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The Right Ventricle Under Pressure*

Cellular and Molecular Mechanisms of Right-Heart Failure in Pulmonary Hypertension*

Harm J. Bogaard, MD, PhD; Kohtaro Abe, MD, PhD; Anton Vonk Noordegraaf, MD, PhD, FCCP; and Norbert F. Voelkel, MD

Pulmonary arterial hypertension (PAH) is a deadly disease in which vasoconstriction and vascular remodeling both lead to a progressive increase in pulmonary vascular resistance. The response of the right ventricle (RV) to the increased afterload is an important determinant of patient outcome. Little is known about the cellular and molecular mechanisms that underlie the transition from compensated hypertrophy to dilatation and failure that occurs during the course of the disease. Moreover, little is known about the direct effects of current PAH treatments on the heart. Although the increase in afterload is the first trigger for RV adaptation in PAH, neurohormonal signaling, oxidative stress, inflammation, ischemia, and cell death may contribute to the development of RV dilatation and failure. Here we review cellular signaling cascades and gene expression patterns in the heart that follow pressure overload. Most data are derived from research on the left ventricle, but where possible specific information on the RV response to pressure overload is provided. This overview identifies the gaps in our understanding of RV failure and attempts to fill them, when possible. Together with the online supplement, it provides a starting point for new research and aims to encourage the pulmonary hypertension research community to direct some of their attention to the RV, in parallel to their focus on the pulmonary vasculature. ***(CHEST 2009; 135:794–804)***

Key words: pulmonary arterial hypertension; pulmonary vascular resistance; right ventricle

Abbreviations: ACE = angiotensin converting enzyme; ATII = angiotensin II; ECM = extracellular matrix; ET-1 = endothelin-1; HO-1 = heme oxygenase 1; IL = interleukin; LV = left ventricle/ventricular; MHC = myosin heavy chain; MMP = matrix metalloproteinase; NO = nitric oxide; PAH = pulmonary arterial hypertension; PDE-5 = phosphodiesterase type 5; RNS = reactive nitrogen species; ROS = reactive oxygen species; RV = right ventricle/ventricular; sST2 = interleukin-1 receptor-like protein soluble isoform; ST2L = interleukin-1 receptor-like protein transmembrane isoform; TGF = transforming growth factor; TNF = tumor necrosis factor; VEGF = vascular endothelial growth factor

In recent years, earlier recognition and new treatment modalities have improved the outlook for patients with pulmonary arterial hypertension (PAH). Nevertheless, PAH is still a deadly disease with a mortality rate of 20 to 40% 3 years after diagnosis.[1,2] PAH, in fact a group of disorders, is characterized by vasoconstriction and remodeling of the pulmonary vascular wall, both leading to a progressive increase in pulmonary vascular resistance. More than a few molecular pathways have

*From the Department of Pulmonary Medicine (Drs. Bogaard and Vonk Noordegraaf), VU University Medical Center, Amsterdam, the Netherlands; Department of Pulmonary Medicine and Critical Care (Dr. Voelkel), Virginia Commonwealth University, Richmond, VA; and Department of Cardiovascular Medicine, Kyushu University Graduate School of Medical Sciences (Dr. Abe), Fukuoka, Japan.
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Correspondence to: Norbert Voelkel, MD, Department of Pulmonary Medicine and Critical Care, Virginia Commonwealth University, 1101 E Marshall St, Sanger Hall, Rm 7-024, Richmond, VA 23284; e-mail: nvoelkel@mcvh-vcu.edu
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been shown to be of pathobiological importance, some of which are pharmacologically modifiable. Most notably, treatment with prostacyclin analogs, endothelin-1 (ET-1) receptor blockade, and phosphodiesterase type 5 (PDE-5) inhibition has shown to be of benefit.[3] Despite these interventions, pulmonary microvascular obstruction usually progresses and imposes an increasingly larger load on the right ventricle (RV). The patient outcome is predominantly determined by the response of the RV to the increased afterload.[4,5] Very little is known about the structural and functional evolution of RV dysfunction in PAH, about the determining molecular and cellular mechanisms, or about direct (not afterload reducing) interventions that could preserve RV function. Importantly, little is known about the effects of current PAH therapies on the heart; for example, the precise sequence of events involved in the increase in cardiac output with epoprostenol treatment are not well understood.[6] What we do know is that RV failure is potentially reversible; there is generally a good recovery of the heart after lung transplantation and pulmonary endarterectomy for chronic thromboembolic pulmonary hypertension.[7,8] This review aims to summarize the available literature on the development of failure of the pressure-overloaded right heart. With this article comes an online supplement that provides interested readers with a more indepth and thoroughly referenced analysis and discussion of all possibly relevant signaling pathways. A considerable amount of data in this review pertains to research on left ventricular (LV) biology. Throughout the text, we specifically indicate when the available literature pertains to the RV. In other instances, it can be assumed that the data are derived from studies on left-heart failure. One can make the provisional assumption that comparable mechanisms are at play in the stressed RV myocardium. However, the reader may keep in mind the various structural, functional, and even developmental differences between the RV and LV.

The RV Under Pressure: Adaptive Hypertrophy

The RV is thinner than the LV and has a different shape (Fig 1), which reflects the low pressure in the pulmonary circulation and allows quick adaptation to changes in preload. It follows from the Laplace relationship that in a thin-walled sphere, an increase in intraluminal pressure results in an increase in wall stress, unless the thickness of the chamber wall is augmented or the internal radius of the chamber is reduced. Since an increase in wall stress not only increases myocardial oxygen demand but also impedes myocardial perfusion, an important adaptation

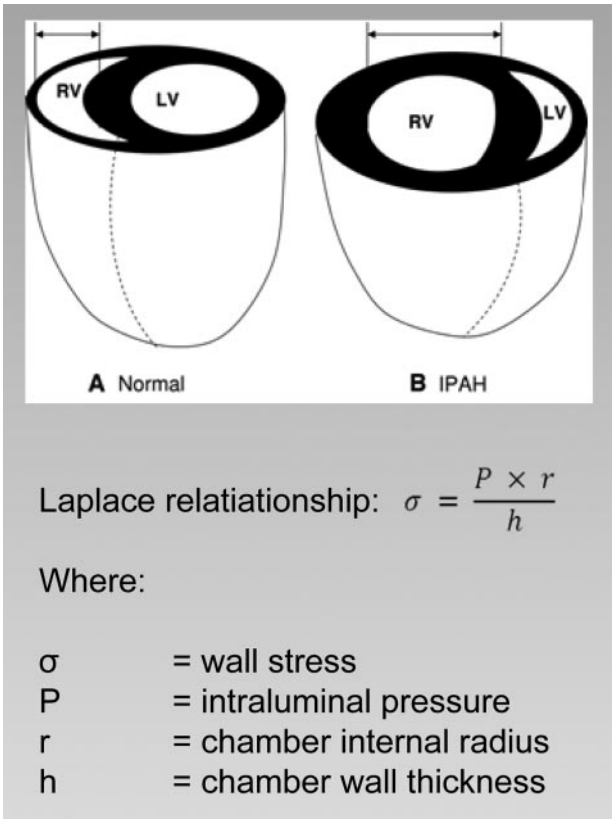

Figure 1. RV configuration in health (*left*, *A*) and pulmonary hypertension (*right*, *B*). According to the Laplace relationship, pulmonary hypertension is characterized by increased RV wall stress (σ) due to an elevated intraluminal pressure (P) and a larger chamber radius (r), unless RV wall thickness (h) is augmented by hypertrophy. IPAH = idiopathic PAH.

of the RV to the high pressure in PAH is to increase wall thickness by accumulating muscle mass (hypertrophy) and to assume a more rounded shape.

The increase in ventricular mass induced by an increase in afterload is predominantly the result of protein synthesis and an increase in cell size through the addition of sarcomeres. Recently, the existence of proliferating cardiac progenitor cells[9] and the influx of bone marrow-derived progenitor cells developing into cardiomyocytes[10] have been demonstrated, but their contribution to the adaptation to RV pressure overload has not been investigated. Protein synthesis in the cardiomyocytes is directly induced by stretch and enhanced by autocrine, paracrine, and neurohormonal influences. An increase in afterload is sensed by integrins and stretch-activated ion channels in cardiac cells (myocytes, fibroblasts, endothelial cells).[11] Integrins are membrane crossing heterodimers that have firm attachments to both the extracellular matrix (ECM) and the cytoskeleton, allowing them to transduce mechanical stress into intracellular chemical signals involved in synthesis of contractile proteins and

proteins for autocrine and paracrine signaling.[12,13] Similarly, activation of stretch-activated ion channels on the cell membrane leads to increased protein expression.[14] The local response to pressure overload is enhanced by systemic (neurohormonal) influences, *eg*, activation of the renin-angiotensin and sympathetic systems.

Pressure-induced growth (and proliferation) of cardiomyocytes needs to be paralleled by ECM synthesis and growth of the supporting vasculature. The matrix scaffold of the heart is predominantly collagen with relatively small amounts of fibronectin, laminin, and elastin. The collagen is organized as an intricate network of fibers that surround, group, and interconnect individual myocytes, myofibrils, muscle fibers, and muscle bundles. Its close proximity to the contractile apparatus implies that the ECM likely influences diastolic and systolic function as well as ventricular size and shape.[15,16] Moreover, the ECM determines the milieu for electrical propagation, and when the matrix is inhomogeneous it predisposes to conduction abnormalities and arrhythmia.[17] Angiogenesis, the growth of new vessels out of existing vessels, is a pivotal element of organ growth and wound healing. Under physiologic circumstances, signaling by vascular endothelial growth factor (VEGF), Angiopoietin 1 and other growth factors provides a tight match between angiogenesis and organ growth.

Transition From Adaptive Hypertrophy to Dilatation and Failure

The RV is not capable to sustain long-term pressure overload (Fig 2). Eventually, cardiac contractile force decreases (due to functional, structural or numerical, *ie*, apoptosis, changes in cardiomyocytes) and the RV dilates. Because the increased wall tension that results from RV dilatation increases myocardial oxygen demand and simultaneously decreases RV perfusion (see previous), a vicious circle of further compromised contractility and dilatation ensues. Maladaptive neurohormonal signaling, unopposed formation of reactive oxygen species (ROS) and reactive nitrogen species (RNS), and exaggerated inflammatory responses may further accelerate the development of right-heart failure in PAH (see following).

The mechanisms that underlie the transition from hypertrophy to dilatation in PAH associated right-heart failure have not been well defined. Although it is well recognized that disease-specific myocardial involvement contributes to cardiac dysfunction in sarcoidosis, systemic sclerosis, and amyloidosis,[18–20] it has not been explored whether the molecular mechanisms determining pulmonary vascular remodeling in idiopathic or familial PAH can also cause myocardial dysfunction. The scant data on right-heart failure are derived from different animal

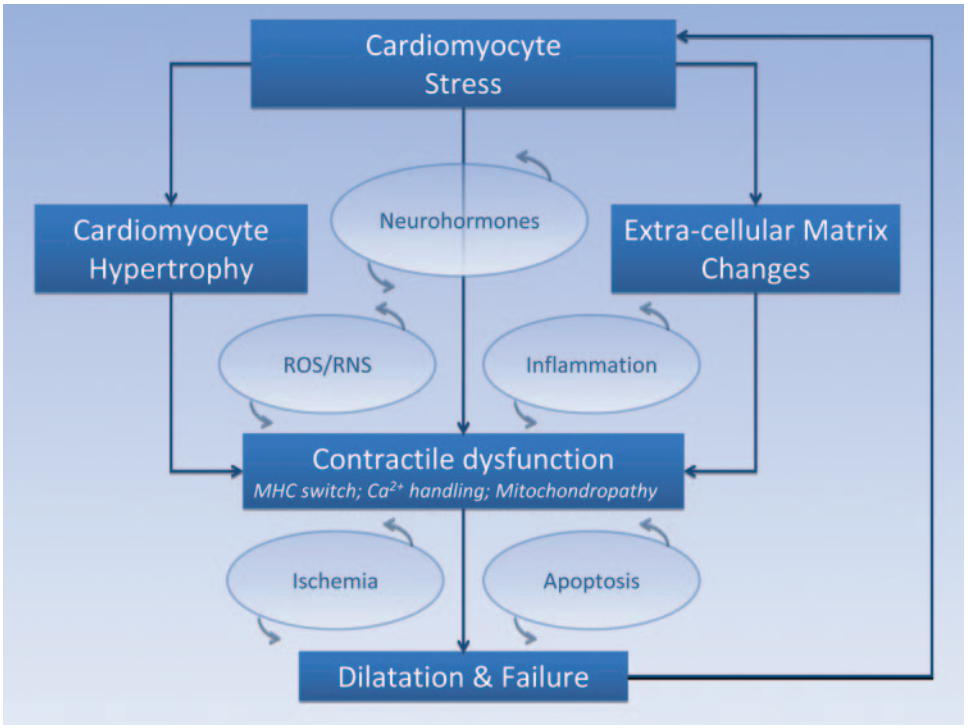

Figure 2. Hypothetical molecular and cellular mechanisms involved in the development of right-heart failure in pulmonary hypertension. Cardiomyocyte stress in the setting of pulmonary hypertension may be predominantly caused by increased pulmonary resistance. Different amplifying and modifying loops lead to contractile dysfunction, imposing further stress on (remaining) cardiomyocytes.

Table 1—*Contractile Protein Alterations in Heart Failure*

Protein	Alteration
α-MHC	↓
β-MHC	↑
α-Skeletal actin	↑
α-Smooth muscle actin	↑
α-Cardiac actin	↓

models of RV pressure overload, which all have their limitations in the study of PAH-associated right-heart failure (see online supplemental data). We focus in this article on events that are triggered by pressure overload; it is possible that other signaling mechanisms are of importance in the pathobiology of heart failure in RV volume overload (*eg*, PAH associated with liver disease and atrial septal defects).

Maladaptive Cardiac Growth and Contractile Dysfunction

One of the hallmarks of maladaptive cardiac growth is the α- to β-isotype switch of the major thick filament protein myosin heavy chain (MHC) [α-MHC/β-MHC switch] in cardiomyocytes (Table 1). In the normal adult human RV, the α-MHC isotype makes up approximately 23 to 34% of total MHC, and β-MHC the remainder. The reduction in α-MHC content (down to ± 5%) that is encountered in PAH-associated right-heart failure[21] can have important functional consequences. β-MHC has lower adenosine triphosphatase activity than α-MHC; the disappearance of the latter results in a significant decrease in systolic function.[22] Stressed hearts not only exhibit thick filament changes but also show increased expression of the thin filaments α-skeletal actin and α-smooth muscle actin at the cost of α-cardiac actin.[23] Since α-skeletal actin is upregulated in the RV of newborn calves with hypoxic pulmonary hypertension, whereas it remains unchanged in the LV of these animals, it seems that pressure overload *per se* and not hypoxia is the stimulus for this response.[24] The functional consequences of the α-actin switch are not clear. The myocardial regulatory proteins troponin, tropomyosin, and tropomodulin may also be involved in the pathobiology of heart failure.[25,26] Proteolytic degradation of troponin subunits likely plays a functional role in ischemic cardiomyopathy. Phosphorylation of troponin T by protein kinase C inhibits troponin T binding to tropomyosin that may contribute to the inhibition of maximal myofibrillar adenosine triphosphatase and contractile performance.[26]

Contractile dysfunction in heart failure is not only associated with alterations in contractile and regulatory protein expression. Other reported abnormalities in heart failure are alterations in enzymes and ion channels involved in myocyte excitation-contraction coupling, mitochondrial defects, depletion of myocardial adenosine triphosphate and high-energy phosphate metabolites (creatine and phosphocreatin), and modifications of myocardial substrate use (from fatty acids to glucose). The vast majority of investigations on contractile dysfunction in heart failure have been conducted with LV strain and failure models; it is unknown to what extent similar mechanisms are at play in PAH-associated right-heart failure (see online supplemental data).

Decreased cardiac performance does not exclusively originate from dysfunctional cardiomyocytes. ECM changes and a degree of angiogenesis that lags behind the degree of cardiomyocyte hypertrophy can potentially contribute to the development of heart failure. Both increased collagen content of the heart (fibrosis), which is tightly linked to transforming growth factor (TGF)-β1 signaling, and excessive degradation of the matrix by matrix metalloproteinases (MMPs) will adversely affect myocardial systolic and diastolic function.[15,17,27] TGF-β1 and MMP signaling are linked in a complex fashion.[17] RV endomyocardial biopsy specimens from patients with PAH show increased levels of fibrosis,[21] confirming earlier findings in rats after pulmonary artery banding.[28] Since scar formation and fibrosis are very common responses to tissue hypoxia, it is possible that these findings are related to RV ischemia and microcirculatory insufficiency (see following). Degradation of the ECM may contribute to decompensated heart failure and ventricular dilatation in PAH because failing hearts have an increased density of mast cells capable of activating MMPs by secreting TNF-α, tryptase, and chymase.[15] The only observation of myocardial mast-cell infiltration in pulmonary hypertension has been in a very specific animal model (nude rats treated with the VEGF receptor blocker SU5416),[29] and it is unclear whether such mast-cell infiltration also exists in other animal models or human PAH.

Modifiers of the Hypertrophic Response Contributing to the Development of Right-Heart Failure

It is generally believed that sustained pressure overload *per se* is enough to induce maladaptive hypertrophy and cardiac failure. It is also recognized that in the pressure-overloaded LV, superimposed pathologic events accelerate myocardial functional deterioration. How the development of PAH-associated right-heart failure is modified by neurohormonal activation, oxidative and nitrosative stress, immune activation, myocardial ischemia, and cardiomyocyte apoptosis is largely unknown.

Neurohormonal Activation

Reduced tissue perfusion due to a decreased cardiac output activates neurohormonal pathways that are first beneficial (maintenance of BP and renal perfusion) but will eventually decrease cardiac function. Heart failure is associated with upregulation of the renin-angiotensin system (with angiotensin II [ATII] as the most important factor involved in cardiac remodeling), adrenergic overstimulation, and increased expression of several counter-regulating peptides (*eg*, natriuretic peptides), all of which have been shown to influence cardiac myocytes, fibroblasts, immune cells, and the ECM. Many of the neurohormones (*eg*, ATII, aldosterone, natriuretic peptides) that reach the heart via the systemic circulation are also secreted locally by resident cardiac cells (myocytes, endothelial cells, and fibroblasts) and, together with factors that are secreted locally only, affect cardiomyocyte growth, proliferation, and survival. Research on hearts of patients with idiopathic PAH has provided some insight into the relative contributions of direct local responses to pressure overload and additional responses to systemic neurohormonal signaling: the RV of PAH patients is subjected to both, while the LV is subjected to systemic influences only and not to pressure overload.[30] It appears that in PAH, pressure overload is the primary determinant of adaptations in β-adrenoreceptor density,[31] Angiotensin type 1 receptor density,[32] atrial natriuretic peptide expression,[21] and MHC and α-actin contents.[21,24] In contrast, the increase in angiotensin-converting enzyme (ACE) expression is likely a response to systemic influences, since it is increased in both ventricles in PAH.[32] Table 2 summarizes important neurohormones and autocrine/paracrine factors involved in heart failure. Some downstream effects that follow on activation of the different receptors are shown in Figure 3. The reader is referred for further details to the supplement.

Oxidative and Nitrosative Stress

ATII, ET-1, and other neurohormones can use the formation of ROS to induce hypertrophic pathways within the cardiomyocyte.[33] ATII activation leads to ROS formation via upregulation of NAD(P)H oxidases; other sources of ROS production in heart failure are xanthine oxidase, cytochrome P450, and autooxidation of catecholamines.[33–35] It is possible that neutrophils recruited to the pressure overloaded myocardium are partly responsible for ROS production because they harbor significant quantities of NAD(P)H oxidases. Constitutively expressed endothelial nitric oxide (NO) synthase and hemoglobin are the principal sources of RNS in the heart. Sustained desaturation of hemoglobin and uncoupling of endothelial NO synthase also contribute to ROS generation.[36,37] Excessive production of ROS and RNS induces contractile dysfunction through suppression of enzymes involved in excitation-contraction coupling and through polynitrosylation of the ryanodine receptor. ROS and RNS favor cardiac remodeling through enzyme

Table 2—*Neurohormones and Autocrine/Paracrine Factors Possibly Involved in Right-Heart Failure

Variables	Known Direct Cardiac Effects	Evidence for Involvement in Right-Heart Failure Associated With Pulmonary Hypertension
ATII	Hypertrophy, inflammation, fibrosis, contractile dysfunction	Increased angiotensin type 1 receptor density after pulmonary artery banding in rabbits[S28]; genetic variation in ACE expression affects PAH survival[S82]
Catecholamines	Contractile dysfunction with sustained activation	Sympathetic hyperinnervation in monocrotaline model[S12]
ET-1	Hypertrophy; inhibition of apoptosis; effects on contractility depending on duration of stimulation	Unknown long-term effects on RV adaptation to pressure overload
Prostaglandins	Unknown whether prostacyclin increases cardiac output by vascular or cardiac effects	Improved RV contractility and capillary-to-myocyte ratio in a flow-associated PAH model[S15]
Aldosterone	Mediates effects AT-II	No data
TGF-β1	Mediates effects AT-II	No data
Natriuretic peptides	Attenuates hypertrophy, antiapoptotic; antifibrotic	Upregulated in experimental and human PAH[S141]; importance for RV adaptation unclear
NO	Complex effects, via cGMP-related and unrelated pathways	Cyclic guanosine monophosphate may acutely increase RV contractility in experimental and human PAH[S153]
Adrenomedulin	Inhibits ET-1, renin-angiotensin and sympathetic signaling; long-term effects unclear	No data
Growth hormones	Hypertrophy, antiapoptotic	No data
Platelet-derived growth factor	Antiapoptotic; antiinflammatory	No data

*References cited in Table 2 can be found in the online supplemental data.

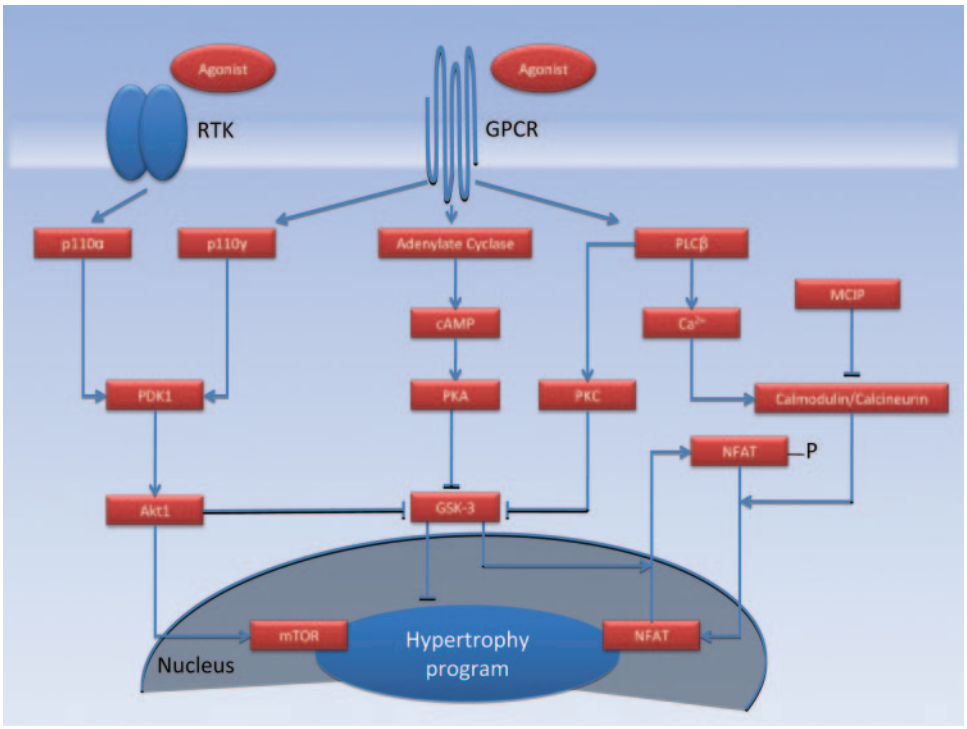

FIGURE 3. G protein-coupled receptors (GPCRs) and receptor tyrosine kinase (RTK) signaling involved in the myocardial hypertrophic response. On binding of ligands such as ATII and ET-1 to their G protein-coupled receptor, phospholipase C (PLCβ) is activated, which is followed by an increase in intracellular Ca^{2+} and protein kinase C (PKC) activation. This ultimately leads to dephosphorylation of the nuclear factor of activated T-cell (NFAT) transcription factor by calcineurin. Dephosphorylated nuclear factor of activated T cell translocates into the nucleus where it activates transcription in cooperation with other transcription factors. Dephosphorylation of nuclear factor of activated T cell by calcineurin is inhibited by glycogen synthase kinase-3 (GSK-3). After binding of catecholamines to the β-adrenergic receptor, adenylate cyclase is activated, cyclic adenosine monophosphate (cAMP) is produced, and protein kinase A (PKA) is activated. Not shown is activation of small guanosine triphosphate binding proteins and mitogen-activated protein kinase cascades that also follows after G protein-coupled receptor activation. Binding of insulin-like growth factor 1, insulin, and others to their membrane receptor tyrosine kinase activates phosphatidylinositol-3 kinase (subtype p110α). Phosphatidylinositol-3 kinase phosphorylates the membrane phospholipid phosphatidylinositol-4,5-biphosphate, which leads to the formation of phosphatylinositol-3,4,5-triphosphate (phosphatidylinositol-3 kinase) and recruitment of the protein kinase Akt1 to the cell membrane. Akt1 induces antiapoptotic and prohypertrophic responses by releasing transcription factors from tonic inhibition by glycogen synthase kinase-3 (GSK-3) and by activating mammalian target of rapamycin (mTOR). Binding of ATII, catecholamines, and ET-1 to their G protein-coupled receptor is associated with a similar pathway, involving Akt1 and another phosphatidylinositol-3 kinase subtype (p110γ).

inactivation and induction of cell damage, apoptosis, and inflammation (see online supplemental data).

LV failure is not only associated with increased generation of ROS and RNS but also with a reduced activity of cytoprotective enzymes. Although it is unknown whether this also plays a role in the pressure overloaded RV, it has been shown in mice subjected to hypoxia that transgenic deletion of the cytoprotective enzyme heme oxygenase 1 (HO-1) leads to severe RV dilatation and failure, unrelated to pulmonary vascular vasoconstriction or remodeling, but associated with myocardial infarction, inflammation, fibrosis, and cardiomyocyte apoptosis.[38] HO-1 is induced in vascular smooth muscle cells and cardiomyocytes by many stressors, such as stretch, shear stress, ROS, hypoxia, cytokines, heme, and heavy metals. HO-1 catalyzes the oxidation of the prooxidant heme to carbon monoxide and biliverdin, which is subsequently reduced to the antioxidant bilirubin.[39] Carbon monoxide stimulates soluble guanylate cyclase (see online supplemental data for the cardioprotective consequences) and induces vasodilatation.[40,41]

Cardiac Inflammation and Immune Activation

As stated above, neutrophils may be an important source of excessive ROS formation in heart failure. Neutrophils are recruited to the myocardium by ischemic damage, which can be present in the failing RV. In addition to neutrophils, other immune cells contrib-

ute to remodeling and the development of heart failure (see online supplemental data). Furthermore, ρ kinase activation associated with RV hypertrophy may exacerbate cardiac inflammation by leading to ineffective clearance of apoptotic cells (efferocytosis).[42]

In parallel with the recruitment of immune cells, proinflammatory cytokines play complex roles in the development of heart failure. Patients with chronic heart failure have increased serum levels and myocyte expression of the proinflammatory cytokines tumor necrosis factor (TNF)-α, interleukin (IL)-1, and IL-6, with elevated levels correlating with disease severity reflected in clinical and hemodynamic parameters.[43] Experimental evidence in left-heart failure shows that TNF-α can depress myocardial contractility[44] and induce apoptosis of cardiomyocytes[45] and endothelial cells.[46] TNF-α is upregulated after transverse aortic constriction in mice and mediates cardiomyocyte apoptosis, fibrotic remodeling through inflammatory cell influx, MMP upregulation, and activation of various cytokines (IL-6, monocyte chemotactic protein 1, and macrophage inflammatory protein 1γ). These changes and an associated decreased LV function can be prevented by TNF-α knock-out.[47] Surprisingly, TNF-α has cytoprotective effects in ischemic cardiomyocytes.[43] Other cytokines modulating the development of heart failure are IL-1 and IL-33. IL-1 has a negative inotropic effect on cardiomyocytes[48] and enhances fetal gene expression.[49] The recently discovered IL-1–related protein IL-33 is a functional ligand of the IL-1 receptor family member (IL-1 receptor-like protein transmembrane isoform [ST2L]) and is produced by cardiac fibroblasts in response to mechanical strain. In mice, IL-33/ST2L signaling antagonizes cardiomyocyte hypertrophy induced by transverse aortic constriction and agonists (ATII and phenylepinephrine), while improving systolic function. IL-1 receptor-like protein soluble isoform (sST2) may function in the myocardium as a soluble decoy receptor for IL-33, interfering with IL-33/ST2L cardioprotective signaling.[50] Elevations of serum sST2 predict worse prognosis in patients with chronic heart failure,[51] and it is speculated that patients with increased sST2 may be inhibiting endogenous IL-33 and IL-1 receptor-like protein cardioprotection through the binding of myocardial IL-33 to sST2, thereby preventing signaling through ST2L.[50] The primary stimulus for elevated levels of sST2 in heart failure patients remains to be determined.

Myocardial Ischemia

It has been known for decades that exercise-related chest pain occurs frequently in patients with pulmonary hypertension despite normal coronary angiograms.[52] Systolic right coronary artery flow (assessed by MRI) is reduced in pulmonary hypertension,[53] which can lead to RV ischemia (demonstrated using myocardial perfusion scintigraphy).[54] Zong et al[55] reviewed the numerous differences in normal physiology of the RV and LV coronary circulations (Table 3). Very little is known about how the RV branches of the right coronary artery adapt to RV remodeling and chronically increased wall stress. It has been suggested[56] that the RV coronary circulation becomes more like that of the LV: a greater oxygen extraction at rest and a higher dependence on an increase in coronary flow (in contrast to an increase in oxygen extraction) to meet an increase in myocardial oxygen demand.

Table 3—*Characteristics of RV Oxygen Demand/Supply Balance That Differ From the LV

Lower oxygen requirements at rest and during exercise
Lower resting coronary blood flow and conductance
Increase rather than decrease in coronary flow during systole; higher systolic contribution to total perfusion
Ineffective pressure-flow autoregulation
Greater effect of flow and pressure on oxygen demand (flow determines oxygen consumption through RV stiffness)
Less coupling between flow and contractile function
Greater oxygen extraction reserve
Different strategies to meet increases in oxygen demand during acute pulmonary hypertension, exercise, and hypoxia
Higher dependency on NO as a regulator of resting right coronary blood flow
Pronounced α-adrenergic vasoconstriction during exercise, with no effect on transmural right coronary flow distribution
Similar reduction in subepicardial and subendocardial flows during hypoperfusion

*From Zong et al.[55]

There are several ways in which pulmonary hypertension can lead to an imbalance between RV oxygen supply and demand. Chronic hypoxemia is not uncommon in pulmonary hypertension and can be due to disturbances in pulmonary gas exchange, right-to-left shunting via a patent foramen ovale, and (in severe output failure) increased peripheral oxygen extraction. An increased wall tension increases oxygen consumption and decreases oxygen supply by compression of the coronary circulation. Systemic hypotension leads to a decreased coronary driving pressure, especially when pulmonary artery pressures are equal to or even higher than systemic pressures. In addition to these hemodynamic alterations, a dysfunctional microcirculation may contribute to tissue ischemia. During the development of cardiac hypertrophy, a mismatch between the number of capillaries and the size of cardiomyocytes can lead to myocardial hypoxia, contractile dysfunction, and apoptosis.[57] Whether microvessels in this setting

vanish, or whether angiogenesis simply lags behind the degree of hypertrophy, is unknown. Work by Sano et al[58] supports the hypothesis that a muscle/capillary mismatch plays an important role in the transition from adaptive hypertrophy to heart failure during LV pressure overload. They showed that in the initial 2 weeks after transverse aortic constriction, the number of microvessels per cardiomyocyte increased while systolic function was preserved. Thereafter, the number of microvessels decreased and systolic dysfunction developed. This response was tightly coupled to VEGF signaling, which was initially upregulated and subsequently downregulated (see online supplemental data). Chronic RV overload in monocrotaline-induced pulmonary hypertension is associated with a reduced capillary density and reduced VEGF expression in the RV, whereas RV capillary density and VEGF expression are increased in chronic hypoxic pulmonary hypertension.[59] Finally, RV ischemia in pulmonary hypertension may ensue due to a decreased NO-mediated vasodilation of RV small arteries, which seems related to increased superoxide production.[60]

Cardiac Cell Death

Cardiomyocyte apoptosis (programmed cell death, an energy-dependent process) is rare in the normal heart with one apoptotic cardiomyocyte in 10^4 to 10^5 cells.[61] However, apoptotic rates increase to up to 1 in 400 in human heart failure.[62,63] In animal models, apoptosis rates vary widely, with rates as high as 14% in ischemia/reperfusion and lower than 1% in chronic pressure overload.[64] The rate of RV cardiomyocyte apoptosis is elevated after pulmonary artery banding in rats.[65,66] Even very low rates of apoptosis (one fifth of that seen in human heart failure) have been shown to cause lethal dilated cardiomyopathy in a mouse model.[67] Pressure overload can induce apoptosis via stretch, ROS, β_1-adrenoreceptor agonists, ATII, and proinflammatory cytokines.[68] Ischemia/reperfusion is another strong activator of apoptosis.[69] Blocking apoptosis using broad-spectrum caspase inhibitors has been shown to reduce infarct size and improve cardiac function after ischemia/reperfusion.[70,71] Obviously, research on apoptosis in heart failure has focused on the cardiomyocyte. The possibility of endothelial cell apoptosis contributing to tissue ischemia in right-heart failure has not been investigated.

While it has been an article of faith that the entire heart is a postmitotic organ incapable of regenerating parenchymal cells, it has recently become clear that the heart harbors clonogenic multipotent cardiac stem cells that can differentiate into myocytes, smooth muscle cells, and endothelial cells.[9] A new paradigm of cardiac homeostasis is that a balance exists between cardiac cell loss due to apoptosis and necrosis, and the formation of new cells through the commitment of cardiac stem cells. Bone marrow-derived hematopoietic stem cells may contribute to cardiac repair after injury, but their role seems less significant.[72] Initially, cell proliferation likely contributes to the adaptation to pressure overload. However, the concomitant aging of the cells (senescence) has detrimental functional consequences, which are discussed in more detail in the supplement.

Pressure-Independent Cardioprotective Treatment in PAH

Current PAH treatment (prostacyclin analogs, ET-1 receptor antagonists, and PDE-5 inhibitors) and experimental drugs (*eg*, ρ kinase inhibitors) are used to induce pulmonary vasodilation and reverse pulmonary vascular remodeling. However, the possibility exists that long-term treatment with these drugs affects RV (mal-)adaptation by pressure-independent, cardiac specific effects. In this context, it is important to realize that the effects of the mentioned treatments on patient survival have not been firmly established. A metaanalysis[73] showed that the primary end point of most clinical trials evaluating prostacyclin analogs, ET-1 receptor antagonists, and PDE-5 inhibitors (*ie*, a short-term improvement in exercise capacity) is not predictive of survival. Conversely, it is important to consider the possibility of new treatments that support the successful adaptation of the RV and reduce RV wall stress, even in the context of continuing pressure overload.

Currently used PAH drugs affect cardiac contractility differently. It can be hypothesized that ET-1 receptor antagonists have negative inotropic effects because ET-1 is known to increase cardiomyocyte contractility.[74] In contrast, PDE-5 inhibition was recently shown to have positive inotropic effects in monocrotaline-induced pulmonary hypertension in rats.[75] On first sight, improving RV contractility may seem advantageous, but a concomitant increase in oxygen consumption may be detrimental. In a patient with a severely dilated RV and a low cardiac output, an improvement in cardiac contractility would reduce RV dilatation (the resultant decrease in RV wall tension in fact lowers myocardial oxygen consumption), and an improved cardiac output would lower maladaptive neurohormonal signaling. However, the same approach may be harmful in a patient with a nonfailing hypertrophic RV that is at risk of repeated bouts of ischemia, for example, during exercise.

The development of a PAH treatment strategy that both reduces the pulmonary vascular resistance

and improves RV function is likely difficult. There are indeed contrasting priorities within the different cell populations of the heart and the lung with respect to contractility (increase in cardiomyocytes vs relaxation of pulmonary vascular smooth muscle cells), angiogenesis (inhibition in the pulmonary vascular plexiform lesions and promotion within the myocardium), and apoptosis (promotion in phenotypically altered endothelial cells in the pulmonary vasculature and inhibition in the heart). Neurohormonal modulation with β-adrenoreceptor blockers and ACE inhibitors carries the risks of a decreased cardiac contractility and systemic vasodilatation. However, we can postulate that the careful use of cardioprotective neurohormonal modulation in selected patients may prove beneficial. Moreover, it is possible that reduction of inflammation and ROS/RNS imbalance, and reversal of ECM remodeling are beneficial for the heart and the pulmonary circulation. These effects may be accomplished by, *eg*, spironolactone[76] or statins.[77] Another strategy to treat PAH-associated RV failure is to specifically support RV contractility without affecting pulmonary vascular tone by levosimendan and ryanodine receptor stabilizers, drugs that do not raise myocardial oxygen consumption.

Conclusions

Right-heart failure is the immediate cause of death in most patients with PAH. The development of right-heart failure in PAH is secondary to the pulmonary vasculopathy, but effective, pathophysiologically based treatment of the latter is lacking. A better understanding of the mechanisms underlying the transition from compensated RV hypertrophy to maladaptive remodeling and dilatation could lead to the development of RV-specific therapies, improving survival in PAH. Decreased cardiomyocyte contractility (related to re-expression of fetal-type contractile proteins and disturbances in Ca^{2+} handling and energy generation) triggers autocrine, paracrine, and neuroendocrine signaling pathways that can either compensate the diminished force generation or lead to further deterioration. Unopposed ROS and RNS formation, inflammation, RV ischemia, and cardiomyocyte apoptosis contribute to the creation of a vicious circle that finally results in right-heart failure. That the heart failure is potentially reversible is a lesson learned from patients that have received a lung transplant. An understanding of the repair program of the recuperating RV may provide important clues directed toward strategies to induce cellular myocardial repair in view of persistent hemodynamic stress.

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