Adaptive capacity of the right ventricle: why does it fail?

Ella M. Poels,1,2 Paula A. da Costa Martins,1 and Vanessa P. M. van Empel2

1Department of Cardiology, CARIM School for Cardiovascular Diseases, Faculty of Health, Medicine and Life Sciences, Maastricht University, Maastricht, The Netherlands; and 2Department of Cardiology, Heart Vessel Center, Maastricht University Medical Centre, Maastricht, The Netherlands

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Poels EM, da Costa Martins PA, van Empel VP. Adaptive capacity of the right ventricle: why does it fail? Am J Physiol Heart Circ Physiol 308: H803–H813, 2015. First published February 13, 2015; doi:10.1152/ajpheart.00573.2014.—Only in recent years has the right ventricle (RV) function become appreciated to be equally important to the left ventricle (LV) function to maintain cardiac output. Right ventricular failure is, irrespectively of the etiology, associated with impaired exercise tolerance and poor survival. Since the anatomy and physiology of the RV is distinctly different than that of the LV, its adaptive mechanisms and the pathways involved are different as well. RV hypertrophy is an important mechanism of the RV to preserve cardiac output. This review summarizes the current knowledge on the right ventricle and its response to pathologic situations. We will focus on the adaptive capacity of the right ventricle and the molecular pathways involved, and we will discuss potential therapeutic interventions.

Adaptive Capacity of the Right Ventricle

In contrast to the LV, RV remodeling seems to be highly reversible. This suggests that distinct adaptive mechanisms play a role in the two different cardiac compartments. Patients with RV failure showed significant improvement of RV function after lung transplant, even if preoperative RV dysfunction was classified as severe. In a study by Shulman and colleagues (111), the degree of RV function improvement seemed to be related to pulmonary artery pressure (PAP) and the duration of disease prior to transplantation, with higher PAP and shorter disease duration correlating with enhanced improvement in RV function (58). This is in line with earlier research, showing that patients with severe pulmonary hypertension have markedly improved RV systolic function as well as a significantly decreased RV wall thickness after lung transplant (102). This

RIGHT VENTRICULAR FAILURE can have many different origins, but independent of the cause, right ventricle (RV) function is an important predictor of outcome (3, 25, 32, 37, 40, 77, 79, 108). In pulmonary hypertension the ability of the RV to adapt to increased afterload, which is caused by rising pulmonary arterial pressures, is the key determinant for the occurrence of symptoms and survival (18, 47). Specifically, RV mass, size, and RV ejection fraction (RVEF) have all been found to be independent predictors of survival (47, 50, 126).

Normal Right Ventricular Function

The RV is connected in series with the left ventricle (LV) and therefore on average has the same stroke volume (41). The RV is connected to a low-pressure pulmonary vascular system with low vascular resistance, in contrast to the LV, which is connected to a high-pressure system with high vascular resistance (29, 41). RV function is closely linked to RV contractility, preload, and afterload (41). Since the ventricular mass of the RV is only about one third of the ventricular mass of the LV, oxygen consumption is also lower (41). Similar to the LV, the RV has several adaptive mechanisms that can acutely regulate RV function, including heart rate, the Frank-Starling mechanism, and the autonomic nervous system (29, 41).

Differences in function between the right and left ventricle can be partly explained by the fact that both ventricles derive from different progenitor cells. The outflow tract, as well as the embryonic RV, derives from the anterior heart field, whereas the LV is formed from the primary heart tube, which finds its origin in the primary heart field (141). This chamber-specific heart formation is regulated by transcription factors such as heart and neural crest derivatives expressed 1 (Hand1) and 2 (Hand2) (74). Hand2 is expressed throughout the precardiacogenic mesoderm at embryonic day 7.75, but becomes restricted to the RV as development of the heart progresses. After embryonic day 10.0, Hand2 expression in the cardiac mesoderm decreases again (116). In contrast, as the heart develops, Hand1 expression is limited to the linear heart tube, which is destined to form the LV (74).

In the fetus, RV and LV free-wall thickness and force development are equal as there is right-to-left flow through the foramen ovale. In addition, a high-resistance pulmonary circulation and a low-resistance systemic circulation characterize this fetal period. After birth, RV and LV circulation become separated and resistance in the pulmonary circulation decreases, causing the heart to remodel to a crescent-shaped RV and elliptical-shaped LV as RV hypertrophy regresses (41).
decrease in wall thickness was also seen in patients with tetralogy of Fallot who underwent corrective surgery. RV endomyocardial biopsies showed a decreased RV cell size after surgery, correlating with RV systolic pressure and RV end-systolic and end-diastolic volumes (81). The mechanisms involved in this recovery of RV hypertrophy and failure remain unknown.

Recently it was demonstrated that after percutaneous pulmonary valve implantation (PPVI) in patients with congenital heart disease, suffering from RV to pulmonary artery conduit dysfunction, RV systolic function improved rapidly after the procedure. Before PPVI, RV mass was positively correlated with maximum velocity over the pulmonary trunk. Following the procedure, this correlation was no longer present, despite the presence of mild residual stenosis. However, restoration of RV diastolic function was delayed and seemed to correlate with RV mass (104). Improvement in RV function paralleled a decrease in electrocardiogram characteristics of RV hypertrophy (94). In tetralogy of Fallot patients undergoing PPVI because of significant pulmonary regurgitation (PR), RV end-diastolic volume decreased and RV stroke volume increased. However, there was no improvement in measures of exercise capacity measured by peak oxygen consumption and anaerobic threshold, suggesting that in contrast to pressure overload, the contractile reserve of chronically volume-overloaded myocardium is limited. The symptomatic improvement after PPVI is most likely explained by an increase in cardiac output in rest (21). Furthermore, a different study in this subgroup of patients showed that rapid volume unloading increases systolic performance; however, it is likely that improvement in diastolic function requires long-term remodeling (128). These data further enhance the notion that pressure and volume overload induce different types of remodeling in the RV.

Other congenital cardiac anomalies, including atrial septal defect (ASD) and Eisenmenger’s syndrome, also coincide with a certain degree of sustained right ventricular adaptation. In ASD, differences in compliance between the left and right ventricle result in a left to right shunt during ventricular diastole, increasing the filling volumes of the RV. RV ejection fraction is maintained, though at higher end-diastolic and end-systolic volumes (33, 95). Therefore, it can remain undiagnosed until adulthood when a selection of patients start to develop symptoms related to RV dysfunction (67). This demonstrates the ability of the RV to adapt immensely to increased filling volumes for a relatively long period before becoming symptomatic.

Patients with Eisenmenger’s syndrome (ES) have a much higher survival rate than those with idiopathic pulmonary hypertension, which is believed to relate to the fact that in ES the RV has been exposed and primed to high pressures since birth and therefore is better adapted (44–46, 57). It is postulated that regression of right ventricular wall thickness never occurs and contractile function is preserved for a longer period in patients with ES compared with idiopathic pulmonary arterial hypertension (PAH), resulting in a fetal RV phenotype (44). Signs of RV dysfunction such as reduction in tricuspid annular plane systolic excursion (TAPSE) and duration of tricuspid regurgitation are strongly related to outcome (82). However, it is unknown why some patients with RV hypertrophy develop RV failure while others do not. A better insight into the mechanisms that enhance the adaptive capacity of the RV could help in improving treatment for RV failure.

Animal Models of RV Failure

Multiple animal models are available to study RV hypertrophy and failure, most of which are models of pulmonary hypertension in which RV failure develops secondary to pulmonary remodeling. A model of isolated RV failure is pulmonary artery banding (PAB) (6). PAB causes pressure overload in the RV and subsequent RV hypertrophy and failure. It is predominantly used in rats and larger mammals. Pulmonary hypertension models consist of single hit (i.e., monocrotaline, chronic hypoxia) (56, 118) and multiple-hit (i.e., chronic hypoxia + VEGFR inhibitor SU5416; SuHx) models (120). Additionally, there are rodent models of specific genetic deletion and overexpression for the induction of pulmonary hypertension (24, 117). Each of these models has their pros and cons; however, the two-hit SuHx model most closely resembles the multiple-hit pathophysiology of human pulmonary hypertension, where genetic predisposition precedes a second hit of variable cause, including a superimposed second genetic hit, increased flow due to pulmonary or cardiac pathology, infectious organisms, or drugs. However, none of these models induce the typical pleomorphic lesions, which can be found in human pulmonary hypertension (39, 72).

Which model is most representative for human RV remodeling and failure remains the subject of debate. It is thought that single hit models could replicate adaptive remodeling, whereas the multiple-hit models and PAB more closely resemble maladaptive remodeling and RV failure. The molecular mechanisms discussed in the following paragraphs have been studied by the wide array of animal models described above.

Molecular Mechanisms of RV Adaptation

There are several causes for right ventricular failure, including pressure overload (e.g., in PAH and left-sided heart failure) and volume overload (e.g., ASD). Although sudden increases in afterload are not tolerated as well in the RV as they are in the LV, more often the increase in afterload is gradual and the RV has time to adapt (11, 130, 132). RV hypertrophy allows for the generation of higher pressures to overcome increased pulmonary afterload. From a morphologic point of view, the RV wall becomes thicker through assembly of new sarcomeres and increased protein synthesis, making the RV more concentric with concomitant flattening of the interventricular septum. Secondary to sarcomere synthesis, cardiomyocyte length increases, allowing for a larger stroke volume and the maintenance of cardiac output (40).

In a swine model of surgically induced postcapillary PH, two distinct groups were identified after follow-up: nonfailing and failing. In the nonfailing group diastolic dysfunction was observed, providing an early marker for RV remodeling. RV fibrosis was increased in both groups; however, RV hypertrophy was only present in the failing group and coincided with RV-PA uncoupling, decreased SERCA2a expression, and hyperaldosteronism (1).

RV adaptation is dependent on many factors, including the type and severity of myocardial injury or stress, the time course of the disease (acute or chronic), and the time of disease onset (fetal or adulthood). Additional processes that need to be taken
into account are altered gene expression, neurohormonal activation, altered mechanosensing, inflammation, and apoptosis (40, 130). These factors are all interlinked and influence each other, making RV adaptation a complex process.

Reactivation of a fetal gene program. RV hypertrophy coincides with a reduction in α-myosin heavy chain and an increase in β-myosin heavy chain, indicating a switch to the slower and less active isoform (71). This isoform switch decreases the ATP requirement of the RV, thereby reducing the amount of energy needed to generate contractile force (71, 98). Besides this switch, increased expression of the thin filaments α-skeletal actin and α-smooth muscle actin is observed at the cost of α-cardiac actin (16). In addition, this switch indicates reexpression of a fetal gene program, coinciding with a preference for the glycolytic pathway over fatty acid supply. It must be noted, however, that during the progression of density, thereby facilitating the need for increased oxygen supply (98, 107). Increased HIF1α has been indicated as an important player in the oxygen-dependent expression of the thin filaments (71).

As hypertrophy of the RV progresses, oxygen demand and diffusion distances increase, creating a need for a higher oxygen supply (98, 107). Increased HIF1α expression induces the transcription of vascular endothelial growth factor (VEGF) and stromal derived factor 1, resulting in increased capillary density, thereby facilitating the need for increased oxygen supply. It must be noted, however, that during the progression to RV failure, HIF1α expression is decreased again due to a sharp rise in pyruvate dehydrogenase kinase driven mitochondrial-derived reactive oxygen species, suppressing angiogenesis and glucose uptake. Hence, the adaptive metabolic shift is not sustained during the progression to RV failure (98, 134).

Mechanosensing. During the development of RV hypertrophy, several signaling pathways are activated. In the case of RV overload, the overload forces are transferred to the cardiomyocytes via integrins, a family of transmembrane adhesion receptors that link the extracellular matrix (ECM) to the cellular cytoskeleton. These transmembrane adhesion receptors signal via a large array of intracellular signaling pathways, including focal adhesion kinase (FAK), which localizes to membrane regions attached to the ECM, so-called focal adhesions, thereby coupling the proteins of the ECM to the cellular cytoskeleton and other specific proteins such as FAK, as has been investigated in several animal models (52, 63, 109, 114, 123). Upon integrin stimulation, FAK undergoes autophosphorylation and activates an intracellular signaling cascade involving several members of the mitogen-activated protein kinases (MAPKs) including the MAPK/ERK kinases (MEKs)-1/2 and 4 (MEK4). Downstream of the MAPKs lie extracellular regulated kinase-2 (ERK2) and c-Jun N-terminal kinase-1 (JNK1) that lead to increased expression of nuclear transcription factors upon phosphorylation, resulting in cytoskeletal reorganization and cell growth (63, 109, 123). Research in mice has shown that signaling through the MAPK superfamily indeed mediates pathologic cardiac remodeling in the RV. MAPKKK-2 (MEKK-2) null mice are protected from hypoxia-induced RV hypertrophy and exhibit inhibited inflammatory gene expression compared with wildtype mice (13). Furthermore, upon stretch, the angiotensin II type 1 receptor associates with Janus kinase-2 (JAK2) leading to activation of ERK in neonatal rat cardiomyocytes (145).

These pathways, in turn activate transcription factors relevant to matrix metalloproteinase (MMP) transcriptional regulation, a family of zinc-dependent proteinases that participate in degradation of extracellular matrix components in humans (64). Both MMP-9 and MMP-2 have been shown to be up-regulated in samples from RV hypertrophy, suggesting that these proteinases have a role in interstitial fibrosis and cardiac remodeling seen in hypertrophy and failure of the ventricle (63, 103, 123). In cats and rats, nitric oxide synthase 1 (NOS1) is similarly involved in integrin stimulation, most likely through a ryanodine receptor-2 (RyR2), MEK1/2, and ERK2 mediated pathway (63, 123, 124).

In parallel to activation of integrins, stretch-activated ion channels (SACs) are mechanosensitively activated in neonatal rat cardiomyocytes upon overload of the RV, allowing the passage of ions such as Na⁺, K⁺, and Ca²⁺. Indeed, direct Ca²⁺ influx is known to be associated with cardiomyocyte hypertrophy (48, 109, 110, 121). The exact mechanism whereby SACs induce hypertrophy through increased Ca²⁺ influx in the RV remains to be elucidated; however, it is postulated that activation of protein kinase C (PKC) plays a role through direct or indirect alteration of gene expression (105, 109). Another putative mechanism whereby Ca²⁺ influx regulates RV hypertrophy is through the Ca²⁺/calmodulin-dependent phosphatase calcineurin. Calcineurin is a serine/threonine-specific phosphatase that is uniquely activated by sustained elevation of intracellular Ca²⁺. This mechanism has been well described in LV hypertrophy, yet remains to be further elucidated in the RV. Calcineurin activation is mediated by binding of Ca²⁺ and calmodulin to the regulatory and catalytic subunits of calcineurin. Calcineurin, in turn, dephosphorylates nuclear factors of activated T-cells-3 (NFAT3), resulting in its translocation to the nucleus, where it interacts with the cardiac-restricted zinc finger transcription factor GATA4 to synergistically activate transcription in mice (22, 43, 83, 84). Indeed, GATA4 expression has been found to be enhanced in the pressure-overloaded rat RV (90). Furthermore, modulatory-calcineurin-interacting-protein-1 (MCPI1) is increased in the RV of mice subjected to pressure overload, indicating calcineurin activation (4).

Similar to pressure-induced LV hypertrophy, the Rho-kinase (ROCK) pathway, and in particular ROCK2, seems to play a crucial role in rodent RV hypertrophy and dysfunction, particularly in the pressure-overloaded RV (54, 93). This is further strengthened by the fact that treatment with atorvastatin decreases mean pulmonary arterial pressure and RV hypertrophy in rats through inhibition of Rho A/ROCK and NF-kB activity (143). In addition, treatment with the Rho-kinase inhibitor, Y-27632, reduces the development of pulmonary hypertension in a hypoxic rat model by diminishing pulmonary artery smooth muscle cell (PASMC) proliferation (76). The ROCK pathway is therefore important in both PASMCs as well as in the RV itself.

Neurohormonal signaling. In LV hypertrophy and remodeling, the cardiac renin-angiotensin-aldosterone system (RAAS) plays a prominent role; however, the exact involvement of the RAAS system in RV remodeling remains unclear. It is known that endothelin-1 (ET-1), angiotensin I (ATI), angiotensin II (ATII), renin, and transforming growth factor β1 (TGF-β1) are
all increased in myocardium from failing rat and human RVs (27, 91). Moreover, increased ATP, ATII, and renin levels are all associated with disease progression and increased mortality in patients with idiopathic PAH (27). In addition, adrenergic signaling plays a role in the failing RV. Additionally, it is known that cardiac sympathetic activity is increased during development of RV failure in humans (73). Sympathetic nervous system activation has been indicated as an independent predictor of clinical deterioration in PAH patients (19).

Endothelin-1 (ET-1) is a potent endothelium-derived vasoconstrictor peptide induced in PAH, leading to vasoconstriction and smooth muscle cell proliferation through interaction with endothelin receptors in patients (35, 88). Furthermore, endothelin receptor antagonists (ERAs) are an important therapeutic target in PAH treatment, inducing vasodilatation of the pulmonary vasculature. Analysis of hypertrophied rat RV samples revealed increased endothelin type A receptor (ET-A) expression. A similar increase was seen for ET-1 protein levels, implicating a role for a ET axis in the myocardium. ET-1 has an inotropic effect on the heart through interaction with ET-A receptors resulting in decreased RV contractility after treatment with ERAs, both in a rat model and in patients (88).

Angiotensin II as well as endothelin-1 modulates cardiomyocyte hypertrophy through interaction with G-protein coupled receptors, activating downstream pathways involving PKC, calcineurin/NFAT activation, or calmodulin-dependent kinase histone deacetylase (HDAC) inactivation (20, 136).

TGF-β1 signaling has a role in pulmonary vascular remodeling as well as in cardiac extracellular matrix and collagen synthesis in human PH (8, 65). In addition, the TGF-β1 pathway has been linked to cardiac hypertrophy in neonatal rat cardiomyocytes; however, it remains to be investigated whether this is true for RV hypertrophy (66).

Prolonged neurohormonal activation can lead to β-adrenergic receptor (βAR) desensitization, with several clinical studies showing loss of βAR density in RV failure and resulting in impairment of both systolic and diastolic function (10, 70, 97, 98). Experimental models of PH have shown that treatment with a β blocker has a beneficial effect on RV function, most likely through reduced desensitization of the βAR. In addition, α1/β1/β2-adrenergic receptor blockade using carvedilol resulted in improved RV function and reversal of maladaptive RV remodeling in rats (7, 26). Small clinical trials using β blockers have resulted in mixed outcomes in patients with RV dysfunction (36, 112). Larger clinical trials will result in a decisive answer on the effect of β-adrenergic blockade in RV failure patients.

Furthermore, there is increasing evidence for natriuretic peptide activation in RV failure, although its biological significance is poorly understood (139, 140). In addition, increases in norepinephrine, ANP, and endothelin-1 were observed in patients with pulmonary hypertension (89, 129). Plasma brain natriuretic peptide (BNP), a cardiac hormone mainly secreted by the ventricles, is a strong predictor of mortality in patients with pulmonary hypertension, especially if an increase in BNP levels is observed during follow-up (85).

A recent study indicates a protective role for estrogen on RV function in a murine SuHx (VEGF receptor inhibitor + hypoxia) PAH model, both through a direct inotropic effect as well as through diminishing pulmonary vascular remodeling (68). In vitro experiments have indicated that the protective effects of estrogen are (partially) mediated through interaction with pro- and antihypertrophic histone deacetylase proteins (HDACs) (92). Further players in this mechanism have been suggested, including estrogen-related receptor gamma (ERRγ)/GATA4 signaling (61). The exact mechanism in the RV remains to be further elucidated.

Inflammation. Immune system activation plays a prominent role in LV failure; however, little is known about immune system involvement in RV failure. In human RV hypertrophy associated with chronic thromboembolic pulmonary hypertension, increased levels of several proinflammatory cytokines including TNFα, sTNFRF1, sTNFR2, IL-6, and IL-10 indicate a role for the immune system (131, 113). The stimulus for cytokine release remains a point of discussion, and it has been suggested that abdominal fluid accumulations predispose bacterial endotoxin release from the bowel into the bloodstream (2, 131). The hypothesis of a role for the immune system in RV failure was further strengthened by postmortem histological analyses of RV muscle from humans with fatal pulmonary embolism, demonstrating an accumulation of monocytes and macrophages in the RV (55, 135). Similar results have been shown in an animal model of RV failure, resulting in accumulation of neutrophils and monocytes/macrophages in the RV (135).

A role for inflammation in the RV is further indicated by increased messenger RNA (mRNA) levels of proinflammatory cytokines, including IL-1β, S100A4, monocyte chemoattractant protein (MCP)-1, stromal cell-derived factor (SDF)-1, and C-X-C chemokine receptor type 4 (CXCR-4) in a mouse model of chronic hypoxia (13). Furthermore, it has been shown in a monocrotaline rat model for RV failure that disease progression coincides with increased 99Ga uptake using scintigraphy, suggesting a role for inflammation. This was confirmed by immunostaining in rats, showing neutrophil infiltrates in monocrotaline-treated hearts compared with control, further strengthening a role for inflammation (14).

Apoptosis. Cardiomyocyte apoptosis is rare in the healthy heart but increases in human heart failure (42). PKC plays a pivotal role in cardiac apoptosis of the LV (122) and influences the balance between proapoptotic (i.e., Bax and caspase-3) and antiapoptotic signaling factors (i.e., Bcl-2) in rats (9, 100). Increased Bax and caspase-3 levels were found in the RV of rats after PAB, whereas Bcl-2 expression remained unchanged compared with sham-operated controls, indicating increased apoptosis in the pressure-overloaded RV. The expression of cardiac PKC isozymes remained unchanged after PAB, implying PKC does not play a major role in PAB-induced RV apoptosis in rats (9). Furthermore, PAB-operated rabbits showed increased levels of RV apoptosis after 4 wk, indicating that apoptosis indeed plays a role in RV hypertrophy (80). Reactive oxygen species, β1-adrenergic receptor agonists, angiotensin II (ATII), and proinflammatory cytokines all induce apoptosis in response to pressure overload (53).

Finally, nicorandil, a mitochondrial ATP-dependent potassium channel opener, inhibits monocrotaline-induced RV murine remodeling and hypertrophy by reducing apoptosis (146). The involvement of apoptosis with RV hypertrophy was further confirmed by in vivo 99mTc-annexin scintigraphy, showing increased apoptosis in the early stages of RV disease progression (15).
Therapeutic Interventions in Right Ventricular Failure

The occurrence of right ventricular failure is an important risk factor for morbidity and mortality in heart failure as well as in pulmonary hypertension. Therefore, adequate treatment of RV failure is imperative. Since the RV differs from the LV in function and pathophysiology, it is imprudent to assume that the well-established treatment for left ventricular failure will have similar effects in RV failure, and currently treatment of RV failure remains mostly empiric. Treatment goals include optimization of preload, afterload, and contractility (115).

Renin-angiotensin-aldosteron inhibition. One of the cornerstones of LV failure therapy is inhibition of the RAAS (51, 75). Apart from inhibiting angiotensin I to angiotensin II-convert- ing enzyme (ACE), ACE inhibitors have been implicated in kinin metabolism. Increasing kinin levels through inhibition of metabolic degradation results in an increase in nitric oxide and vasodilatory prostaglandins (5). In a model of PAB in rabbits, pulmonary constriction lead to complete functional uncoupling of the AT$_1$-receptor from its contractile effects through a signaling defect downstream of the AT$_1$-receptor, despite an increase in AT$_1$-receptor density, meaning that the inotropic effects of angiotensin II are markedly decreased. Treatment with the ACE inhibitor ramipril resulted in preservation of cardiac contractile responsiveness to angiotensin II, suggesting that the reduction of angiotensin II or blockade of the AT$_1$-receptor prevents functional uncoupling of the receptor downstream. This observed effect of ramipril partly seems to involve kinins, since simultaneous treatment with a kinin receptor blocker eliminated many of the beneficial effects. Furthermore, treatment with ramipril led to a trend toward decreased RV hypertrophy. The effect of losartan, an AT$_1$-receptor blocker, was less pronounced in this setting (106). In a study observing the effect of the AT$_1$-receptor blocker valsartan on ventricular function in cases of systemic RV, there was no effect on right ventricular ejection fraction, exercise capacity, or quality of life compared with control (127).

A monocrotaline rat model has been used to show that treatment with the ARB valsartan results in delayed onset of RV hypertrophy and failure, coinciding with reduced levels of apoptosis and fibrosis compared with control (15). This is in accordance with decreased RV afterload and pulmonary vascular remodeling, as well as restored right ventricular arterial coupling in monocrotaline rats after treatment with losartan (27).

Since the RV has the capacity to adapt to increased volume load, volume loading in a patient with RV failure can be beneficial (38, 40, 62). However, this must be done with caution, as too much loading can be detrimental, especially in patients with low mean arterial pressure, whereby excessive filling will lead to septic shifting and even further decreased LV output (38).

β-Adrenergic receptor blockade. β Blockade is one of the cornerstones of treatment in patients with systolic heart failure. Multiple clinical trials have shown reduction in mortality with 3.8 lives saved in every 100 treated patients. In addition, hospitalization rates and symptoms are decreased after treatment in selected patients with LV failure (12, 17). The most frequent cause of RV failure is LV failure, and these patients are therefore often put on a treatment regime including β blockade. Information about the efficacy of β blockade in these patients is limited.

In preclinical research both the SuHx and monocrotaline rat models of pulmonary hypertension have been used to research the effect of adrenergic blockade in RV failure. Treatment with carvedilol was associated with reversed RV remodeling and improved RV function (7). Furthermore, treatment with bisoprolol in a monocrotaline rat model delayed the time to onset of right heart failure, as well as increasing RV contractility and filling and restoring β-adrenergic receptor signaling (26). It has been shown that β-blockade in RV failure induces a different gene expression pattern compared with control. Gene expression for proteins involved in hypertrophy and protein ubiquitination pathways was decreased by carvedilol treatment, in contrast to an increase of genes that are part of mitochondrial dysfunction pathways (31).

In a study using a population of chronic systolic HF patients, it was found that concomitant RVEF < 20% on background treatment with renin-angiotensin inhibition, diuretics and digoxin did not result in an association with increased mortality. However, contrary to results in animal models of RV failure, adding the β-blocker bucindolol to therapy lead to an independent significant increase in mortality, suggesting a detrimental effect of β-blockade in patients with RV failure (30). Moreover, discontinuation of β-blockade in patients with portopulmonary hypertension resulted in improved exercise capacity and resting pulmonary hemodynamics (96). A normal RVEF was significantly associated with positive effect of β-blockade on LVEF in patients with LVEF ≤ 30% (99).

Vasodilators. Many patients suffering from PAH eventually develop RV failure, and pulmonary disease is characterized by proliferative vasculopathy, including smooth muscle cell proliferation, vasoconstriction, fibrosis, and thrombosis (49). These patients may benefit from pulmonary vasodilation, as decreasing afterload will improve ventricular function. This can be achieved by vasodilators such as nitric oxide (NO). NO dilates the pulmonary vasculature through increasing production of cyclic guanosine monophosphate as well as through a possible mechanism of reducing pulmonary cytokine production. An alternative to NO is the prostacyclin family, which promotes vasodilation through activation of cyclic adenosine monophosphate. Furthermore, Phosphodiesterase type 5 (PDE5) inhibitors can be used to promote vasodilation by blocking degradation of cyclic guanosine monophosphate (38, 62, 78). PDE5 is not expressed in the normal RV but becomes markedly upregulated in the hypertrophied RV. Inhibition of PDE5 results in vasodilatory and antiproliferative effects on the pulmonary vasculature, as well as an increase in cAMP and contractility in the RV myocardium (86). Prophylactic treatment of rats exposed to hyperoxia from birth with the phosphodiesterase inhibitor sildenafil resulted in improved right ventricular hypertrophy (28). In addition, early treatment with sildenafil also prevented T-tubule dysfunction and Ca$^{2+}$ handling dysfunction (137).

In PAH, the expression of endothelin-A (ET$_{A}$-A) receptors is increased in pulmonary arteries. In addition PAH induces an increase in the ET$_{A}$-A to ET$_{B}$ receptor ratio in the RV compared with normal hearts (60). Both dual receptor antagonism as well as ET$_{A}$-A receptor antagonism are used in a clinical setting in patients with pulmonary hypertension and improve symptoms, RVEF, and outcome (34). Prolonged treatment with the endo-
the lin receptor antagonist bosentan in patients with Eisenmenger’s syndrome resulted in sustained, improved PAH and RV function (59).

**Experimental Therapies/Possible Future Targets**

Baicalin, a flavonoid compound, has been shown to have a beneficial effect on pulmonary vascular structure remodeling and hypoxic pulmonary hypertension in rats, by downregulation of the production of HIF-1α through the AKT pathway and thereby preventing degradation of p27, a crucial mediator in vascular smooth muscle cell proliferation (142). A role for the protein kinase B (AKT) pathway as a therapeutic target was further elucidated by Xu et al. (138), showing that \(^{27}\text{kip}^1\), a critical cyclin dependent kinase inhibitor, can be increased by treatment with \(\beta\)-estradiol through inhibition of S phase kinase associated protein 2, which is an important player in the AKT pathway.

Resveratrol, a polyphenolic compound, attenuated right ventricular systolic pressure, pulmonary arterial remodeling, and smooth muscle cell proliferation as well as inflammatory cytokine expression (TNFα, IL-1β, IL-6, PDGF-α/β) in a monocrotaline rat model. Additionally, expression of endothelial NO synthase was increased (23). Similarly, trimethoxystilbene, a resveratrol analog, improved pulmonary vascular remodeling and RV hypertrophy in rats (69).

Mitochondrial membrane potential, in indicator of mitochondrial function, correlates with the degree of right ventricular hypertrophy and is associated with nuclear factor of activated T lymphocytes (NFAT). Treatment of neonatal rat cardiomyocytes from the right ventricle with a selective NFAT inhibitor, VIVIT, prevented nuclear translocation of NFAT upon phenylephrine stimulation, highlighting NFAT as an interesting therapeutic target in RV hypertrophy. Dichloroacetate is an alternative for VIVIT since it increases glucose oxidation, thereby decreasing mitochondrial membrane potential (87).

**Conclusions**

In this review we have described the different molecular pathways known to play a role in RV hypertrophy and RV failure (Fig. 1). The described differences between the RV and LV, on a morphologic and functional level, make it plausible that the reaction to stress and development of hypertrophy and failure are due to separate mechanisms. Nevertheless, the described molecular signaling pathways for the overloaded RV are, at least to some extent, involved in LV pressure overload as well.

More and more research is being done to identify signaling pathways specifically involved in the RV. In a murine model the Wnt signaling pathway was upregulated in the pressure-
overloaded RV but not in the pressure-overloaded LV (125). This is further emphasized by differential expression of transcription factors, messenger ribonucleic acid (mRNA), and microRNAs in failing left and right ventricles (101, 133, 144). However, their (possible) role in RV remodeling remains to be determined.

Furthermore, an overview is given of therapeutic options for RV failure. However, research into RV hypertrophy and failure and its subsequent treatment remains sparse compared with the LV, resulting in unspecificity and unclarity of efficacy of current treatment options. More research is therefore necessary to further elucidate the signaling pathways and mechanisms involved in RV hypertrophy and failure. Finally, a better understanding of the mechanisms involved will provide novel candidates for biomarkers to detect the disease at an early stage and for treatment to prevent or reverse disease progression.

DISCLOSURES

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AUTHOR CONTRIBUTIONS


REFERENCES


