

# A metabolism-based, right ventricle-specific mechanism of heart failure

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## Abstract

There are many differences in the embryology, structure, vascularity, and physiology between the right and the left ventricles. Compared with left ventricle failure, right ventricle failure is understudied preclinically and clinically. Therapies or disease mechanisms proposed for the left ventricle cannot necessarily be extrapolated to the right ventricle. Here, we discuss a recently proposed mechanism that may be specific to the right ventricle and explain why the right ventricle fails much sooner when exposed to increased afterload compared with the left ventricle. A beneficial metabolic remodeling that develops in compensating right ventricle hypertrophy (ie, inhibition of mitochondrial glucose oxidation and upregulation of glycolysis) is lost early compared with the left ventricle, triggering right ventricle decompensation, a process that may be due to a differentially regulated Mef2c/miR208 axis between the two hypertrophied ventricles. This chamber-specific axis may provide a platform for the development of much-needed right ventricle-specific therapies and biomarkers. ■ *Heart Metab.* 2018;77:19-23

**Keywords:** Mef2c; miR208; pulmonary hypertension; right ventricle

## Introduction

Despite the remarkable attention that left ventricular failure receives in research, right ventricular failure is understudied both preclinically and clinically. Yet, as the two ventricles are in series, failure of either has the same impact, ie, decreasing cardiac output, resulting in heart failure and premature death. While secondary right ventricular failure is an independent and strong negative prognostic factor in patients with primary left ventricular failure,<sup>1,2</sup> the right ventricle is primarily affected by pulmonary hypertension due to many conditions, including chronic lung and thromboembolic disease or pulmonary arterial

hypertension (PAH), a deadly proliferative vascular disease. In patients with PAH, the status of the right ventricle is the most important predictor of both morbidity and mortality, which are quite high in this disease.<sup>1,2</sup> In addition, right ventricular failure is a major cause of morbidity and mortality in heart/lung transplant patients, both peri- and postoperatively.<sup>1</sup>

### The two ventricles are different

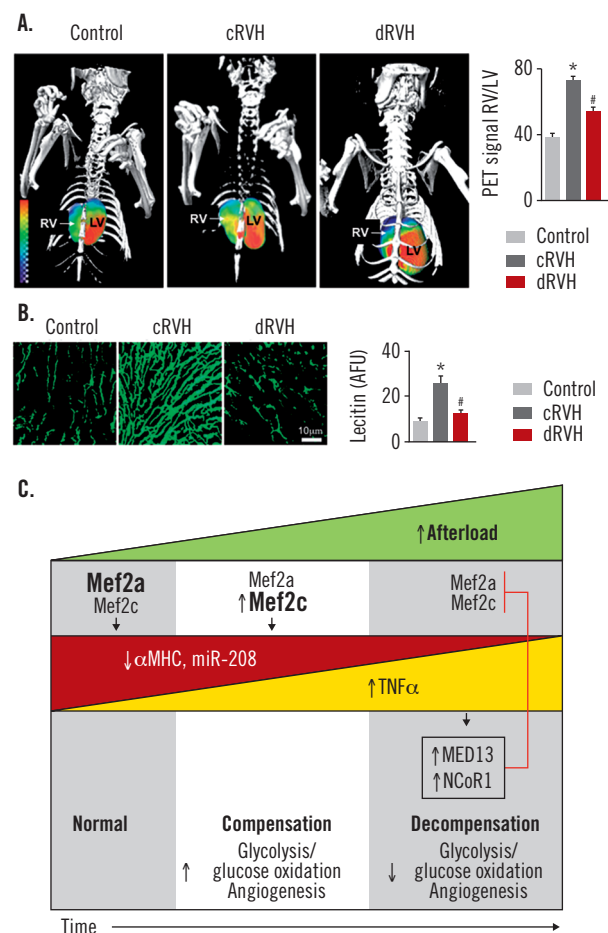
The two ventricles have a different embryologic origin, vascularity, and response to pressure overload.<sup>3</sup> Overall, the right ventricle is less capable of long-term adaptation to pressure overload than the left ventricle.

A patient with systemic hypertension can develop adaptive left ventricular hypertrophy and remain asymptomatic for decades. A patient with PAH and a similar increase in right ventricular afterload develops right ventricular failure and dies in less than 3 years from the time of diagnosis.<sup>4</sup> Despite the difficulty of the right ventricle to adapt to disease states, it has a remarkable ability to adapt to physiologic changes. For example, in utero, the afterload of the right ventricle is high and, as a result, the right ventricle at birth is hypertrophied. With the first breath and the transition to the low-pressure adult pulmonary circulation, within a few weeks, the right ventricle remodels to the thin-walled, nonhypertrophied right ventricle. However, in some patients, this transition does not occur at birth (eg, patients with congenital heart anomalies) and the right ventricle remains hypertrophied. These patients can survive for many decades without right ventricular failure despite severe PAH, perhaps because of the persistence of the “fetal heart gene program.”<sup>1</sup> The differences in the two ventricles are apparent by the opposing responses to experimental therapies. For example, histone deacetylase (HDAC) inhibitors decrease left ventricular hypertrophy (eg, due to aortic banding) and improve function.<sup>5-7</sup> However, HDAC inhibition in right ventricular hypertrophy due to pulmonary artery banding results in the opposite effect, ie, worsening right ventricular function.<sup>8</sup> Thus, it cannot be assumed that therapies designed to treat left ventricular failure will be beneficial in patients with right ventricular failure.

### Metabolism and myocardial hypertrophy

Myocardial metabolism is critical to the ability of the myocardium to adapt to ischemia or hypertrophy. The normally thin-walled right ventricle is much less vascularized than the left ventricle, as its oxygen demand is less, considering its lower workload pumping against a lower afterload, as the normal pulmonary artery pressure is lower than the normal systemic arterial pressure. There is ample evidence that the hypertrophied right ventricle is ischemic<sup>1,9</sup> (perhaps more than the hypertrophied left ventricle). Right ventricular hypertrophy exhibits a metabolic remodeling that is similar (but perhaps stronger) to that of the hypertrophied left ventricle, characterized by a decrease in mitochondrial glucose oxidation and a secondary increase in glycolysis.<sup>9</sup> This uncoupling between glucose oxida-

tion and glycolysis has many causes, but inhibition of the mitochondrial pyruvate dehydrogenase (PDH; the gate-keeping enzyme of glucose oxidation) is central. The enhanced glycolysis can compensate for the loss of ATP from glucose oxidation inhibition, as it is associated with an increase in glucose uptake due to an upregulation of glucose transporters (explaining why the hypertrophied right ventricle exhibits higher 18-fluorodeoxy-glucose (FDG) uptake than the normal myocardium during FDG-PET imaging; *Figure 1A*).<sup>9</sup>



**Fig. 1** Metabolic and physiologic changes in the compensated and decompensated right ventricle (decreased cardiac output, increased right atrial pressure, chamber dilatation) in animals.

**Panel A.** Glucose uptake, measured by [<sup>18</sup>F]-deoxyglucose (FDG) PET-CT imaging, was increased in the animals with compensated right ventricular hypertrophy (cRVH), but not in the animals with decompensated right ventricular hypertrophy (dRVH) compared with control animals. A pseudo-color map indicates FDG levels, with red signifying a high FDG signal and purple signifying low FDG levels (*n*=5 animals/group; \**P*<0.05 vs control; #*P*<0.05 vs cRVH animals). **Panel B.** The capillary network, measured by lectin imaging and confocal microscopy, was increased in cRVH, but not dRVH compared with controls (*n*=5 animals/group; \**P*<0.05 vs control; #*P*<0.05 vs cRVH). **Panel C.** Schematic representation of molecular mechanisms involved in a right ventricle-specific transition from a compensated to a decompensated state (see text).

From reference 9: Sutendra G et al. *J Mol Med.* 2013;91:1315-1327. © 2013, Springer-Verlag Berlin Heidelberg.

Hypoxia inducible factor-1 $\alpha$  (HIF1 $\alpha$ ) is central to this process since its activation in the ischemic state of the hypertrophied myocardium results in an induction of pyruvate dehydrogenase kinase (PDK; which inhibits PDH), as well as an induction of several glycolysis enzymes and glucose transporters.<sup>9</sup> The concomitant HIF-induced angiogenesis gene program allows at least a partial decrease in ischemia (*Figure 1B*). Additional benefits from this metabolic remodeling include:

1. Pyruvate is not oxidized in the Krebs' cycle (due to the inhibition of PDH), allowing glycolytic intermediates to shift toward biosynthetic pathways and support the increasing mass of the myocardium in a manner similar to cancer.<sup>10,11</sup>
2. Again similar to cancer, the inhibition of glucose oxidation is associated with mitochondrial hyperpolarization and closure of the voltage-gated mitochondrial transition pore, which allows a leak of proapoptotic factors (like cytochrome c and apoptosis-inducing factor), allowing the "stressed" myocardium to avoid cardiomyocyte loss.<sup>9,11</sup>

However, these benefits regarding the structural remodeling of the heart come with a price when it comes to myocardial function. Inhibition of glucose oxidation results in a shift in the type of fuel used for oxidative phosphorylation, ie, from glucose to fatty acids, a less efficient fuel since it requires more oxygen for the generation of each ATP molecule compared with glucose.<sup>12</sup> This is particularly true in ischemic states, such as right ventricular hypertrophy. Therefore, drugs that can acutely reverse this remodeling in isolated heart models and inhibit fatty acid oxidation (like trimetazidine<sup>13,14</sup>) or directly activate PDH and increase glucose oxidation (like the PDK inhibitor DCA<sup>14,15</sup>) result in improved contractile function of the hypertrophied or ischemic myocardium of both ventricles.

Thus, the left and right ventricle exhibit a similar metabolic response to hypertrophy and/or ischemia, which means that this by itself cannot explain the much weaker chronic response of the right ventricle to increased afterload.

### **A right ventricle-specific mechanism of heart failure?**

The more clinically relevant question here is not how the right ventricle hypertrophies (since hypertrophy is, in general, a beneficial and protective response), but rather why it enters a decompensation stage (de-

creased contractility and increased apoptosis leading to right ventricle dilatation and fibrosis) so much earlier than the left ventricle. We have proposed that this happens because the hypertrophied right ventricle cannot sustain its beneficial metabolic remodeling and paradoxically switches to "normal metabolism," while the afterload remains high.<sup>9,16</sup> We have shown that, at late stages of right ventricle hypertrophy and just before the right ventricle starts to fail (cardiac output decreases, filling pressures increase, right ventricle dilatation begins), its metabolism is "paradoxically normalized," with an increase in glucose oxidation and a decrease in glycolysis.<sup>9,16</sup> Why does this happen in the right ventricle and not the left ventricle?

To answer this, one has to look into the embryology of the two ventricles. The right and left ventricle come from different heart fields in the developing embryo and the embryogenesis of the right ventricle is driven by different transcription factors than that of the left ventricle. Myocyte enhancer factor 2c (Mef2c) is a master transcription regulator and specific for the development of the right ventricle, but not the left ventricle.<sup>17</sup> Inactivation of Mef2c in mice results in embryonic lethality with right ventricle morphogenetic defects and vascular abnormalities.<sup>18</sup> While Mef2c is critical in early development, Mef2a operates a similar adult transcriptional program; its deletion allows a few mice to survive to adulthood having malfunctioning and dilated right ventricles with a significant decrease in vascularity and mitochondrial number and function.<sup>19,20</sup> Mef2 DNA binding activity in the heart is upregulated 3-fold by pressure-overload hypertrophy and is implicated in the regulation of the alpha myosin heavy chain gene ( $\alpha$ MHC).<sup>21</sup> In addition to the angiogenesis gene program, Mef genes also regulate a metabolic package of genes, including many mitochondrial factors and enzymes,<sup>19</sup> a reminder that the metabolism of a hypertrophied organ needs to be coordinated with growth and development as well as vascularization in order to offer an optimal balance of fuel supply/demand. Upon pressure overload and activation of the "fetal gene program," the Mef2a/Mef2c ratio decreases and Mef2c becomes the dominant transcription factor.<sup>16</sup> A well-described Mef-driven decrease in the transcription of  $\alpha$ MHC follows.<sup>22</sup>

miR-208 is a cardiac-specific miRNA encoded within the  $\alpha$ MHC gene.<sup>23</sup> In the left ventricle, there is an increase in miR-208 from the fetal to the adult left ventricle, which remains stable during pathologic left

ventricle remodeling.<sup>23</sup> miR-208 inhibits the MED13/NCoR1 axis, thus activating Mef2 and sustaining the fetal gene program.<sup>23</sup> However, in right ventricular hypertrophy, the Mef2c-driven decreased transcription of the  $\alpha$ MHC gene also causes a progressive decline in miR-208 transcription.<sup>16</sup> The decreased miR-208 levels result in increased levels and activity of the MED13/NCoR1 complex and inhibition of Mef2c, triggering an exit from the fetal gene program and entrance into a decompensating stage (Figure 1C).<sup>16</sup> The activation of MED13/NCoR1 is also promoted by increasing levels of the inflammatory cytokine tumor necrosis factor  $\alpha$  (TNF $\alpha$ ).<sup>16</sup> PAH is characterized by a profound activation of inflammation.<sup>24,25</sup> TNF $\alpha$  does not increase in pulmonary artery banding models of right ventricular hypertrophy (or in patients with right ventricular hypertrophy due to congenital heart disease), perhaps explaining why, in these conditions, right ventricle decompensation is delayed. Interestingly, the synergy of miR-208 loss and TNF $\alpha$  increase in activating MED13/NCoR1 and inhibiting Mef2c did not take place in left ventricle cardiomyocytes.<sup>16</sup> The fact that miR-208 levels do not change during left ventricular hypertrophy suggests that this Mef2c-miR208 axis may be the Achilles' heel of the right ventricle and may explain the predisposition of right ventricular hypertrophy to fail, compared with left ventricular hypertrophy.

### Clinical implications

Earlier, we discussed how DCA and trimetazidine improve right ventricle function when given acutely in compensated right ventricular hypertrophy in isolated heart models. However, the above discussion suggests that the chronic reversal of the compensating metabolic remodeling in right ventricular hypertrophy may promote decompensation and cardiomyocyte loss, since the normalized metabolism will not be able to support the stressed conditions in the myocardium if the afterload is fixed (eg, pulmonary valve stenosis). However, in PAH, these drugs, when given in vivo, also reverse vascular remodeling in the lung and decrease pulmonary artery pressure, allowing the normalized metabolism to take place in a less-stressed right ventricle with a now decreased afterload.<sup>26-28</sup>

The Mef2c-miR208 axis, along with the inflammation that characterizes PAH (Figure 1C), may underlie a right ventricle-specific mechanism for right ventricular failure and explain the loss of adaptive meta-

bolic remodeling and angiogenesis in right ventricular hypertrophy, triggering decompensation and failure (Figure 1A-B). This axis provides many targets for rational drug and biomarker development. One example is the potential of declining serum levels of the cardiac-specific miR-208 to serve as a much-needed biomarker, exposing an entrance into decompensated heart failure in patients with PAH. ■

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