. These models provide novel insights into the mechanisms of cardiac adaptation to PAH (76,77). Similarly, pre-load can be defined as the combination of the factors that contribute to passive end-diastolic ventricular wall stress (or tension). Optimal pre-load is the pre-load that leads to maximal cardiac output without causing significant systemic congestion or renal impairment (27). This is especially important in tailoring pre-load in patients with acute RHF and is discussed in the section on management.

Molecular insights into RV remodeling and failure. In recent reviews, the different pathways involved in remodeling of the pressure-overloaded right ventricle have been summarized (40,78). The different animal models used to study the pressure-overloaded right ventricle were recently reviewed by Guihaire *et al.* (79). More recent investigations are using induced pluripotent stem cells for screening of novel molecules in PAH and RHF; proof-of-concept results for these novel strategies should be available within the next few years. Although genetic studies are identifying novel

susceptibility loci in PAH, identifying a susceptibility locus to RHF will require larger sample sizes and matching for degree according to ventricular dysfunction and afterload.

Several mechanisms contribute to maladaptive remodeling of the pressure-overloaded ventricle, including increased levels of reactive oxygen species, activation of myocardial apoptotic pathways, and neurohormonal activation (e.g., adrenergic and angiotensin pathways) (80–82). Importantly, cardiomyocyte hibernation and growth arrest contrast with the resistance to apoptosis seen in the pulmonary vasculature in PAH (Table 3, Fig. 3) (83).

When comparing the failing right and left ventricles, both overlapping and varying expression in transcription factors, messenger ribonucleic acid (RNA), and micro-RNA are observed. The differences between the right and left ventricles originate in part from their different embryologic origins as well as their different mechanical boundary conditions, the right ventricle being exposed to lower impedance post-partum. From an embryologic point of view, the right ventricle arises from the anterior heart field, whereas the left ventricle develops from the posterior heart field (84). These differences may explain the lack of Iroquois homeobox and atrial natriuretic peptide expression in the normal right ventricle (41,85,86). Although B-type natriuretic peptide is also expressed in the failing right ventricle, the responsiveness to recombinant B-type natriuretic peptide may be different in the failing right heart; whether this is due to differences in loading conditions still requires further study (87,88). As in the left ventricle, down-regulation of fast alpha-myosin heavy chain and synchronous over-expression of slow beta-isoform are also observed in the pressure-overloaded right ventricle (89). The long-term consequences of alpha-cardiac actin down-regulation on contractile performance remain unknown (40). Because alpha-myosin heavy chain requires larger amounts of adenosine triphosphate to generate force, a decreased alpha-myosin/beta-myosin ratio may provide an energy-sparing profile that may have some advantages for long-term

Table 3 Comparative Remodeling of Right Ventricle and Pulmonary Circulation in Patients With PAH: Main Cellular and Interstitial Features (19–22)

	Pulmonary Circulation	Right Ventricle
Differences		
Cellular changes	Resistance to apoptosis and aberrant proliferation (PAECs and PSMCs), hyperplasia, and migration (PSMCs)	Growth arrest apoptosis (CMs)
Microcirculation changes	Dysregulated angiogenesis	Decreased capillary density
Similarities		
Extracellular matrix	Increased interstitial fibrosis	Increased interstitial fibrosis
Mitochondrial remodeling	Decreased number abnormal shape and size, increased oxidative capacity	Decreased number abnormal shape and size, decreased oxidative capacity
Metabolic transformation	Glycolytic shift	Glycolytic shift
Controversies		
Inflammation	Increased mononuclear cells and inflammatory cytokines	Increased mast cells and inflammatory cytokines
Neurohormonal modulation	Increased ACE activity (PAECs); down-regulation of β_1 -adrenergic receptor (PSMCs)	Impairment of AT-R1 signaling pathway

ACE = angiotensin-converting enzyme; AT-R1 = angiotensin II receptor type 1; CM = cardiomyocyte; PAEC = pulmonary artery endothelial cell; PAH = pulmonary arterial hypertension; PSMC = pulmonary artery smooth muscle cells.

compensation of the right ventricle. Studies using microarray gene chips have highlighted that 1 of the pathways that appears to be more activated in the pressure-overloaded right ventricle compared with the pressure overloaded left ventricle is the Wnt pathway, which regulates glycogen synthase kinase-3 β activity, a serine/threonine protein kinase involved in cell proliferation, migration, inflammation, glucose regulation, and apoptosis (90). Chamber-specific expression of phosphodiesterase type 5 in the pressure-overloaded right ventricle has also been demonstrated in experimental and human studies (91,92). Although most expressed micro-RNA is similar in right and left heart failure, Reddy et al. (93) showed that 4 micro-RNAs (34a, 28, 148a, and 93) are upregulated in RHF/RV hypertrophy that are down-regulated or unchanged in left heart failure/left ventricular hypertrophy.

A change in myocardial metabolism is a prominent feature of RHF. A switch from fatty acid oxidation to glycolysis is presumably a protective response of the stressed left heart, as carbohydrate metabolism requires less oxygen amount than fatty acid oxidation (81). Decreased mitochondrial activity resulting in a switch from aerobic to anaerobic metabolism might also be involved in the transition from compensated RV hypertrophy to maladaptive remodeling (81). Insufficient adaptation of the capillary network and myocardial ischemia may also impair vascular endothelial growth factor signaling and the hypertrophic response (94). Increased rate of myocardial fibrosis has been reported in RV failure and may contribute to decreased ventricular compliance (56,95).

Recent animal and human studies support a role of inflammation in the pressure-overloaded right ventricle (82,96). Studies by Watts et al. (97) have shown that neutrophils are found in the RV myocardium early after an acute increase in afterload, whereas macrophages may be involved during progressive remodeling in the setting of chronic pulmonary hypertension (97). Ongoing studies are investigating the role of macrophages, T-regulatory cells, and leukotriene in the development of RHF in patients with PAH.

Evaluation of Right Heart Size and Function: From Resting Parameters to Dynamic Evaluation

The assessment of the right heart plays an essential part in managing patients with PAH (98). Although echocardiography is the mainstay in the evaluation of the right heart in clinical practice, magnetic resonance imaging has emerged as the most accurate method for evaluating RV mass, RV volume, and RVEF. In addition, magnetic resonance imaging offers the possibility to quantify regurgitant volumes; delayed enhancement, a marker for focal scar burden; myocardial strain; coronary perfusion; and pulmonary pulsatility (98). Positron emission tomography is used experimentally to assess RV and pulmonary metabolism and, at specialized centers, for apoptosis imaging. Finally conductance catheterization represents the gold-standard

method for evaluating ventricular elastance, arterial elastance, and ventriculoarterial coupling (5,43).

The American Society of Echocardiography guidelines offer the most comprehensive review of normative echocardiographic values of the right heart (99). The guideline also highlights the need for future scaled echocardiographic references for right heart dimensions as well as references adjusted for age, sex, and race. Using a large cohort of 4,204 participants, the MESA (Multi-Ethnic Study of Atherosclerosis) investigators were able to develop these normative equations for RV mass and systolic function on the basis of age, sex, and race (100). Kawut et al. (100) demonstrated that in general, younger age, male sex, and Hispanic ethnicity are associated with higher RV mass, while older age and female sex are associated with higher RVEF.

More recently, several investigators are working on defining dynamic right heart and pulmonary circulation measures. These dynamic measures include the mean pulmonary arterial pressure–cardiac output slope as well as RV reserve, usually defined either as peak RVEF, peak stroke volume, or peak cardiac index after exercise or pharmacological stress (101,102). In controls, mean pulmonary arterial pressure–cardiac output slope is usually <1.5 to 2.5 mm Hg·min/l, with older healthy subjects having higher average slope values (22,103–113).

The committee wants to emphasize that the commonly used indexes of RV systolic performance, such as RVEF and tricuspid annular plane systolic excursion, are markers of ventriculoarterial coupling rather than ventricular contractility, which is increased in PAH (65). Another caveat the committee members want to emphasize is that the reduction in tricuspid annular plane systolic excursion after cardiac surgery does not reflect corresponding changes in RVEF, because annular plane motion is preferentially compromised (114).

Prediction of Outcomes in Patients With Pulmonary Arterial Hypertension: The Importance of the Right Heart

Outcome prediction in patients with PAH has been extensively studied using large-cohort designs as well as in smaller studies incorporating imaging parameters (7,8,10,12,13,16–19,115–123). One consistent finding among studies is that survival in PAH is closely related to RV adaptation to the increased pressure overload. Hemodynamic studies have demonstrated the predictive value of right atrial pressure and cardiac index (7,14,117,118,124). Echocardiographic studies have highlighted the predictive value of tricuspid annular plane systolic excursion, RV myocardial performance index, atrial size, and pericardial effusion (10,12,13,17,125). Magnetic resonance imaging studies have emphasized the predictive value of stroke volume index, RVEF, and indexed RV end-diastolic and end-systolic volumes (18,115,116,122,126). Although delayed enhancement has been associated with the severity of PAH, its independent predictive value has not yet been proved (127). More recent studies have shown the potential predictive value of RV strain

(17). In terms of cardiac biomarkers, B-type natriuretic peptide (and N-terminal B-type natriuretic peptide) and troponin have been the most investigated cardiac biomarkers in PAH and have both been found to be predictive of outcomes (8,119,128–132). More recent studies are also highlighting the role of high-sensitivity troponin assays in PAH (129,130). Exercise testing has highlighted the value of maximal oxygen consumption, right-to-left shunting, maximal cardiac index with exercise, and the pulmonary pressure–cardiac output slope (48,101).

Particularly with regard to the right heart, future outcome studies in PAH will have 2 main objectives. First, studies are needed to evaluate the role of novel imaging biomarkers, such as right atrial function, ventricular strain, and myocardial acceleration during isovolumic contraction, as well as more recent reported biomarkers such as ST2 and cystatin C. Second, multivariate studies will be needed to validate a simplified predictive score incorporating imaging parameters of the right heart.

Management of Right Heart Failure From Pulmonary Vasodilation to Targeted Right Ventricular Therapy

In addition to their effects on exercise capacity and pulmonary vascular resistance, approved therapies for PAH lead to reverse remodeling of the right heart. This is mediated mainly through their vasodilatory or afterload-reducing effects (133). Nagendran *et al.* (91) demonstrated that the vasodilator sildenafil may in addition have direct inotropic effects. Whether this will translate into long-term clinical benefits compared with endothelin receptor blockers still requires further study. Digoxin is the other oral inotropic agent occasionally used in symptomatic patients with PAH; a small study of 17 patients has suggested the acute hemodynamic effects of digoxin use in PAH (134).

Targeted right heart therapy has been the focus of recent investigation in PAH. These usually fall into 2 categories, the first being the investigation of medication proved to be beneficial in left heart failure with decreased ejection fraction and the second being the investigation of novel and potentially specific targets of RHF. Because of the embryologic and molecular differences between the right and left heart, results for chronic left heart failure cannot be directly extrapolated to RHF. Moreover, a pressure-overloaded ventricle may respond differently than a non-pressure-overloaded ventricle. Although recent experimental studies have suggested beneficial effects of carvedilol or bisoprolol on ventricular remodeling in PAH, these beneficial effects may be mitigated in patients with severe PAH, in whom contractile reserve is significantly reduced (135,136). In fact, a small clinical study by Provencher *et al.* (137) showed detrimental effects of nonselective and selective beta-blockade on exercise capacity in patients with portopulmonary PAH. Clinical trials regarding the effects of resynchronization therapy in patients with PAH are currently

ongoing, on the basis of early clinical and experimental studies showing promising results (48,49). At this time, the role of angiotensin-converting enzyme inhibitors, angiotensin or aldosterone blockade, myosin activators, implantable defibrillator or destination RV assist device implantation has not been comprehensively investigated in patients with RHF and PAH.

For novel targeted RV drug therapy, the most promising data are for metabolic modulation. On the basis of the metabolic changes that are observed in the right heart and pulmonary vasculature in patients with PAH, investigators have at this time completed phase 1 and 2 clinical trials using mitochondrial modulators such as dichloroacetate in PAH (37,138). At this time, stem cell therapy or gene therapy specifically targeting the right heart in PAH still needs to be investigated.

In managing acute RHF in patients with PAH, the committee wants to emphasize 3 important aspects. First, volume loading should be avoided in patients with evidence of increased filling pressures (right atrial pressure >10 to 15 mm Hg) because this can worsen ventricular performance by further distending the right ventricle and increasing septal shift and pericardial constraint through ventricular interdependence. Second, every effort should be made to avoid the vicious circle of hypotension and ventricular ischemia and further hemodynamic compromise; this can include prompt cardioversion of atrial arrhythmias, early initiation of inotropic or vasopressor support, and avoiding hypercapnia or increased intrathoracic pressure, as well consideration of extracorporeal membrane oxygenation when appropriate. Third, it remains unclear which agent is the inotrope or vasopressor of choice; the most commonly used agents include dobutamine, dopamine, norepinephrine, and levosimendan (2,139–141).

Role of Right Heart Investigation in the Development of Novel Pulmonary Arterial Hypertension Therapy

Because medications affecting the pulmonary vasculature may be detrimental to the right heart, the task force recommends that any new drug developed for PAH should therefore be experimentally tested for its effects on the pressure-overloaded right heart. For example, imatinib, which was shown to be promising for pulmonary vascular remodeling, was shown to have potential cardiotoxic effects (142,143). The variable effects can be explained by the fact that although the remodeled lung in PAH vasculature is characterized by angiogenesis, apoptosis resistance, and cell proliferation, the failing right ventricle may be subject to ischemia, capillary rarefaction, and cardiomyocyte apoptosis.

Future Directions

In this report, we have outlined the recent progress made in understanding of the RHF syndrome, identifying key areas

of future investigation. Areas of research priority are diverse and include refining the definition of normal right heart structure and function; investigating novel genetic, epigenetic, and molecular pathways of RHF; and developing more effective management strategies for refractory RHF. Furthermore, before proceeding to clinical trials, the effects of any new medication should also be experimentally tested on a pressure-overloaded right ventricle. Importantly, we also recommend that clinical trials in PAH incorporate as secondary outcome analysis parameters of right heart size and function.

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