Right Ventricular Metabolism: A Brief Review

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The primary function of the right ventricle (RV) is to receive systemic venous return and pump it into the normally low-pressure, highly distensible pulmonary arterial system.[1] Compared to the left ventricle (LV), the RV is thinner with less mass, has 2 layers of muscles rather than 3, and has a bellow shape rather than an ellipsoid shape. Due to its typically low afterload, the metabolic demand for the RV is lower. The normal RV stroke work index is at 25% of the LV.[2] Animal studies have shown that the right coronary artery flow is lower, the oxygen extraction is lower in the RV compared to the LV, and the mean RV myocardial oxygen consumption is less than half that of the LV.[3,4] The study of myocardial metabolism has been dominated by studies of the LV metabolism until recently, with increasing recognition that RV performance affects patients' morbidity and mortality in patients with pulmonary hypertension[5] and even in patients with left-sided heart failure.[6]

MYOCARDIAL METABOLISM

Contraction of the heart muscle requires conversion of the chemical energy received from the substrates to mechanical energy in the form of adenosine triphosphate (ATP). In the adult heart, fatty acid metabolism is the major contributor to ATP production, whereas during early embryogenesis, anaerobic glycolysis is the major energy-producing metabolic pathway. The transition to fatty acid oxidation (FAO) as the primary source of energy for the heart begins right after birth, with increased expression of the genes encoding for the enzymes in the FAO pathway. In fact, in its basal metabolic state, the adult heart utilizes 60% to 90% of the fatty acids as the energy source and 10% to 40% of the carbohydrates, with minimal contributions from ketones and lactate.[7] In the adult heart under stress or exercise, the efficiency of glucose as substrates exceeds the efficiency of fatty acids quite significantly, resulting in the carbohydrates as the preferred fuel.[8]

Randle et al[9] proposed the glucose-fatty acid cycle (Figure 1), where the fuel selection and uptake are controlled by the competition between the substrates. In this reciprocal inhibitory mechanism, fatty acids inhibit glucose oxidation at the level of pyruvate dehydrogenase complex, and the inhibition of FAO by glucose is through the inhibition of the enzyme carnitine-palmitoyl transferase I by malonyl-CoA.

With comorbidities (hypertension, diabetes, heart failure), various studies have shown a shift in the predominant metabolic pathway in the heart with decreased reliance on the fatty acid oxidation pathway. The factors commonly attributed to this alteration include changes in the mitochondrial lipid content, increased cellular oxidative stress, the decrease in the myocardial enzyme activity, or changes in the myocardial nuclear receptor peroxisome proliferator activated-receptor leading to downregulation of genes controlling the FAO pathway.[11,12] The long-term dependency on glucose as the primary substrate, especially glycolysis, may lead to energy starvation and heart failure.[12] The overview of myocardial metabolism in normal and diseased states is presented in Table 1.[13-15]

RV METABOLISM IN DISEASE

Pulmonary arterial hypertension (PAH) is associated with increased pulmonary vascular resistance (PVR), which leads to higher afterload for the right ventricle (RV). The thin-walled RV hypertrophies initially followed by dilation and eventually failure. Metabolic imaging in humans and mammals allowed interrogation of metabolic alterations that accompany RV hypertrophy (RVH) and RV failure.

The relationship of RV fatty acid metabolism and functioning was first studied using single-photon emission computerized tomography (SPECT) and a branched chain analog of iodophenyl pentadecanoic acid (BMIPP) in 21 patients with pulmonary hypertension (PH).[16] Patients with normal myocardial fatty acid uptake had higher RV ejection fraction, and patients with impaired fatty acid metabolism had higher death rates when compared to patients with normal fatty acid metabolism.[16] In another study of 27 subjects, the existence of impaired fatty acid metabolism in patients is correlated with severe RV hypertrophy.[17]

^{18}F-FDG, a glucose tracer analog used in positron emission tomography (PET), is taken up by viable myocytes in a similar manner to glucose, but cannot be metabolized further after being converted to ^{18}F-FDG 6-phosphate and thus trapped in myocytes. The uptake of ^{18}F-FDG in the heart depends on the glucose concentration in the plasma, the rate of glucose delivery to the heart, and its use. Oikawa et al[18] studied the impact of PH on RV FDG uptake in 24 patients. Increased RV free wall FDG uptake correlated with the underlying RV pressure overload. In 10

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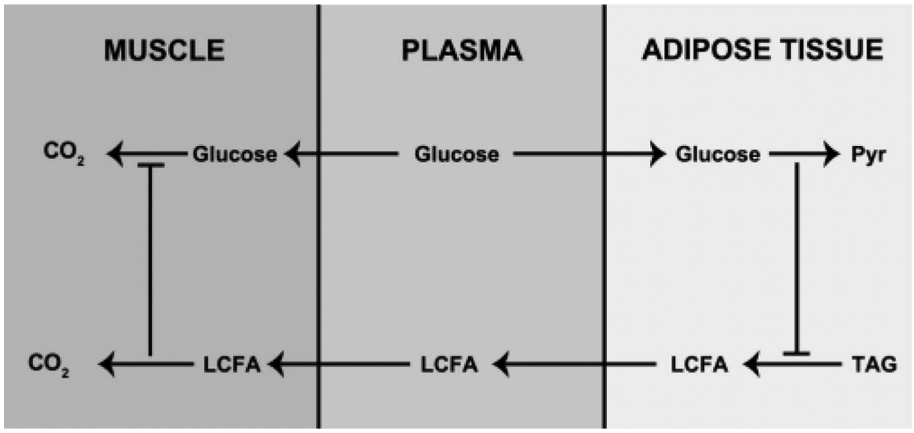

Figure 1: The "glucose-fatty acid cycle," a homeostatic mechanism to control circulating concentrations of glucose and fatty acids. The term "cycle" is used here to describe a reciprocal control between glucose and fatty acid metabolism. The effect of glucose is mediated by insulin. LCFA, long-chain fatty acid; TAG, triacylglycerol; Pyr, pyruvate. Adapted with permission from Hue L, Taegtmeyer H. The Randle cycle revisited: a new head for an old hat. *Am J Physiol Endocrinol Metab*. 2009;297(3):E578-E591.[10]

patients (NYHA Class III/IV) who received epoprostenol therapy for a period of 3 months and a follow-up PET showed decreased RV FDG accumulation, which correlated with improved RV function (Figure 2). Bokhari et al[19] evaluated myocardial blood flow (MBF) using ^{13}N-NH_3 for perfusion and ^{18}F-FDG for glucose metabolism in 16 patients with idiopathic PAH. MBF was normal in all patients, but RV/LV glucose uptake ratio was correlated with pulmonary arterial pressures (PAP).[19]

Alteration in RV metabolism can also be seen in disease where pulmonary pressures might not be significantly elevated or secondary to elevated pulmonary diastolic pressure. Choi et al reported an increase in FDG uptake in the RV myocardium in patients with chronic obstructive lung disease, which is correlated with the severity of lung obstruction and pack-year of smoking.[20] Meilniczuk et al[21] studied 68 patients with a history of congestive heart failure (NYHA Class II-III) with moderate PH. As the RV function worsened, the ratio of RV/LV glucose uptake increased.

^{18}F-FDG studies are limited as the information gathered only pertains to the glucose uptake in the disease state. Further probing of oxidative component of the metabolism was performed by Yoshinaga et al[22] using ^{11}C-acetate as a marker in 36 subjects (27 PH patients and 9 healthy controls). PET imaging showed higher RV k_{mono} (indicative of higher oxidative metabolism) than controls that correlated significantly with mean PAP, PVR, and brain-natriuretic peptide values. However, no correlation was noted between RV k_{mono} and RV end-diastolic volume index, RV mass index, or 6-minute walk test. LV K_{mono} was not elevated compared to controls. These data indicate that increased RV oxidative metabolism might exist as a compensatory mechanism before RV failure ensues.

The cause of increased RV FDG in RV metabolic derangement was further investigated by Paio et al, who hypothesized that RV dysfunction in RVH is in part caused by activation of pyruvate dehydrogenase kinase (PDK)-induced glycolytic shift from glucose oxidation (GO) to glycolysis in the RV.[23] Two different rat models were compared: one RVH with PAH (induced using monocrotaline) and the other RVH without PAH (induced using pulmonary artery banding). In RVH with PAH, glucose transporter-1 expression and pyruvate dehydrogenase (PDH) phosphorylation were increased, along with reduced RV oxygen consumption and increased glycolysis. A PDK inhibitor, dichloroacetate, increased glucose oxidation and reversed the effects of monocrotaline on RV function. In the RVH without PAH model, the glycolytic shift and the benefit with dichloroacetate inhibition were also seen, albeit less compared to RVH with PAH.

Studies aimed at targeting the reversal of this metabolic shift by using partial inhibitors of FAO and exploiting the reciprocal relationship between FAO and GO (Randle's cycle) showed that both trimetazidine and ranolazine decreased FAO and restored PDH activity and GO in a rat pulmonary banding model.[24] Potential beneficial effect has been seen in patients with PAH associated with heart failure with preserved ejection fraction.[25] An ongoing trial of ranolazine in patients with PAH is enrolling and cardiac magnetic resonance imaging, ^{18}F-FDG, and ^{11}C-acetate PET are used as readouts for the effect of ranolazine on the metabolic shift (NCT01839110).

Table 1: Overview of Myocardial Metabolism in Physiological and Pathological Conditions

Condition	Glucose Metabolism	Fatty Acid Metabolism
Sex (Female)	Decreased	Increased
Aging	Increased	Decreased
Obesity	-	Increased
Diabetes	Decreased	Increased
Heart Failure/Hypertension	Increased	Decreased

CONCLUSION

Cardiac metabolism in general and specifically RV metabolism changes in response to the oxygen and substrate availability. The RV is dependent on the fatty acid oxidation pathway for energy production and its performance under rest and normal conditions. Under conditions of increased metabolic demand, there is an initial increased oxidative metabolism associated with increased glucose utilization. Accompanying this process, a metabolic switch is also observed, which leads to inhibition of the fatty acid pathway and activation of the glycolytic pathway. Key molecular pathways that are involved in compensated metabolic remodeling in RV

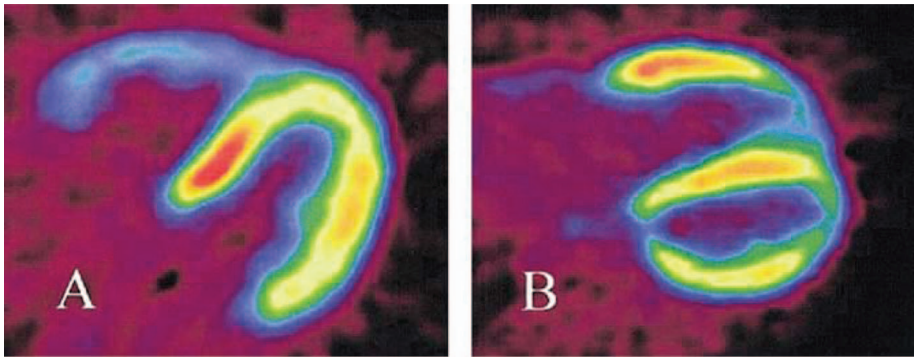

Figure 2: PET images of ^{18}F-FDG uptake in PAH patients with mild (A) vs severe (B) PH. Adapted with permission from Elsevier from Oikawa M, Kagaya Y, Otani H, et al. Increased [18F]fluorodeoxyglucose accumulation in right ventricular free wall in patients with pulmonary hypertension and the effect of epoprostenol. *J Am Coll Cardiol*. 2005;45(11):1849-1855.[18]

hypertrophy vs. the eventual RV failure still need to be better elucidated. Minimal data are currently available to support metabolic interventions for the management of impaired RV function and the failing heart.

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