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The Right Ventricle in Pulmonary Arterial Hypertension: *Disorders of metabolism, angiogenesis and adrenergic signaling in right ventricular failure*

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Abstract

The right ventricle (RV) is the major determinant of functional state and prognosis in pulmonary arterial hypertension (PAH). 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), whilst 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 NT-proBNP levels, troponin release, elevated catecholamine levels, RV dilatation and late gadolinium-enhancement on magnetic resonance imaging, increased ^{18}fluorodeoxyglucose uptake on positron emission tomography and QTc prolongation on the electrocardiogram. In maladaptive RVH there is reduced inotrope responsiveness due to G-protein receptor kinase (GRK2)-mediated downregulation, desensitization and uncoupling of β-adrenoreceptors. RV ischemia may result from capillary rarefaction and/or decreased right coronary artery perfusion pressure. Maladaptive RVH shares metabolic abnormalities with cancer including aerobic glycolysis (resulting from a FOXO1-mediated transcriptional upregulation of pyruvate dehydrogenase kinase, PDK), and glutaminolysis (reflecting ischemia-induced cMyc activation). Augmentation of glucose oxidation is beneficial in experimental RVH and can be achieved by inhibition of PDK, fatty acid oxidation, or glutaminolysis. Therapeutic targets in RV failure include chamber-specific abnormalities of metabolism, angiogenesis, adrenergic signaling and phosphodiesterase-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.

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Keywords

Right ventricular failure (RVF); aerobic glycolysis; glutaminolysis; G protein receptor kinase 2 (GRK2); Forkhead box protein O1 (FOXO1); adrenoreceptors; pyruvate dehydrogenase (PDH); glutaminolysis; microvascular ischemia; Congenital Heart Disease; fluorodeoxyglucose positron emission tomography (FDG-PET); cardiac magnetic resonance imaging (CMR)

Introduction

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 precursors cells in the secondary heart field[1]. The transcriptional regulation of myoblast differentiation also differs between the RV and LV. RV myocytes are directed in their development by chamber-specific transcription factors, such as dHAND and MEF2C[2, 3]. In contrast, LV myocyte development is guided by Nkx2.5 and eHAND[1]. 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[4]. Postnatally the pulmonary circulation transitions to a low-pressure circuit and the RV wall thickness remains ~4 mm whilst the LV, faced with 4-times 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, comprised of the tricuspid valve, chordae tendineae, and papillary muscles (2) the trabeculated apical myocardium and (3) the outflow region (called the conus or infundibulum), which has a smooth myocardial surface[5]. RV contraction starts at the inflow section and progresses towards 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 (TAPSE). TAPSE predicts RV function and prognosis in adults with Pulmonary Arterial Hypertension (PAH). A TAPSE <18mm indicates a poor prognosis[6].

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%[7]. However, cardiac output is essentially identical, because the RV has slightly larger volumes. In adults the normal RVEF is 62% compared to a normal LVEF of 65%[8]. RVEF is reduced by half in adults with WHO Group 1 PH (to a mean of 34±10%)[9].

The Multi-Ethnic Study of Atherosclerosis (MESA) study used magnetic resonance imaging (MRI) to determine normal values for RV size and function in 4123 normal adults, age 61.5±10.1 years (47.5% males)[10]. Normal values for RV mass in females and males were 19.2±3.6g and 23.1±4.4g, respectively. Normal values for RV end-diastolic volume in females and males were 108.9±23.2mL and 140.9±29.7mL, respectively. Males 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 two 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[11]. 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 is maintained in these patients, provided 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[12].

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)[13] or congenital heart diseases, such as pulmonic stenosis[14]. 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 to 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 due to microvascular ischemia and/or reduced epicardial coronary artery perfusion pressure and 3) a high, fixed transpulmonary gradient[15]. 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 over 40%[16, 17], far higher than the 13–14% mortality for patients admitted to hospital with LVF requiring inotropes[18]. 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 etiology and design of therapies for RV hypertrophy (RVH) and RVF[19].

Although the RV is somewhat unique, there are lessons about RVH and RVF to learn from LV hypertrophy (LVH) and LVF. Although the RV has poorer tolerance to sustained afterload than the LV, both ventricles respond to increased afterload with β-receptor downregulation[20, 21], increased glycolysis[22, 23], and decreased capillary density[15, 24]. In LVH, proto-oncogenes, such as c-Myc, reactivate fetal gene expression[25], including the β-

isoform of myosin heavy chain, α-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[26].

The right ventricle in pulmonary hypertension

Chronic pressure overload, as occurs in World Health Organization (WHO) Categories 1-5 pulmonary hypertension (PH)[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[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 two 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[29]. However these changes observed in RVH and RVF after lung transplant for PAH, pale in comparison to that seen in, chronic thromboembolic pulmonary hypertension (CTEPH), where RV function typically returns to normal within weeks after pulmonary endarterectomy (PEA)[30]. This likely reflects a much more multi-faceted disease process in PAH compared with CTEPH, but also may reflect distinct patterns of the development of RVH. The pattern of recovery seen after PEA for CTEPH and in some PAH patients post-lung 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 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/m^2) and increased RV filling pressures (right atrial pressure > 8 mmHg[31]). The normal values for RV hemodynamics in humans and rodents are contrasted with those observed in PAH in Table 1 & Table 2, respectively. On physical examination, RVF is manifest as an elevation in jugular venous pressure (JVP), 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 euvolemic on medical therapy the exam 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 JVP with inspiration) and hepatojugular reflux (a rise in JVP 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, due to 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[32]. 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 CO demonstrated little relationship to survival. 5-year survival exceeds 90% in PAH patients with a stable or 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 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[33]. 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 decompensation. 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, leads to LV under-filling, which reduces cardiac output. The resulting phenotype, a small LV and a dilated RV, portends poor prognosis[34]. In severe RVF, low cardiac output can reduce pulmonary artery pressure, which portends a worsening prognosis[35]. Reduction in RVEF and/or late gadolinium enhancement (LGE) at the RV-LV septal hinge points on MRI predicts clinical worsening in PAH[36].

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 whilst others remain stable for decades, despite similar elevations in RV pressure and RVH[22] (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 (i.e. Eisenmenger's syndrome[37]) versus in those with scleroderma-associated PAH[38, 39]. Patients with RV pressure overload without pulmonary vascular disease, such as those with pulmonic stenosis, retain concentrically hypertrophied, contractile RVs for decades[40–42].

Animal models of RVH recapitulate this separation into adaptive and maladaptive categories, as judged by their exercise performance and survival[20]. 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 (VEGF-R) antagonist, Sugen 5416, plus chronic hypoxia (CH+SU)[43]. 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 al have studied the transition period between adaptive and maladaptive RVH[44]. In this work, the transition to maladaptive RVH is associated with a decrease in RV HIF1α, a decline in angiogenesis, a fall in glucose uptake and a reversion towards 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 glycolytic shift on FDG-PET[22, 45]. 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 PDK4, 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[46] (relating to epigenetic silencing of SOD2[47]). In the lung vasculature, HIF1α appears to account for aerobic glycolysis; in contrast, the metabolic remodeling in the RV appears to be more related to pathologic activation of FOXO1 and c-Myc[26, 48]. 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 towards more rigorous, molecular fingerprints of these RVH phenotypes. Several abnormalities appear common to maladaptive RVH, including RV ischemia[49] and two forms of cancer metabolism, aerobic glycolysis[22, 45, 50] and glutaminolysis[26]. In addition maladaptive RVH shows greater impairment of angiogenesis, manifest as capillary rarefaction and decreased expression of angiogenic genes (VEGF, IGF-1, apelin and angiopoeitin-1). There is also greater dysregulation of the autonomic nervous system in maladaptive RVH with a broad downregulation and sensitization of α, β and dopaminergic receptors in the RV myocytes[45, 50–52]. 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 viable myocardium, representing a form of myocardial hibernation. Evidence of RV ischemia in PAH includes angina-like chest pain, ischemia on nuclear perfusion stress imaging[53], and increased RV uptake of ^{18}fluorodeoxyglucose on positron emission tomography (FDG-PET)[45, 54]. Evidence of ischemia, such as elevation of troponin levels, indicates poor prognosis[49, 55]. 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[56–58]. Nuclear perfusion scans commonly demonstrate perfusion defects with concordant regional wall motion abnormalities after repair of transposition of the great arteries[56].

RV ischemia may reflect reduced right coronary artery (RCA) perfusion pressure, and/or decreased coronary flow reserve[59]. The low RV systolic pressure (RVSP) in normal individuals permits filling of the RCA during both systole and diastole. In RV pressure overload, the systolic perfusion gradient (Aortic pressure$_{systole}$-RVSP)may be eliminated and the diastolic RCA perfusion pressure (Aortic pressure$_{diastole}$-RV end diastolic pressure) be reduced, thereby impairing RCA flow[60, 61]. RV contractile function remains constant until RCA perfusion pressures fall below 50 mmHg[62].

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[15]. RV capillary density is reduced in CH+SU and monocrotaline RV with little change in PAB RVs[15, 26] (Figure 3). RV capillary rarefaction may occur in PAH patients, particularly those with scleroderma PAH[26]. Since CH+SU and monocrotaline rats have similar elevation in RVSP and similar RVH as PAB rats, their reduced functional capacity and greater mortality suggests that ischemia cannot be explained solely by diminished RCA perfusion pressure[50].

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 PAH rats appears to be reversible with β-blockers[63]. It is likely that ischemia precipitates many of the metabolic changes that occur in RVH.

Metabolism of the right ventricle in PAH

Aerobic Glycolysis

In the fetal heart, where circulating fatty acid levels are low, glycolysis and glucose oxidation are the major sources of ATP production[64]. In the adult heart fatty acid oxidation (FAO) becomes the predominant energy source (60–90%) but glucose metabolism continues to contribute 10%-40% of ATP production[65].

In RVH the metabolic fate of glucose is altered because mitochondrial metabolism is actively (although reversibly) suppressed[66]. 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 and FADH) for the electron transport chain and ATP generation[67].

Pyruvate dehydrogenase kinase (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-$\propto$ subunit. The predominant cardiac PDK isoforms in the RV are PDK2 and PDK4[48]. When PDH is inhibited, supply of electron donors to Krebs' cycle is limited, which reduces energy production[68]. This PDK-mediated metabolic switch is associated with decreased RV contractility and reduced cardiac output[50].

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 to the 32 ATP generated during glucose oxidation[50]. 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[45, 54, 66] (Figure 1C).

Increased RV glucose uptake, reflective of increased glycolysis, has been shown in a small series of PAH patients undergoing FDG-PET[45, 54]. Moreover, there is some evidence that effective reduction of afterload reduces RV uptake of FDG[45]. 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*[45].

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[22]. 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[22] (Figure 2).

In rodents, PDH is inhibited more in maladaptive monocrotaline RVH than in adaptive PAB RVH[22]. Dichloroacetate (DCA), a PDK inhibitor, reduces PDH phosphorylation and partially restores RV contractility in rodent models of PAH[50, 69,70] (Figure 5). The possibility that RV function can be improved by metabolically targeted therapies, even without reducing the afterload, is intriguing. There is a similar metabolic shift towards aerobic glycolysis in the lung vasculature in PAH[66, 71]. Thus a PDK inhibitor might be expected to have beneficial effects on both the RV and lung circulation[54, 66, 69]. A therapeutic strategy of enhancing glucose oxidation has the potential to dramatically change the treatment paradigms of PAH patients with RV failure. DCA has been used safely in children with lactic acidosis[72] and in adults with glioblastoma multiforme[73], with the main toxicity being reversible peripheral neuropathy. A phase 1 clinical trial is currently assessing

DCA in PAH (Dichloroacetate (DCA) for the Treatment of Pulmonary Arterial Hypertension; NCT01083524)[74].

Pathologic activation of transcription factors in the RV in PAH (e.g. HIF1α, and FOXO1) leads to changes in metabolism, notably activation of PDK2 and PDK4. This decreases expression of repolarizing voltage-gated potassium channels (Kv), such as Kv1.5, in cardiac myocytes. In rodent models of RVH this ionic remodeling results in prolongation of the RV's monophasic action potential duration and mild QTc interval prolongation on the surface electrocardiogram. Therapy with the PDK inhibitor DCA restores oxidative glucose metabolism and restores Kv channel expression leading to normalization of QTc intervals (Figure 5D, 5E)[75]. In PAH patients QTc intervals are also prolonged compared with normal subjects (454.8±29 ms vs. 429.8±18 ms) and the QTc interval correlates directly with increasing RV end-diastolic volume and mass and inversely with RVEF. QTc interval is thus a potential simple biomarker of RVH. Prognostically, a QTc interval >480 ms portends decreased survival in PAH[76].

Fatty Acid Oxidation and the Randle Cycle

There is a reciprocal relationship between the two major oxidative metabolic pathways, such that inhibiting FAO increases the glucose oxidation. This is called the Randle cycle[77] (Figure 4B). A therapeutic strategy of enhancing glucose oxidation by inhibiting FAO might be beneficial in RVH since FAO uses 12% more oxygen than glucose oxidation to generate the same amount of ATP[78]. FAO's demand for oxygen may be difficult to sustain in the presence of RV ischemia. Partial inhibitors of fatty acid oxidation (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[79–82]. Another pFOXi, ranolazine, is approved for refractory ischemia in America[83–85] (although there is some controversy whether it works through inhibition of FAO and activation of PDH[86–88]).

The reciprocal relationship between FAO and glucose oxidation reflects (in part) citrate production during FAO. Citrate inhibits phosphofructokinase (PFK), 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[75]. FAO inhibitors elevated RV ATP and increased glucose oxidation, reflecting activation of the Randle cycle[75]. Like PDK inhibitors, pFOXi also partially regressed RVH and increased cardiac output[75]. The beneficial effect of trimetazidine has also been shown in monocrotaline-induced RVH[89]. In this model, trimetazidine enhanced cardiac mitochondrial function and increased oxygen consumption, while reducing the formation of oxygen free radicals[90].

PET studies have shown that in patients with idiopathic dilated cardiomyopathy, trimetazidine decreases FAO and causes a compensatory increase in glucose oxidation[91]. 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[48].

Glutaminolysis

The Warburg phenomenon (aerobic glycolysis) and glutaminolysis are metabolic pathways that are common in cancer and permit rapid cell growth without apoptosis[92]. 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 the monocrotaline model had greater ischemia as determined by larger reductions in RV VEGFα 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[50]. 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 ^{14}C-glutamine metabolism in monocrotaline-RVH, which was not seen in PAB. As with aerobic glycolysis, glutaminolysis appears 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 appears 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/min). However, the choice of inotropes for RVF is highly variable amongst practitioners, even at a single institution, and inotrope use is also associated with extremely high mortality[17]. 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, since the adrenergic system is arguably maximally activated in RV failure in PAH[20]. PAH patients with RVF have high circulating catecholamine levels and lose the normal ability to augment catecholamine levels with exercise[93]. Autonomic activation, loss of inotropy to β-AR agonists and downregulation of β1-AR expression also occurs in maladaptive rat PAH models[94, 95].

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

isoproterenol-induced cAMP production[96]. In humans with PAH and RVF, RV β-AR density is decreased and the response to inotropes is similarly impaired[97]. However, whereas Bristow *et al* found no impairment of LV β-AR signaling in human RVF associated with PAH, β-AR density decreases in the non-hypertrophied LV in monocrotaline RVH[98], a finding that was recently reproduced[20].

We recently discovered a broad downregulation of adrenoreceptors in rodent RVH, including α1, β1 and dopamine (1–5) receptors[20]. While changes occurred in all forms of RVH, the adrenoreceptor 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 (GRK2) (also called β-adrenergic receptor kinase 1 (BARK1)). Interestingly, GRK2 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 desensitization occurs in RVH.

β1-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 gallein, inhibits GRK2 activity and improved cardiac function when administered chronically *in vivo*[20].

In left heart failure, β-blockers improve survival and LV function[99]. 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 RVSP in experimental models of chronic hypoxic pulmonary hypertension and in the CH+SU model[100]. Small clinical trials have demonstrated that β-blockade with carvedilol can improve RV systolic function[101]and a clinical trial of β-blockers for RVH in WHO Group 1 PH is underway[102].

Phosphodiesterase-5 and Endothelinin RVH

In the normal heart quantitative differences in expression of many pumps and transporters exists between the RV versus LV[103]. This is a reminder that there may be other chamber-selective therapeutic targets in RVH. Sildenafil, a phosphodiesterase (PDE) 5 inhibitor has been found to have a direct RV inotropic effect[104, 105]. Interestingly PDE5 is not present in the normal RV myocytes but is induced during RVH, both in rodents and humans[104]. By inhibiting PDE5, sildenafil increases cGMP levels, which then inhibits PDE3. Sildenafil's modest inotropic effects are due (in part) to this indirect inhibition of PDE3. Thus there are mechanistic similarities between sildenafil's actions in RVH and the more potent direct PDE3 inhibitor of milrinone[105]. This *de novo* appearance of a selective RV target accounts in part for sildenafil's ability to increase cardiac output in PAH[105].

Patients with PAH also have up-regulation 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 (ERAs) decrease contractility[106]. This is of interest because of the published trials failing to show a benefit of ERAs in left heart failure[107] although ERAs have demonstrated an established clinical improvement in PAH[108, 109].

Both the effects of PDE5 inhibitors and ERAs 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[110].

Right ventricular fibrosis

In adult patients with PAH, late gadolinium-enhancement on MRI at the RV insertion points is likely evidence of localized fibrosis and is associated with worsened prognosis[111]. 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[112]. 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[113]. In PAH, the aldosterone pathway has been identified as a potential therapeutic target[114].

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).

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Non-standard Abbreviations and Acronyms

CH+SU	Chronic hypoxia plus Sugen 5416

CTEPH	Chronic Thromboembolic Pulmonary Hypertension
DCA	Dichloroacetate
EF	Ejection fraction
ERA	Endothelin receptor antagonist
FAO	Fatty acid oxidation
FDG-PET	^{18}fluorodeoxyglucose positron emission tomography
GRK2	G protein receptor kinase
HIF1α	Hypoxia-inducible factor 1 alpha
LGE	Late gadolinium enhancement
LV	Left ventricle
LVF	Left ventricular failure
LVH	Left ventricular failure
MRI	Magnetic Resonance Imaging
PAH	Pulmonary Arterial Hypertension
PDE	Phosphodiesterase
PDH	Pyruvate dehydrogenase
PDK	Pyruvate dehydrogenase kinase
PEA	Pulmonary Endarterectomy
PH	Pulmonary Hypertension
PVR	Pulmonary vascular resistance
RCA	Right coronary artery
RV	Right ventricle
RVF	Right ventricular failure
RVH	Right ventricular hypertrophy
TAPSE	Tricuspid annular plane systolic excursion
VEGF	Vascular endothelial growth factor receptor;

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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 appears 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 paper in this collection, the symptoms in 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 due to 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 lumen but because the pressure in the water pump feeding the hose is decreasing.

This is a very important realization that sometimes may even confuse physicians. For example, let’s say that a therapy is initiated to treat PAH aiming to decrease the narrowing of lung blood vessels. Let’s assume that this therapy may also unexpectedly suppress the function of the heart muscle in the right ventricle. Such unexpected effects (sometimes called “off 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 appear 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.

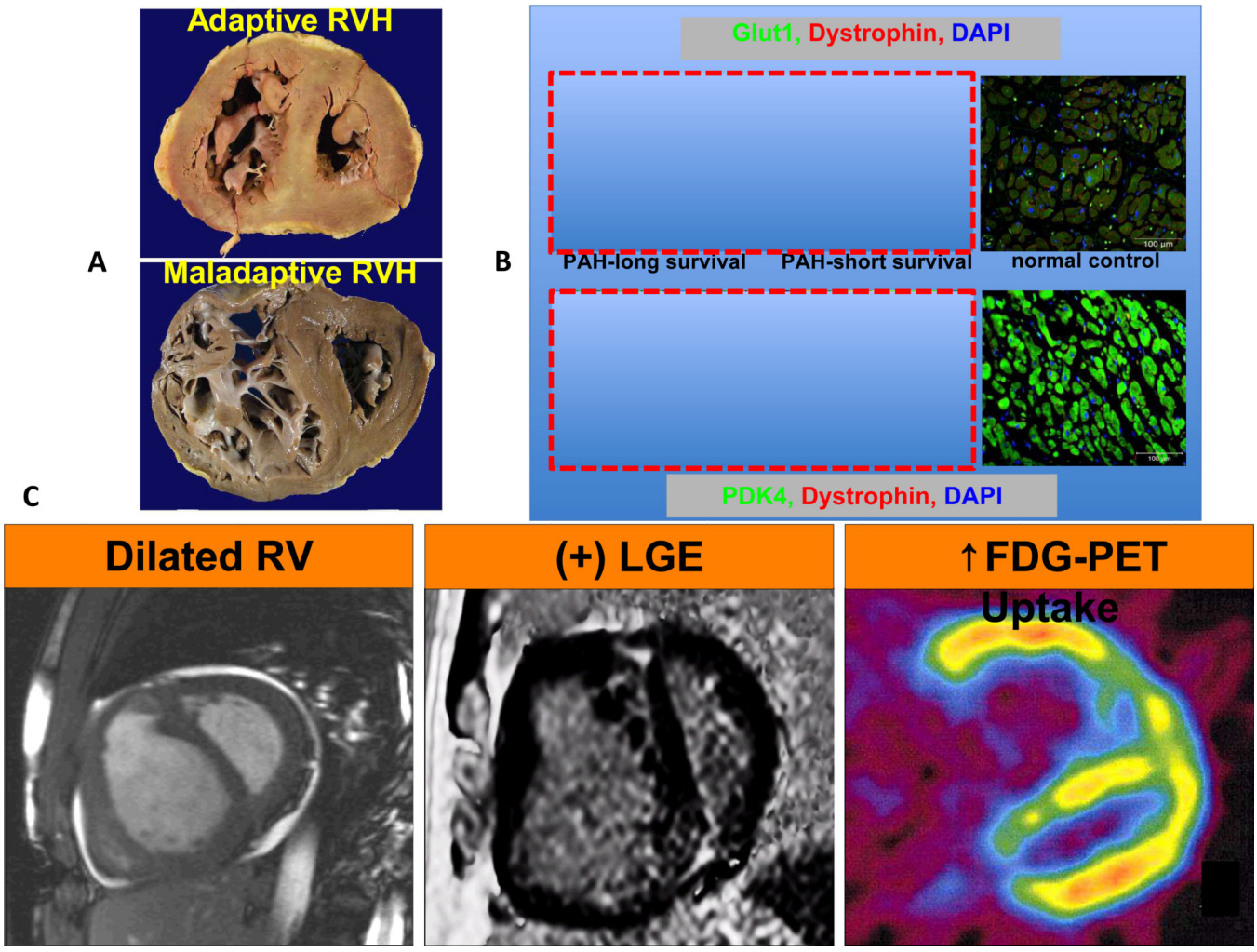


Figure 1.

Increased glycolysis in the right ventricle (RV) in right ventricular hypertrophy (RVH) in PAH patients. **(A)** The cross sections of RVs from patients with adaptive versus maladaptive RVH. RV chambers are enlarged in both patients however adaptive RVH is concentric with less dilatation and fibrosis. **(B)** Immunostaining shows up-regulation of Glut1 and PDK4 expression in RV myocytes and is less profound in the PAH patient with adaptive RVH. **(C)** Imaging modalities showing RV dilatation in MRI, RV fibrosis in MRI and increased FDG uptake in PET scan. The figure is partially adapted from references[22, 36, 45]with permission.

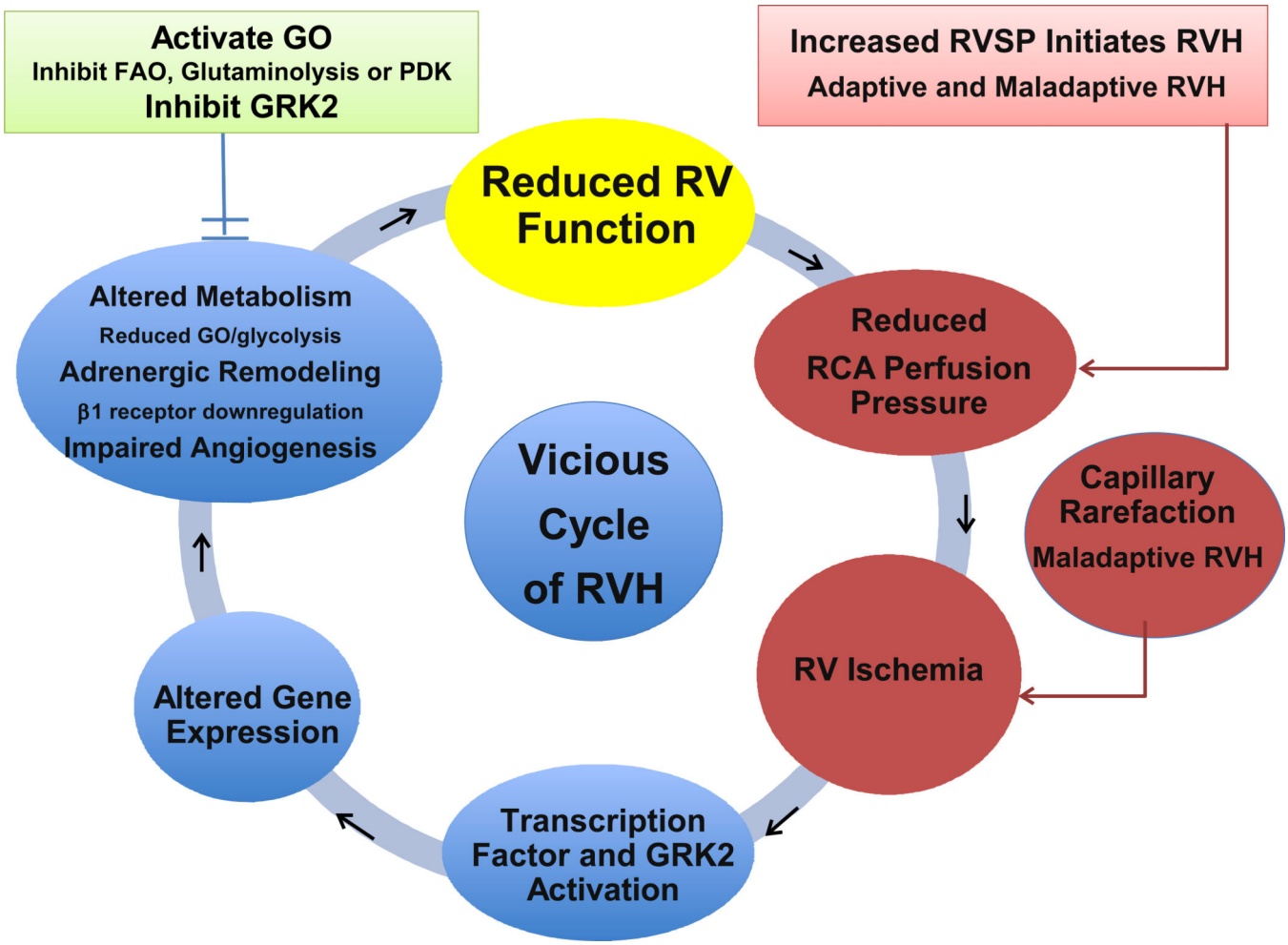


Figure 2.
Vicious cycle of right ventricular failure including metabolic changes and RV ischemia.

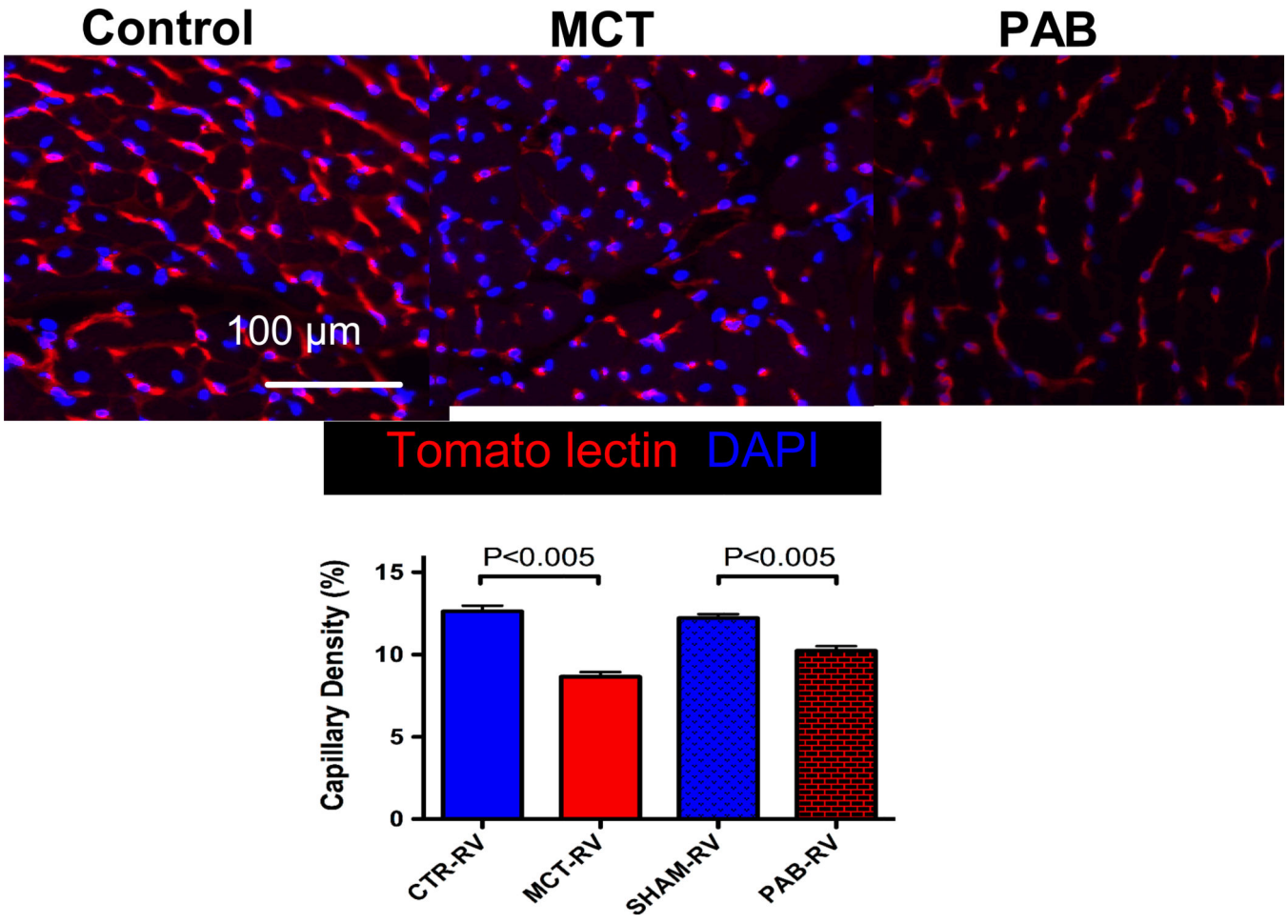


Figure 3.
Decreased capillary density in animal models of maladaptive PAH but not in adaptive PAH.

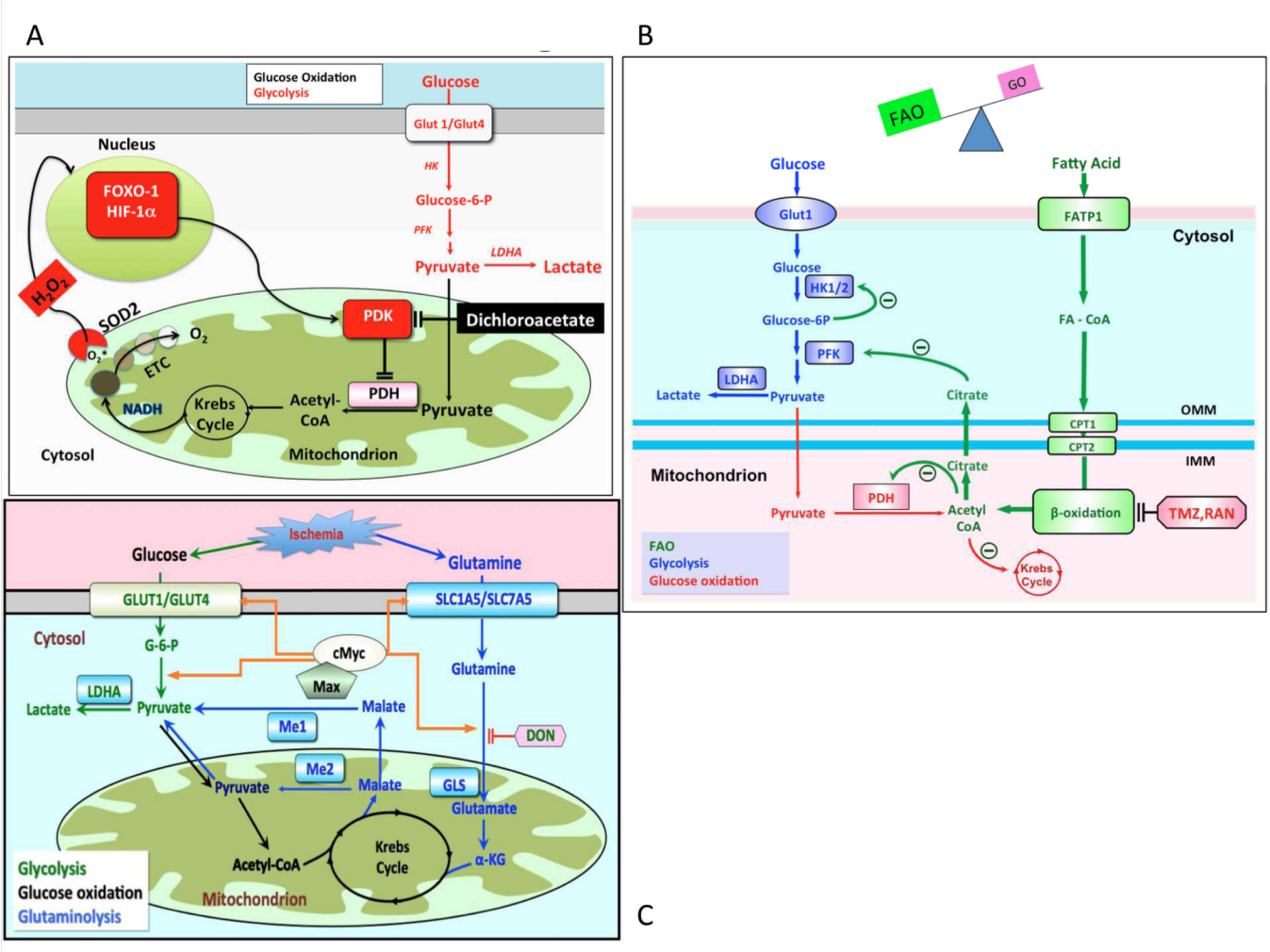


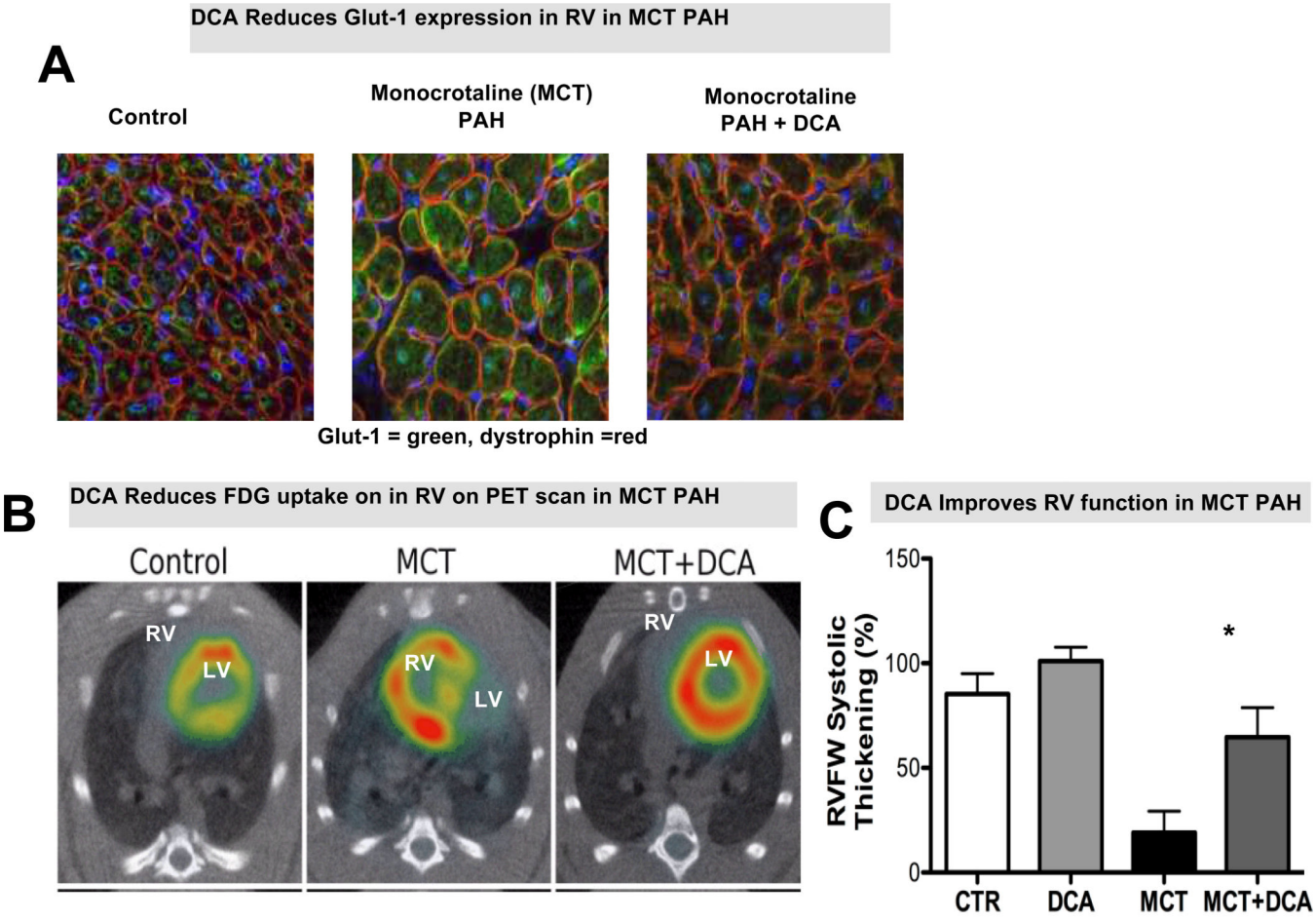
Figure 4.

A: Mechanism of impaired glucose oxidation and enhanced glycolysis in RVH. In RVH, activation of various transcription factors, including FOXO1, cMyc and HIF-1α upregulates expression of many glycolytic gene. A common finding in RVH is increased 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 that seen in the RV. Dichloroacetate inhibits PDK and thereby promotes glucose oxidation and inhibits glycolysis. ETC = electron transport chain, HK = hexokinase, H_2O_2 = hydrogen peroxide, LDHA = lactate dehydrogrenase A, PFK = phosphofructokinase. Adapted from [50]

B: The Randle cycle in RVH The inhibition of β-FAO by trimetazidine and ranolazine increases PDH activity and improves GO. This reciprocal relationship between GO and FAO is referred to as the Randle cycle. Adapted with permission from [75].

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. Reproduced from [26] (Illustration Credit: Ben Smith).



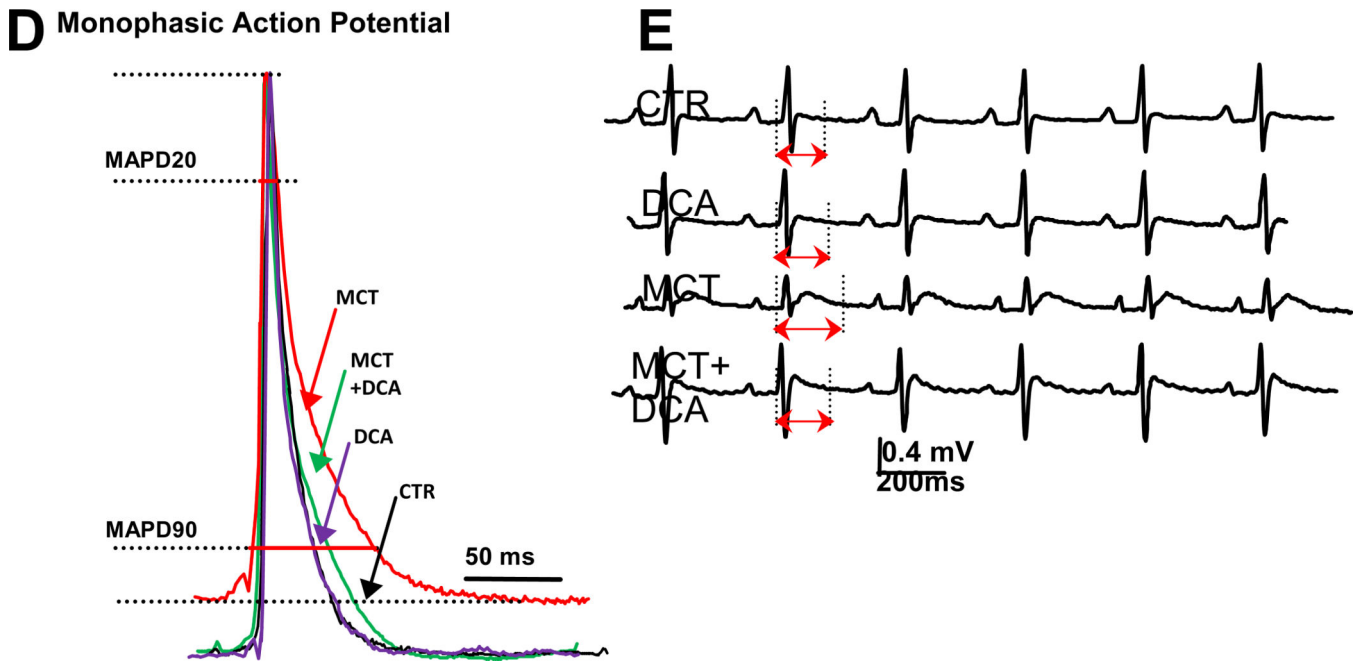


Figure 5.

(A)DCA Reduces Glut-1 expression in RV in monocrotaline-PAH. **(B)** DCA Reduces FDG uptake on in RV on PET scan in monocrotaline-PAH. **(C)** DCA Improves RV function in monocrotaline-PAH.**(D)**Representative traces and mean data showing MAPD20 and MAPD90 are significantly prolonged in the monocrotaline (MCT) group vscontrol (CTR) and that repolarization is improved by DCA. **(E)** Representative traces and mean data of lead II surface ECG. DCA reduces the QTc prolongation in RVH. Red highlighted arrows indicate QTc intervals. Adapted with permission from [50, 75]

Table 1

Normal pressure ranges and vascular resistance in humans (adapted from [115] and [116]). PAH range is derived from patients with severe Group 1 PH, reference[116]. 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.

Hemodynamics	**Normal Range**	**PAH Range (mmHg)**
Right atrium - Mean (mmHg)	1–5	11–13
Pulmonary Artery - Mean (mmHg)	9–20	57–61
Pulmonary Capillary Wedge - End-expiratory (mmHg)	4–12	9–11
Systemic artery pressure - Mean (mmHg)	90–96	87–91
Heart beat (bpm)	60–90	84–88
Cardiac index (L/min/m^2)	2.6–4.2	1.9–2.3
Pulmonary vascular resistance (dynes sec cm^{-5})	20–130 (0.25–1.625 Wood Units)	1200–1360 (15–17 Wood Units)
Systemic vascular resistance (dynes sec cm^{-5})	700–1600 (9–20 Wood Units)	1840–2000 (23–25 Wood Units)

Table 2

Normal pressure ranges and vascular resistance in rodents (adapted from [20, 117]** represents statistical significance)

Hemodynamics	Normal rats	Monocrotaline rats
Pulmonary artery systolic pressure (mmHg)	25±1	60±5**
Pulmonary artery diastolic pressure (mmHg)	3±1	13±2**
Systemic artery mean pressure (mmHg)	110±8	95±6
Heart rate (bpm)	320±7	294±5**
CO (ml/min)	110±5	76±5**
Pulmonary vascular resistance (dynesseccm^{-5})	0.07±0.01	0.44±0.08**
Systemic vascular resistance (dynesseccm^{-5})	0.85±0.12	1.01±0.6