The right ventricle (RV) and left ventricle (LV) have discrete embryological origins. The LV develops first, originating from the primary heart field; subsequently, the RV develops from precursor cells in the secondary heart field. The transcriptional regulation of myoblast differentiation also differs between the RV and LV. RV myocytes are directed in

**Compendium**

*Circulation Research Compendium on Pulmonary Arterial Hypertension*

Pulmonary Arterial Hypertension: Yesterday, Today, Tomorrow
Pulmonary Arterial Hypertension: The Clinical Syndrome
Current Clinical Management of Pulmonary Arterial Hypertension
The Metabolic Theory of Pulmonary Arterial Hypertension
Inflammation and Immunity in the Pathogenesis of Pulmonary Arterial Hypertension
The Right Ventricle in Pulmonary Arterial Hypertension: Disorders of Metabolism, Angiogenesis and Adrenergic Signaling in Right Ventricular Failure
The Genetics of Pulmonary Arterial Hypertension

**Guest Editor: Evangelos Michelakis**

The Right Ventricle in Pulmonary Arterial Hypertension
Disorders of Metabolism, Angiogenesis and Adrenergic Signaling in Right Ventricular Failure

John J. Ryan, Stephen L. Archer

**Abstract:** The right ventricle (RV) is the major determinant of functional state and prognosis in pulmonary arterial hypertension. RV hypertrophy (RVH) triggered by pressure overload is initially compensatory but often leads to RV failure. Despite similar RV afterload and mass some patients develop adaptive RVH (concentric with retained RV function), while others develop maladaptive RVH, characterized by dilatation, fibrosis, and RV failure. The differentiation of adaptive versus maladaptive RVH is imprecise, but adaptive RVH is associated with better functional capacity and survival. At the molecular level, maladaptive RVH displays greater impairment of angiogenesis, adrenergic signaling, and metabolism than adaptive RVH, and these derangements often involve the left ventricle. Clinically, maladaptive RVH is characterized by increased N-terminal pro–brain natriuretic peptide levels, troponin release, elevated catecholamine levels, RV dilatation, and late gadolinium enhancement on MRI, increased fluorodeoxyglucose uptake on positron emission tomography, and QTc prolongation on the ECG. In maladaptive RVH there is reduced inotrope responsiveness because of G-protein receptor kinase–mediated downregulation, desensitization, and uncoupling of β-adrenergoreceptors. RV ischemia may result from capillary rarefaction or decreased right coronary artery perfusion pressure. Maladaptive RVH shares metabolic abnormalities with cancer including aerobic glycolysis (resulting from a forkhead box protein O1–mediated transcriptional upregulation of pyruvate dehydrogenase kinase), and glutaminolysis (reflecting ischemia-induced cMyc activation). Augmentation of glucose oxidation is beneficial in experimental RVH and can be achieved by inhibition of pyruvate dehydrogenase kinase, fatty acid oxidation, or glutaminolysis. Therapeutic targets in RV failure include chamber-specific abnormalities of metabolism, angiogenesis, adrenergic signaling, and phosphodiestrase-5 expression. The ability to restore RV function in experimental models challenges the dogma that RV failure is irreversible without regression of pulmonary vascular disease. (*Circ Res. 2014;115:176-188.*)

**Key Words:** adrenergic receptors ■ fluorodeoxyglucose ■ Forkhead box protein O1 (FOXO1) ■ G protein receptor kinase 2 (GRK2) ■ glutamine ■ glycolysis ■ pyruvate dehydrogenase complex

The right ventricle (RV) and left ventricle (LV) have discrete embryological origins. The LV develops first, originating from the primary heart field; subsequently, the RV
their development by chamber-specific transcription factors, such as dHAND and MEF2C. In contrast, LV myocyte development is guided by Nkx2.5 and eHAND. The RV’s unique embryology foreshadows differences in its response to pressure and volume overload.

**Right Ventricular Anatomy**

The fetal/neonatal RV is a thick-walled chamber that ejects blood at relatively high pressure into a high-resistance vascular bed. The wall thickness of both ventricles increases in parallel to 3.5 mm at term. Postnatally the pulmonary circulation transitions to a low-pressure circuit and the RV wall thickness remains ~4 mm, while the LV, faced with 4x greater afterload, increases in thickness to ~11 mm.

The RV’s crescentic geometry is distinct from the cone-shaped LV. The RV can be divided into 3 segments, including (1) the inlet, comprising the tricuspid valve, chordae tendineae, and papillary muscles; (2) the trabeculated apical myocardium; and (3) the outflow region (called the conus or the infundibulum), which has a smooth myocardial surface. RV contraction starts at the inflow section and progresses toward the outflow tract. A superficial, circumferential layer of RV myocardial fibers is in continuity with the LV fibers, accounting for the systolic motion of the RV free wall toward the interventricular septum. A deeper layer of vertically arranged RV fibers mediates RV systolic shortening. This longitudinal shortening is exploited in echocardiography to measure RV function using the M-mode measurement, tricuspid annular plane systolic excursion. Tricuspid annular plane systolic excursion predicts RV function and prognosis in adults with pulmonary arterial hypertension (PAH). A tricuspid annular plane systolic excursion <18 mm indicates a poor prognosis.

**Right Ventricular Function**

After birth, with closure of the ductus arteriosus and foramen ovale, the RV conveys the same cardiac output as the LV, but at ~20% of the LV’s pressure. The RV ejection fraction (EF) in normal children is 53%, while the LVEF is 68%. However, cardiac output is essentially identical, because the RV has slightly larger volumes. In adults the normal RVEF is 62% compared with a normal LVEF of 65%. RVEF is reduced by half in adults with World Health Organization (WHO) group 1 pulmonary hypertension (PH; to a mean of 34±10%).

The Multi-Ethnic Study of Atherosclerosis (MESA) study used MRI to determine normal values for RV size and function in 4123 normal adults, aged 61.5±10.1 years (47.5% males). Normal values for RV mass in males and females were 19.2±3.6 and 23.1±4.4 g, respectively. Normal values for RV end-diastolic volume in females and males were 108.9±23.2 and 140.9±29.7 mL, respectively. Men had 4% lower RVEF than females. Age was associated with lower RV mass but higher RVEF.

The RV in normal individuals increases cardiac output during exercise. However, at rest, the cardiac output can be maintained at near-normal levels without a functional RV, provided that the LV function is normal and there is no pulmonary vascular disease. This is illustrated by 2 surgical studies in which the RV is removed from the circulation. First, in normal dogs replacement of the RV with a noncontractile Dacron patch reduces cardiac output by only 25%, and many animals survive without heart failure. The Dacron patch is pulled toward the septum by the LV, and the septum bulges into the RV cavity in systole, creating sufficient force to eject blood into the normal pulmonary circulation. The second example is the Fontan procedure, performed in patients with tricuspid or pulmonic valve atresia. In the Fontan procedure, all caval flow bypasses the RV and enters directly into the pulmonary circulation. Cardiac output and functional capacity are maintained in these patients, provided that there is no pulmonary vascular disease. If performed before age 5 years these patients maintain normal resting cardiac output more than a decade later, although maximal exercise capacity is reduced.

**Rationale for Study of the RV**

RV function is a major determinant of functional capacity and prognosis when RV afterload is elevated, as in WHO group 1 PH (PAH) or congenital heart diseases, such as pulmonic stenosis. RV failure (RVF) in PAH differs from LV failure (LVF) in etiology (being more related to increased afterload), prognosis (having higher mortality rates during acute decompensation), and therapy (benefiting from different approved therapies). Compared with LVF the following features are more common in PAH-associated RVF: (1) compression of the LV by the enlarged RV, reflecting ventricular interdependence; (2) decreased RV perfusion because of microvascular ischemia or reduced epicardial coronary artery perfusion pressure; and (3) a high, fixed transpulmonary gradient. These changes are uncommon in most types of LVF. In adult PAH patients, RV failure requiring inotropic support and admission to an intensive care unit has an inpatient mortality rate of ≥40%, far higher than the 13% to 14% mortality for patients admitted to hospital with LVF requiring inotropes. A National Heart Lung and Blood Institute–sponsored working group recently highlighted the need to develop a robust basic understanding of the RV’s unique properties and apply this to...
advance the understanding of cause and design of therapies for RV hypertrophy (RVH) and RVF.\textsuperscript{19}

Although the RV is somewhat unique, there are lessons about RVH and RVF to learn from LV hypertrophy and LVF. Although the RV has poorer tolerance to sustained afterload than the LV, both ventricles respond to increased afterload with $\beta$-receptor downregulation,\textsuperscript{20,21} increased glycolysis,\textsuperscript{22,23} and decreased capillary density.\textsuperscript{15,24} In LV hypertrophy, proto-oncogenes, such as c-Myc, reanimate fetal gene expression,\textsuperscript{25} including the $\beta$-isoform of myosin heavy chain, $\alpha$-skeletal muscle actin, and atrial natriuretic factor. RVH is also associated with reactivation of the fetal gene package, with activation of c-Myc and a switch to the fetal isoforms of myosin and actin.\textsuperscript{26}

**RV in Pulmonary Hypertension**

Chronic pressure overload, as occurs in WHO categories 1 to 5 PH,\textsuperscript{27} stimulates RVH. RVH can compensate for the increased afterload and maintain cardiac output. However, RVH is rarely fully compensatory and may create RV ischemia and lead to RV failure.\textsuperscript{28}

The ideal means of regressing RVH is reduction in afterload. Unfortunately, approved PH therapies cause only modest reductions in mean pulmonary artery pressure and pulmonary vascular resistance (PVR). There are 2 circumstances where substantial reductions in PVR demonstrate the expected regression of RVH in response to effective therapy. In a small study of 12 patients with PAH who underwent lung transplantation, there was modest decrease in RV volume after 3 months.\textsuperscript{29} However, these changes observed in RVH and RVF after lung transplant for PAH pale in comparison to that seen in chronic thromboembolic PH, where RV function typically returns to normal within weeks after pulmonary endarterectomy.\textsuperscript{30} This likely reflects a much more multifaceted disease process in PAH compared with chronic thromboembolic PH, but also may reflect distinct patterns of the development of RVH. The pattern of recovery seen after pulmonary endarterectomy for chronic thromboembolic PH and in some PAH patients postlung transplant indicates that the RV dysfunction is triggered by increased afterload but does not explore the possibility that cardiac-targeted therapies, such as modulators of adrenergic signaling, angiogenesis, fibrosis, or metabolism, might serve as a bridge to definitive afterload reduction. This review focuses on identifying pathophysiologic mechanisms that might be exploited to optimize RV function in conditions where RV afterload cannot be corrected.

**RV Failure**

Clinically, RVF reflects the inability of the RV to perfuse the lung circulation adequately to maintain LV filling at low venous/diastolic pressures. Although there is no standard hemodynamic definition, RVF can be characterized by a reduced cardiac index (<2.5 L/min per square meter) and increased RV filling pressures (right atrial pressure $\geq$ 8 mm Hg).\textsuperscript{31} The normal values for RV hemodynamics in humans and rodents are contrasted with those observed in PAH in Tables 1 and 2, respectively. On physical examination, RVF is manifest as an elevation in jugular venous pressure, reflecting elevated right atrial pressure. Appreciation of an RV lift on palpation of the precordium indicates RV enlargement. A right-sided third heart sound on auscultation indicates a noncompliant and failing RV. In patients with RV dysfunction that are rendered euveolic on medical therapy the examination may be unremarkable at rest but signs of impaired RV reserve can be elicited by maneuvers that increase venous return to the RV. Kussmaul’s sign (a paradoxical increase in jugular venous pressure with inspiration) and hepatojugular reflux (a rise in jugular venous pressure upon pressure over the liver/abdomen) are features of impaired RV reserve. In addition, RVF frequently results in peripheral edema and hepatic congestion on physical examination.

Although elevated afterload, because of pulmonary vascular disease, initiates RVH in PAH, it is the decline in RV function (manifest as reduced RVEF and RV dilatation) that best predicts adverse prognosis. Consistent with this, impaired RVEF predicts clinical worsening in PAH more accurately than elevated PVR.\textsuperscript{33} In fact, the RV response to therapy is the key determinant of clinical outcomes in PAH. Even though PAH therapies target pulmonary vasoconstriction, survival has been shown to be significantly associated with changes in RVEF, whereas therapeutic changes in PVR or cardiac output demonstrated little relationship to survival. Five-year survival exceeds 90% in PAH patients with a stable or an increased RVEF and an accompanying fall in PVR. However, in some patients, despite a demonstrable therapeutic decrease in afterload, there is continued deterioration in RV function and increased RV dimensions. Increases in RV end-systolic and

<table>
<thead>
<tr>
<th>Table 1. Normal Pressure Ranges and Vascular Resistance in Humans</th>
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<td>Hemodynamics</td>
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<tr>
<td>Right atrium: mean, mm Hg</td>
</tr>
<tr>
<td>Pulmonary artery: mean, mm Hg</td>
</tr>
<tr>
<td>Pulmonary capillary wedge: end expiratory, mm Hg</td>
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<tr>
<td>Systemic artery pressure: mean, mm Hg</td>
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<tr>
<td>Heart beat, bpm</td>
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<tr>
<td>Cardiac index, L/min per square meter</td>
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<tr>
<td>Pulmonary vascular resistance, dynes s/cm$^2$</td>
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<tr>
<td>Systemic vascular resistance, dynes s/cm$^2$</td>
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PAH range is derived from patients with severe group 1 pulmonary hypertension, reference 32. In this patient population, 74% of patients were NYHA functional class III and 26% were NYHA functional class IV. This study is chosen because it represents a modern untreated cohort. Reprinted from Grossman\textsuperscript{20} (Copyright Lea & Febiger, 2006) and Barst et al\textsuperscript{32} (Copyright Massachusetts Medical Society, 1996) with permission of the publisher. NYHA indicates New York Heart Association; and PAH, pulmonary arterial hypertension.
end-diastolic volumes correlate with mortality, an association which may be related to the law of Laplace (higher wall tension related to chamber dilatation) combined with increased intraluminal pressure.36 Thus, the RV may ultimately decompensate because of persistently elevated wall stress. The variability in RV response between patients may suggest intrinsic genetic or epigenetic differences in susceptibility to decompression. Ventricular interdependence is also important when considering the status of the RV in PAH. Inadequate RV perfusion and impingement of the pressure and volume overloaded RV on the LV lead to LV underfilling, which reduces cardiac output and impingement of the pressure and volume overloaded RV on the LV lead to LV underfilling, which reduces cardiac output and ventricular interdependence.37 In severe RVF, low cardiac output can reduce pulmonary artery pressure, which portends a worsening prognosis.38 Reduction in RVEF or late gadolinium enhancement at the RV-LV septal hinge points on MRI predicts clinical worsening in PAH.39

Adaptive Versus Maladaptive RVH

There is heterogeneity in RVH in terms of its effects on cardiac output and the likelihood of progression to RVF that is not explained by differences in RV mass or RV pressure overload. Some patients have maladaptive forms of RVH and rapidly decompensate, while others remain stable for decades, despite similar elevations in RV pressure and RVH (Figure 1A). Within the WHO classification there is subclass heterogeneity in the predilection to RVF, even within the relatively homogenous group 1 patients. RVF is much less prevalent and occurs later in those with congenital heart disease (ie, Eisenmenger syndrome)40 versus those with scleroderma-associated PAH.41,42 Patients with RV pressure overload without pulmonary vascular disease, such as those with pulmonic stenosis, retain concentrically hypertrophied, contractile RVs for decades.43–45

Animal models of RVH recapitulate this separation into adaptive and maladaptive categories, as judged by their exercise performance and survival.46 RVH in rats post-pulmonary artery banding (PAB), which models pulmonic stenosis, is better tolerated than RVH induced by endothelial toxins, such as monocrotaline or the vascular endothelial growth factor receptor antagonist, Sugen 5416, plus chronic hypoxia.46 That RV failure is more prevalent in PAH models with endothelial injury suggests a potential role for endothelial dysfunction in the coronary vasculature of the RV itself.

Using monocrotaline rats, Sutendra et al47 have studied the transition period between adaptive and maladaptive RVH. In this work, the transition to maladaptive RVH is associated with a decrease in RV hypoxia-inducible factor 1α (HIF1α), a decline in angiogenesis, a fall in glucose uptake, and a version toward normal metabolism. The authors argue that metabolic shift observed in the RV is not sustained throughout the progression of RV failure. A rise in mitochondrial derived ROS potentially results in HIF1α inhibition, thereby suppressing angiogenesis. The resultant ischemia from the decrease in angiogenesis may contribute to the rapid deterioration of RV function in maladaptive RVH.

Although this is an elegant theory, the time course over which this maladaptive metabolism regresses in undefined and the clinical relevance is unclear. In the limited data available patients with advanced PAH manifest persistent

Table 2. Normal Pressure Ranges and Vascular Resistance in Rodents

<table>
<thead>
<tr>
<th>Hemodynamics</th>
<th>Normal Rats</th>
<th>Monocrotaline Rats</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pulmonary artery systolic pressure, mm Hg</td>
<td>25±1</td>
<td>60±5*</td>
</tr>
<tr>
<td>Pulmonary artery diastolic pressure, mm Hg</td>
<td>3±1</td>
<td>13±2*</td>
</tr>
<tr>
<td>Systemic artery mean pressure, mm Hg</td>
<td>110±8</td>
<td>95±6</td>
</tr>
<tr>
<td>Heart rate, bpm</td>
<td>320±7</td>
<td>294±5*</td>
</tr>
<tr>
<td>Cardiac output, mL/min</td>
<td>110±5</td>
<td>76±5*</td>
</tr>
<tr>
<td>Pulmonary vascular resistance, dynes s/cm²</td>
<td>0.07±0.01</td>
<td>0.44±0.08*</td>
</tr>
<tr>
<td>Systemic vascular resistance, dynes s/cm²</td>
<td>0.85±0.12</td>
<td>1.01±0.6*</td>
</tr>
</tbody>
</table>

Derived from data presented in Piao et al20 with permission of the publisher.

*Statistical significance.
glycolytic shift on 18fluorodeoxyglucose on positron emission tomography (FDG-PET).

Moreover, there is disagreement regarding the predominant transcription factor involved in aerobic glycolysis in the heart. HIF1α is not consistently upregulated in our rodent RVH experiments, and HIF1α is not known to upregulate transcription of pyruvate dehydrogenase kinase (PDK) 4, the predominant cardiac form of PDK that leads to aerobic glycolysis. In contrast to the heart, HIF1α is upregulated in the lung in PAH models and in adaptive PAH.

The lung vasculature, HIF1α seems to account for aerobic glycolysis; in contrast, the metabolic remodeling in the RV seems to be more related to pathological activation of FOXO1 and c-Myc. Emerging concepts regarding the molecular basis for these adaptive and maladaptive RVH phenotypes and their therapeutic implications are discussed subsequently.

There are many factors that determine whether RVH will be well tolerated, such as the presence and severity of RV fibrosis, ischemia, autonomic dysregulation, and metabolic changes (Figure 1B). Adaptive RVH is provisionally defined by preservation of normal cardiac output, RVEF, RV filling pressures, and exercise capacity. It is usually characterized by concentric hypertrophy with minimal RV dilatation or fibrosis. Conversely, the maladaptive phenotype can be defined by significant reductions in cardiac output, RVEF with elevation of RV filling pressures, and reduced exercise capacity. Maladaptive RVH commonly displays RV fibrosis and dilatation (Figure 1C). While these definitions are imprecise, there is progress toward more rigorous, molecular fingerprints of these RVH phenotypes. Several abnormalities seem common to maladaptive RVH, including RV ischemia and 2 forms of cancer metabolism, aerobic glycolysis and glutaminolysis. In addition maladaptive RVH shows greater impairment of angiogenesis, manifest as capillary rarefaction and decreased expression of angiogenic genes (vascular endothelial growth factor, IGF-1 [insulin-like growth factor], apelin, and angiopoietin-1).

There is also greater dysregulation of the autonomic nervous system in maladaptive RVH with a broad downregulation and sensitization of α, β, and adrenergic receptors in the RV myocytes. Finally, in maladaptive RVH changes in RV perfusion, angiogenesis, adrenergic signaling, and metabolism tend to involve the LV, whereas they tend to be confined to the RV in adaptive RVH. Although these changes have yet to shape clinical practice, they do offer opportunities for research and suggests new therapeutic strategies (Figure 2).

**Right Ventricular Ischemia**

RV dysfunction in PAH may reflect chronic reduction in RV perfusion in the presence of myocardial hibernation. Evidence of RV ischemia in PAH includes angina-like chest pain, ischemia on nuclear perfusion stress imaging, and increased RV uptake of FDG-PET. Evidence of ischemia, such as elevation of troponin levels, indicates poor prognosis. Ischemia is also relevant to RVF in congenital heart disease. Late failure of the systemic RV after the Mustard repair of transposition of the great arteries is associated with impaired myocardial flow reserve. Nuclear perfusion scans commonly demonstrate perfusion defects with concordant regional wall motion abnormalities after repair of transposition of the great arteries.

RV ischemia may reflect reduced right coronary artery (RCA) perfusion pressure or decreased coronary flow reserve. The low RV systolic pressure in normal individuals permits filling of the RCA during both systole and diastole. In RV pressure overload, the systolic perfusion gradient (aortic pressure − RV systolic pressure) may be eliminated and the diastolic RCA perfusion pressure (aortic pressure − RV end-diastolic pressure) be reduced, thereby impairing RCA flow. RV contractile function remains constant until RCA perfusion pressures fall <50 mm Hg.

It has been suggested that an additional cause of ischemia contributes to RVF in PAH, namely capillary rarefaction, defined as a reduction in the density of capillaries and small intramyocardial arterioles in the RV. RV capillary density is reduced in chronic hypoxia plus Sugen 5416
Aerobic Glycolysis

In the fetal heart, where circulating fatty acid levels are low, glycolysis and glucose oxidation are the major sources of ATP production. In the adult heart fatty acid oxidation (FAO) becomes the predominant energy source (60%–90%), but glucose metabolism continues to contribute 10% to 40% of ATP production.

In RVH the metabolic fate of glucose is altered because mitochondrial metabolism is actively (although reversibly) suppressed. Glucose metabolism starts with cytosolic glycolysis, which ultimately converts glucose to pyruvate. In the normal adult RV myocyte, pyruvate is transferred to the mitochondria where it serves as substrate for pyruvate dehydrogenase (PDH). If the PDH complex in mitochondria is active, pyruvate is converted to acetyl CoA, fueling Krebs cycle and providing electron donors (NADH [nicotinamide adenine dinucleotide] and FADH [flavin adenine dinucleotide]) for the electron transport chain and ATP generation.

PDK, a key inhibitory regulator of PDH (and thus of glucose oxidation), is transcriptionally upregulated in RVH (Figure 1B). All 4 PDK isoforms inhibit PDH by phosphorylating its E1-α subunit. The predominant cardiac PDK isoforms in the RV are PDK2 and PDK4. When PDH is inhibited, supply of electron donors to Krebs cycle is limited, which reduces energy production. This PDK-mediated metabolic switch is associated with decreased RV contractility and reduced cardiac output.

The shift to aerobic glycolysis in RVH has several consequences (Figure 4A). First, lactate is produced, resulting in acidosis, which impairs RV function. Second, only 2 ATP molecules/glucose are obtained per mole of glucose compared with the 32 ATP generated during glucose oxidation. To support the increased glycolysis required to maintain energy homeostasis there is marked upregulation of glucose uptake, which can be detected by FDG-PET scans in RVH. Increased RV glucose uptake, reflective of increased glycolysis, has been shown in a small series of PAH patients undergoing FDG-PET. Moreover, there is some evidence that effective reduction of afterload reduces RV uptake of FDG. Likewise, in experimental RVH, there is increased RV glycolysis, evidenced by direct measurement of metabolism in isolated RV working heart and increased uptake of FDG-PET in vivo.

In a case report comparing a long-term PAH survivor with an individual who rapidly decompensated from RV failure, the markers of aerobic glycolysis (the glucose transporter, GLUT 1, and PDK4) were less elevated in the adaptive versus the maladaptive RVH patient. Perhaps the hypokinetic RV in maladaptive RVH reflects a form of myocardial hibernation, precipitated by impaired RV perfusion and metabolic shifts in the RV myocytes (Figure 2).

In rodents, PDH is inhibited more in maladaptive monocrotaline RVH than in adaptive PAB RVH. Dichloroacetate, a PDK inhibitor, reduces PDH phosphorylation and partially restores RV contractility in rodent models of PAH (Figure 3). RV capillary rarefaction may occur in PAH patients, particularly those with scleroderma PAH. Because chronic hypoxia plus Sugen 5416 and monocrotaline rats have similar elevation in RV systolic pressure and similar RVH as PAB rats, their reduced functional capacity and greater mortality suggest that ischemia cannot be explained solely by diminished RCA perfusion pressure.

Correctly identifying the cause of RV ischemia in RVH has therapeutic ramifications. If RVF were initiated primarily by a drop in coronary perfusion pressure, then strategies such as infusion of phenylephrine to increase the aortic-RV pressure gradient to drive coronary perfusion might be rational. However, if capillary rarefaction contributes to RV ischemia it would be more logical to treat RV failure by pharmacologically changing metabolism to do more with less or by enhancing RV angiogenesis. In rodent models capillary rarefaction observed in PAB rats seems to be reversible with β-blockers. It is likely that ischemia precipitates many of the metabolic changes that occur in RVH.

**FAO and the Randle Cycle**

There is a reciprocal relationship between the 2 major oxidative metabolic pathways, such that inhibiting FAO increases glucose oxidation. This is called the Randle cycle (Figure 4B). A therapeutic strategy of enhancing glucose oxidation by inhibiting FAO might be beneficial in RVH because FAO uses 12% more oxygen than glucose oxidation to generate the same amount of ATP. FAO’s demand for oxygen...
may be difficult to sustain in the presence of RV ischemia. Partial inhibitors of FAO (pFOXi) are approved for human use for several cardiovascular indications. Trimetazidine, a long-chain 3-ketoacyl coenzyme A thiolase, is used in Europe to treat refractory ischemia in patients with coronary artery disease.82–85 Another pFOXi, ranolazine, is approved for refractory ischemia in the United States86–88 (although there is some controversy whether it works through inhibition of FAO and activation of PDH).89–91

The reciprocal relationship between FAO and glucose oxidation reflects (in part) citrate production during FAO. Citrate inhibits phosphofructokinase, causing accumulation of glucose-6-phosphate, which inhibits hexokinase and glucose oxidation. In addition, acetyl CoA, generated from FAO, inhibits PDH. FAO inhibition can reduce these inhibitory mechanisms and enhance glucose oxidation. A study of trimetazidine and ranolazine in rats with PAB-induced RVH showed that pFOXi increased cardiac output and treadmill exercise capacity, suggesting that the increased FAO in PAB-RVH is maladaptive.78 FAO inhibitors elevated RV ATP and increased glucose oxidation, reflecting activation of the Randle cycle.78 Such as PDK inhibitors, pFOXi also partially regressed RVH and increased cardiac output.78

Figure 4. A, Mechanism of impaired glucose oxidation and enhanced glycolysis in right ventricular hypertrophy (RVH). In RVH, activation of various transcription factors, including forkhead box protein O1 (FOXO1), cMyc, and hypoxia-inducible factor 1α (HIF-1α), upregulates expression of many glycolytic gene. A common finding in RVH is increased pyruvate dehydrogenase kinase (PDK) expression, which inhibits PDH and reduces mitochondrial respiration. PDK activation also occurs in the lung in PAH, although the transcriptional regulation and isoform specificity may differ than those seen in the RV. Dichloroacetate inhibits PDK and thereby promotes glucose oxidation and inhibits glycolysis. Reprinted from Piao et al53 with permission of the publisher. B, The Randle cycle in RVH. The inhibition of β-fatty acid oxidation (FAO) by trimetazidine and ranolazine increases PDH activity and improves glucose oxidation (GO). This reciprocal relationship between GO and FAO is referred to as the Randle cycle. Reprinted from Fang et al78 with permission of the publisher. C, Proposed mechanism of glutaminolysis in RVH. RV ischemia and capillary rarefaction activate cMyc and Max, which increases glutamine uptake and production of α-ketoglutarate (α-KG). α-KG enters Krebs cycle leading to production of malate. Krebs cycle-derived malate generates cytosolic pyruvate, which is converted by lactate dehydrogenase A (LDHA) to lactate. In conditions of high glutaminolysis GO is inhibited. Reprinted from Piao et al26 with permission of the publisher (Illustration Credit: Ben Smith). DON indicates diazoo-5-oxo-4-norleucine; ETC, electron transport chain; HK, hexokinase; H2O2, hydrogen peroxide; IMM, inner mitochondrial membrane; OMM, outer mitochondrial membrane; PFK, phosphofructokinase; RAN, ranolazine; and TMZ, trimetazidine.
PET studies have shown that in patients with idiopathic dilated cardiomyopathy, trimetazidine decreases FAO and causes a compensatory increase in glucose oxidation. Whether combining PDK inhibitors and pFOXi would have additive or synergistic benefit in RVH has not been studied. It should also be noted that FAO is not increased in all models of RVH.

Glutaminolysis

The Warburg phenomenon (aerobic glycolysis) and glutaminolysis are metabolic pathways that are common in cancer and permit rapid cell growth without apoptosis. Perhaps in maladaptive RVH these cancer metabolic pathways permit inappropriate myocyte enlargement. We recently examined the possibility that glutaminolysis might also occur in RVH. In comparisons of monocrotaline-RVH and PAB-RVH, we noted that the monocrotaline model had greater ischemia as determined by larger reductions in RV vascular endothelial growth factor-α expression, greater reduction in coronary blood flow, and reduced RV microvascular density. Consistent with increased glutaminolysis in monocrotaline-RVH, RV expression of glutamine transporters (SLC1A5 and SLC7A5) and mitochondrial malic enzyme were elevated. This is analogous to the upregulation of glut-1 transporter that is seen in aerobic glycolysis. In both scenarios, transporter upregulation ensures that substrate provision is not a limiting factor in metabolic capacity. Direct measurement of metabolism in the RV working heart model, using a dual-isotope technique, demonstrated a 6-fold increase in 14C-glutamine metabolism in monocrotaline-RVH, which was not seen in PAB. As with aerobic glycolysis, glutaminolysis seems to be maladaptive. In vivo, the glutamine antagonist, 6-diazo-5-oxo-l-norleucine (DON), at doses that inhibited glutaminolysis, increased glucose oxidation and elevated cardiac output. Longer term therapy with DON restored PDH activity, reduced RVH, and increased cardiac output. The transcriptional basis for this RV metabolic pathway seems to be activation of the cMyc–Max pathway, perhaps as a consequence of RV ischemia. Glutaminolysis may be a therapeutic target in maladaptive RVH, although DON has nonspecific systemic toxicity (Figure 4C).

Right Ventricular Sympathetic Activation in PAH

Dopamine and dobutamine are commonly used as inotropic agents to treat acute RVH in PAH patients. Some centers also use the pure α-adrenergic agonist, phenylephrine, as a vasopressor, to increase coronary perfusion pressure. Dobutamine and dopamine primarily exert their inotropic effects by stimulating β1-adrenergic receptors (β1-AR), but dopamine has some reliance on α-adrenergic receptors (α-AR) at higher doses (10–20 μg/kg per minute). However, the choice of inotropes for RVH is highly variable among practitioners, even at a single institution, and inotrope use is also associated with extremely high mortality. This may reflect the dire condition of PAH patients that suggests the need for inotropic support.
but should provoke the question whether catecholamines might actually worsen prognosis in RV failure. The latter interpretation is possible, because the adrenergic system is arguably maximally activated in RV failure in PAH. PAH patients with RVF have high circulating catecholamine levels and lose the normal ability to augment catecholamine levels with exercise. Autonomic activation, loss of inotropy to β-AR agonists, and downregulation of β-AR expression also occur in maladaptive rat PAH models. 

In a canine RVF model, which combined PAB and tricuspid valve avulsion, downregulation of the β-AR was confined to the RV and resulted in chamber-specific reduction of iso-proterenol-induced cAMP production. In humans with PAH and RVF, RV β-AR density is decreased and the response to inotropes is similarly impaired. However, whereas Ishikawa et al found no impairment of LV β-AR signaling in human RVF associated with PAH, β-AR density decreases in the nonhypertrophied LV in monocrotaline RVH, a finding that was recently reproduced.

We recently discovered a broad downregulation of adrenoceptors in rodent RVH, including α, β, and dopamine (1–5) receptors. While changes occurred in all forms of RVH, the adrenoceptor downregulation was more severe in maladaptive RVH and extended to the LV. The cause of this broad downregulation of adrenergic receptor expression and function was activation of G protein receptor kinase (also called β-adrenergic receptor kinase 1). Interestingly, G protein receptor kinase activity was as high in RVH at baseline as could be stimulated by catecholamines in normal RVs. This suggests a near-maximal receptor downregulation and that desensitization occurs in RVH.

β-Receptor uncoupling and downregulation reduced the RV response to all inotropes in RVH, perhaps indicating why patients with PAH and RVF respond poorly to inotrope infusion. In rodent models, dobutamine was superior to dopamine in terms of its ability to increase RV contractility in RV Langendorff models and in vivo. Dobutamine’s superiority was associated with its superior coupling to adenylyl cyclase (evident as a greater increase in cAMP levels). Interrupting Gβγ-signaling, using galleen, inhibits G protein receptor kinase activity and improves cardiac function when administered chronically in vivo.

In left heart failure, β-blockers improve survival and LV function. However, β-blockers are not used clinically in PAH and concerns about their safety exist. However, the α/β-blocker carvedilol and the β-blocker propranolol have been shown to regress RVH and lower RV systolic pressure in experimental models of chronic hypoxic PH and in the chronic hypoxia plus Sugen 5416 model. Small clinical trials have demonstrated that β-blockade with carvedilol can improve RV systolic function, and a clinical trial of β-blockers for RVH in WHO Group 1 PH is under way.

**Phosphodiesterase-5 and Endothelin in RVH**

In the normal heart quantitative differences in expression of many pumps and transporters exist between the RV versus LV. This is a reminder that there may be other chamber-selective therapeutic targets in RVH. Sildenafil, a phosphodiesterase 5 inhibitor, has been found to have a direct RV inotropic effect. Interestingly phosphodiesterase 5 is not present in the normal RV myocytes but is induced during RVH, both in rodents and humans. By inhibiting phosphodiesterase 5, sildenafil increases cGMP levels, which then inhibits phosphodiesterase 3. Sildenafil’s modest inotropic effects are due (in part) to this indirect inhibition of phosphodiesterase 3. Thus, there are mechanistic similarities between sildenafil’s actions in RVH and the more potent direct phosphodiesterase 3 inhibitor of milrinone. This de novo appearance of a selective RV target accounts in part for sildenafil’s ability to increase cardiac output in PAH.

Patients with PAH also have upregulation of the RV myocardial endothelin axis, which may be a compensatory mechanism to increase contractility and cardiac output in the setting of the increased afterload observed. In the working heart model, endothelin receptor antagonists decrease contractility. This is of interest because of the published trials failing to show a benefit of endothelin receptor antagonists in left heart failure, although endothelin receptor antagonists have demonstrated an established clinical improvement in PAH.

Both the effects of phosphodiesterase 5 inhibitors and endothelin receptor antagonists on the RV were unanticipated by PAH trials which focused on the effects of these drugs on the pulmonary vasculature. Future trials should directly examine the effects of putative PAH therapies on the RV to detect both benefit and harm.

**Right Ventricular Fibrosis**

In adult patients with PAH, late gadolinium enhancement on MRI at the RV insertion points is likely an evidence of localized fibrosis and is associated with worsened prognosis. In children with congenital heart disease, fibrosis may also be an important determinant of RVF.

Whether trials should be performed to reduce RV fibrosis is unclear. There are several potential means by which fibrosis could be inhibited, such as using inhibitors of the renin–angiotensin–aldosterone system, including angiotensin receptor blockers or mineralocorticoid antagonists. A study in patients with congenital heart disease and a systemic RV tested the ability of the angiotensin receptor blocker, losartan, to improve cardiac function. In this study, losartan failed to improve hemodynamics or exercise capacity. In PAH, the aldosterone pathway has been identified as a potential therapeutic target.

**Conclusions**

Although a cure for PAH will require regression of pulmonary vascular lesions or transplantation, substantial improvement in longevity and functional state might be achieved by an effective treatment for RV failure. Hopefully, an increased understanding of adrenergic, angiogenic, fibrotic, and metabolic derangements in the RV in PAH will offer new therapeutic targets to enhance RV function (Figure 2).
A Patient Asks Questions…

I met this patient in the PAH group meeting… She has lower pulmonary artery pressures than I do, but she is much sicker…What does that mean; how is it possible?

At first, this seems to be a paradox; one would assume that higher lung blood pressure would mean more advanced disease and more symptoms. However, as it was discussed in the first article in this collection, the symptoms in pulmonary arterial hypertension (PAH; i.e., shortness of breath) are not caused by the pressure in the arteries of the lungs, but by the function of the right chambers of the heart (right ventricle). At some point the muscle of the right ventricle starts getting exhausted because of pumping against higher than normal pressures. Its contractile strength is suppressed, causing a decrease in the amount of blood ejected with each contraction and thus decrease in the amount of blood (and thus oxygen) that reaches the organs of the body, generating the sensation of shortness of breath. However, as the contractile power of the heart muscle decreases, so does the pressure of the blood that it ejects; in other words, the pressure in the lung blood vessels decreases. This is similar to the decrease in the pressure of the water at a water hose, not because there is narrowing of the hose lumens but because the pressure in the water pump feeding the hose is decreasing. This is an important realization that sometimes may even confuse physicians. For example, let us say that a therapy is initiated to treat PAH aiming to decrease the narrowing of lung blood vessels. Let us assume that this therapy may also unexpectedly suppress the function of the heart muscle in the right ventricle. Such unexpected effects (sometimes called offset-target effects) are much more common than we assume in medicine. In this case, the pressures in the lung arteries will decrease not because the therapy improved the function of the blood vessels, but because it adversely decreased the contractile power of the heart. While the pressures in tests (for example, an echocardiogram) may seem to be decreasing, the patient will actually feel worse. If the patient does not communicate well with the treating physician and if the treating physician does not look at the big picture, he/she may actually prescribe an increase in the dose of the therapy, rather than stopping it. This would obviously make things even worse. This is why it is important to approach the right ventricle in parallel to the lung vessels in PAH, an idea that is changing the way that we approach PAH. This article discusses many mechanisms that may explain why the right ventricle may worsen and perhaps why it may worsen in one patient but not another. In our patient’s question, the one with lower pressures was feeling worse because she has worse right ventricular function. What makes the right ventricle start deteriorating at some point and why this happens earlier in some patients is one of the most critical questions that we need to answer in PAH. Understanding this concept may also help the patients to better understand their symptoms and their response to standard or investigative therapies.

For the case description, see introductory article by E.D. Michelakis, page 109.

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