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Metabolism of the right ventricle and the response to hypertrophy and failure

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Abstract

Profound transcriptional, translational and energetic derangements develop in the right ventricle (RV) in response to physiologic and pathophysiologic stress. The transition from pressure and volume overload to cardiac hypertrophy and subsequent failure is accompanied by a distinct switch from preferential fatty acid to glucose utilization for ATP generation. The failing RV is characterized by an energy-starved state with insufficient ATP levels. Modern non-invasive imaging using positron emission tomography using specific radioactive tracers allows a detailed spatial and temporal characterization of RV metabolism. While the current role for pharmacologic interventions on RV metabolic abnormalities is unclear, several potentially promising molecular targets have been identified and clinical trials targeting molecular dysfunction in RV hypertrophy and failure have been designed.

Keywords

Right ventricular failure; Heart failure; Oxidative Metabolism; Glycolysis

Physiologic cardiac metabolism

The healthy heart derives energy from multiple oxidizable energy sources in order to preserve contractile function throughout varying states of myocardial stress.¹ Requiring the most energy of any organ in the body, the heart relies nearly exclusively on aerobic oxidation to produce ATP.² Research into which substrates the myocardium preferentially uses as energy sources began primarily in canine models. Bing et al.³ were among the first to quantify major sources in human myocardium in a basal metabolic state, showing a predominant extraction of free fatty acids (60%) compared to carbohydrates (35%) with a lesser contribution from ketone and lactate metabolism (5%). Further studies confirmed these results and have shown that mitochondrial metabolism of fatty acids ranges from 60% to 90% of total energy extraction in the form of ATP with carbohydrates (glucose) between 10% and 40%, depending on nutritional state.⁴ The predilection for fatty acids over carbohydrates relates to the greater ATP yield per molecule of substrate oxidized.⁵

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Statement of Conflict of Interest

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At birth, patterns of substrate usage switch from primarily carbohydrate and lactate as major sources of ATP synthesis consistent with a low oxygen state to fatty acid oxidation that persists into adulthood.⁶ The adult heart, however, can switch energy sources for ATP generation depending on nutritional supply, as first described by Randle et al.⁸ and subsequently confirmed by numerous investigators.⁷ This “Randle Cycle” describes the process through which fatty acid oxidation inhibits glucose oxidation, acting via feedback inhibition to adapt myocardial metabolism to different forms of supply primarily driven by nutritional status.

With age, this physiologic suppression of glucose oxidation by fatty acids is altered, with greater dependence on glucose metabolism with relatively less fatty acid use. This was initially shown in rat models,^{9,10} but it has also been demonstrated in humans. By evaluation with positron emission tomography (PET) using radioactive tracers specific for distinct metabolic pathways, it has been shown that with aging, decreased myocardial fatty acid uptake and oxidation develops.¹¹

Metabolic specifics of the failing myocardium

The human heart responds to stress, such as ischemia as well as pressure and volume overload, by adjustment of its metabolic function to switch preferential substrate usage from fatty acid to glucose. It is flexible in its use of energetic substrate to use the most efficient source available, which depends on supply and the specific ability to oxidize substrates for ATP generation.¹² Each substrate yields a different amount of ATP, with fatty acids providing the highest amount of ATP.¹³ However, glucose metabolism requires less oxygen consumption for an equivalent amount of ATP synthesis, making it a more efficient substrate in states with higher metabolic demand during short-term states of higher myocardial stress.¹² However, long-term preferential dependency on glucose utilization for ATP generation has been shown to lead to energy starvation and cardiac failure.¹⁴

The inhibition of glucose oxidation by fatty acids is suppressed under stress conditions. During periods of acute supply–demand mismatch, balance is maintained by shifting substrate metabolism through existing pathways.¹² In the setting of sustained increased myocardial energetic requirements, transcriptional adaptations occur to adjust to metabolic needs.¹² The nuclear receptor peroxisome proliferator-activated receptor- α (PPAR α) has been identified as an important regulator in substrate switching from fatty acid to glucose metabolism.¹⁵ These pathways have been validated in clinical studies as well. For example, in a study of explanted hearts from heart transplant recipients, a down-regulation of pathways controlling fatty acid uptake and oxidation was found compared with non-transplantable donor hearts.¹⁶ In ventricular biopsies from five patients with end-stage heart failure, Karbowska et al.¹⁷ found a 54% reduction in PPAR α protein levels compared to controls. These findings have been linked to impaired mitochondrial function in advanced heart failure¹⁵ and mechanical unloading of the failing myocardium has been shown to normalize mitochondrial function.¹⁸ Most recently, our group has demonstrated the accumulation of toxic lipid intermediates likely resulting from impaired fatty acid oxidation and myocardial insulin resistance in patients with advanced heart failure. Metabolic derangements, lipotoxicity as well as myocardial and systemic insulin resistance improved following mechanical unloading of the failing myocardium with subsequent hemodynamic correction following left ventricular assist device implantation.¹⁹

Ultimately, how cardiac metabolic substrate use in periods of stress ultimately leads to a heart failure phenotype remains incompletely elucidated. It is not clear whether transcriptional and functional changes in myocardial metabolism are poorly adaptive. While during short-term stress such as ischemia or acute pressure overload the substrate switch

from fatty acids to glucose seems metabolically and energetically beneficial, long-term adaptations and continued preferential reliance on glucose for ATP generation appear energetically insufficient to provide the energy required for the preservation and restoration of myocardial function and structure ultimately leading to an energy-starved cardiac status with detrimental effects on the myocardium.²⁰

Metabolism of the right ventricle

The majority of information available on the specific metabolism of the right ventricle (RV) is based upon studies of the left ventricle (LV). However, assuming similar mechanisms for the control of metabolic pathways and their importance for energy storage and utilization may be overly simplistic. To start, the RV is thinner owing to lower afterload in the pulmonary bed and has a different shape than the LV for better adaptation to preload changes. The stroke volumes of RV and LV are the same, but the RV has about 25% of the stroke work of the LV due to the low vascular resistance of the pulmonary bed.²¹ There appears to be genetic differences between the two ventricles as well. A study by Drake et al.²² looking at comparative gene expression patterns in normal right and left ventricles showed differences in both mRNA and miRNA profiles including the transcription factor *Irx2* that is not expressed in the RV and *IGF-1* that is expressed predominantly in the LV. They hypothesize that these differences are either resultant from differential embryologic development or the fact that the RV is a low-pressure chamber compared to the LV. Embryologically, the two ventricles arise from different origins—the RV develops from the anterior heart field, while the LV develops from the early heart tube.²³ Reddy et al.²⁴ showed for the first time that alterations in microRNAs are present in RV remodeling from RVH to RV failure in a pulmonary artery constriction model, finding overall similar patterns to pressure-stressed LVs, but with a somewhat different regulatory pathway. Physiologically, there are differences between RV and LV as well. A canine study simultaneously compared coronary blood flow and oxygen extraction between the RV and LV, finding that both were lower in the RV than in the LV.²⁵ Again, this might relate to differences in ventricular wall stress and intraventricular pressure dynamics (Fig. 1).

Despite differential embryologic origins, gene expression, and oxygen extraction, there appears to be a similar impairment in fatty acid metabolism in the RV hypertrophy and failure as identified in the LV. In rat aortic constriction models, myocardial glucose utilization was increased, while fatty acid uptake and oxidation were decreased in the hypertrophied LV.²⁶ The same group later showed that in rat models of RV pressure overload with PA constriction, myocardial glucose uptake is increased in the RV free wall consistent with a direct influence of RV wall stress on myocardial metabolism.²⁷ Moving to humans, several groups have shown similar findings in PET imaging studies comparing patients with severe RV hypertrophy to normal controls.^{28,29} It remains unclear whether impairment in fatty acid metabolism leads to or is the result of contractile dysfunction in the RV myocardium.

Adaptation of RV metabolism in to pressure overload and hypertrophy

In response to high ventricular afterload, the thin-walled RV hypertrophies but then quickly dilates and fails. The initial adaptive response of the RV is to hypertrophy, tested in a goat model of pulmonary trunk banding to increase RV afterload.¹³ This increase in RV mass comes at a greater oxygen requirement. In a canine study, Saito et al.³⁰ showed that both normal and hypertrophied RVs are able to augment coronary flow to meet oxygen requirements but that the hypertrophied myocardium has a lower oxygen extraction reserve ultimately making it less efficient at oxygen utilization despite higher demand. Following further increase in RV mass, the contractile force decreases with subsequent chamber

dilatation to maintain stroke volume in the face of decreasing fractional shortening. Ultimately, the RV fails with rising filling pressures and decreasing stroke volume due to a vicious cycle of increasing wall tension with increasing myocardial oxygen demand that leads to further decreased contractility and dilatation.³¹

Pulmonary arterial hypertension (PAH) remains a deadly disease characterized by vasoconstriction and remodeling of the pulmonary vascular bed with subsequent increase in pulmonary vascular resistance. This presents a higher afterload on the RV, with RV function a primary predictor of long-term survival in this disease.³² The mechanism underlying progression from adaptive RV hypertrophy in this setting to maladaptive remodeling is not clear, but based on experiences with lung transplant patients, RV failure appears to be reversible in most cases following RV pressure unloading.³³

In cases of ventricular pressure overload with hypertrophied myocardium, animal models show that myocardial glucose uptake and glycolytic rate are increased while fatty acid metabolism is decreased.^{34,26} Therefore, metabolic changes in the hypertrophied RV mimic changes in metabolism demonstrated in the hypertrophied and failing LV. Evaluation with magnetic resonance spectroscopy can correlate cardiac structure with metabolic function and Nagaya et al.²⁸ assessed 21 patients with RV hypertrophy due to pulmonary hypertension and found disproportionately decreased RV contractility in patients with impaired myocardial fatty acid uptake. Bokhari et al.³⁵ have validated PET imaging as a viable method for quantifying myocardial glucose uptake and utilization in a study of 16 patients with idiopathic PAH. They found that RV glucose use correlates with hemodynamic parameters including mean PA pressure, presumably indicating RV functional impairment with the shift in myocardial glucose uptake serving as a marker of RV dysfunction. Similar findings were shown by Can et al.³⁶ who studied 23 patients with PAH and 16 healthy controls studied by PET. They found that increased fludeoxyglucose accumulation in the RV myocardium was correlated with increased RV loading conditions and the presence but not severity of elevated pulmonary artery pressures.

So far, little is known on lipid storage in the normal or failing RV. Localized ¹H magnetic resonance spectroscopy is the only imaging modality at this time that can measure triglyceride content in tissue.^{37,38} Szczepaniak et al.³⁷ found that increased myocardial triglyceride content is associated with elevated LV mass and suppressed septal wall thickening.³⁷ Magnetic resonance spectroscopy measurement of myocardial triglyceride content has been shown to have good statistically significant correlation with triglyceride levels by RV biopsy, proving it a reliable tool in metabolic imaging of cardiac disease.³⁹ However, no study has quantified levels of lipid intermediates in the RV.

Metabolic interventions in heart failure—role for RV failure?

Very little is known on the effects of pharmacologic interventions on RV metabolism in PAH, RV hypertrophy or failure. While interventions such as PDE5 inhibition, endothelin antagonism or PDG2 agonists are effective in reducing RV pressure overload in PAH, data on their direct or indirect effects of RV metabolism are sparse.⁴⁰ One might speculate that the decrease in pulmonary artery pressure with resulting improvement in RV load results in improved cardiac metabolism and increased fatty acid utilization but this is unclear at this point. Myocardial substrate specificity and oxidation can be modulated through pharmacologic partial inhibitors of fatty acid oxidation. Several compounds that uniformly increase glucose utilization for ATP generation have been tested in animal studies and small human trials of LV dysfunction including ranolazine (blocking Na channels, reducing cellular calcium-load and inhibiting fatty acid oxidation),⁴¹ trimetazidine (direct inhibition of mitochondrial fatty acid oxidation),⁴² perhexiline (inhibiting the mitochondrial fatty acid

transporter carnitine palmitoyltransferase-1),⁴³ the niacin derivative acipimox (blocking triglyceride production in the liver and reducing circulating levels of fatty acids),⁴⁴ or insulin sensitizers such as glucagon-like peptide-1.⁴⁵ No data are available on interventions that specifically increase fatty acid uptake and oxidation in animal models of or patients with LV or RV dysfunction or failure. Several trials testing direct metabolic interventions to modify RV glucose or fatty acid uptake and oxidation are currently under way.

Summary and conclusion

Profound transcriptional, translational and energetic derangements develop in the RV in response to physiologic and pathophysiologic stress. The transition from pressure and volume overload to cardiac hypertrophy and subsequent failure is accompanied by a distinct switch from fatty acid to glucose as the preferential substrate for ATP generation. The failing RV is characterized by an energy-starved state with insufficient ATP levels. While the current role for pharmacologic interventions on these metabolic abnormalities is unclear, several potentially promising molecular targets have been identified and clinical trials targeting molecular dysfunction in RV hypertrophy and failure are currently being performed.

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Abbreviations and Acronyms

RV	right ventricle
ATP	adenosine triphosphate
PET	positron emission tomography
PPARα	peroxisome proliferator-activated receptor- α
LV	LV left ventricle
IGF-1	insulin-like growth factor 1
RVH	right ventricular hypertrophy
PA	pulmonary artery
PAH	pulmonary arterial hypertension
PDE5	phosphodiesterase 5
PDG2	prostaglandin D2

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- High oxidative metabolism
- ATP generation (70% fatty acids, 30% glucose)
- Stable ATP levels
- Stable mitochondria

- Reduced FA uptake and oxidation with increased glycolytic gene expression
- Increased glycolysis
- ATP generation (<50% fatty acids, >50% glucose)
- Low ATP levels
- Decreased mitochondrial content and function

Fig. 1.
Right ventricular metabolism.