Evolving Technology

A dynamic and chamber-specific mitochondrial remodeling in right ventricular hypertrophy can be therapeutically targeted

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Supplemental material is available online.

Objectives: The right ventricle fails quickly after increases in its afterload (ie, pulmonary hypertension) compared with the left ventricle (ie, systemic hypertension), resulting in significant morbidity and mortality. We hypothesized that the poor performance of the hypertrophied right ventricle is caused, at least in part, by a suboptimal mitochondrial/metabolic remodeling.

Methods/Results: We studied mitochondrial membrane potential, a surrogate for mitochondrial function, in human (n = 11) and rat hearts with physiologic (neonatal) and pathologic (pulmonary hypertension) right ventricular hypertrophy in vivo and in vitro. Mitochondrial membrane potential is higher in the normal left ventricle compared with the right ventricle but is highest in the hypertrophied right ventricle, both in myocardium and in isolated cardiomyocytes ($P < .01$). Mitochondrial membrane potential correlated positively with the degree of right ventricular hypertrophy in vivo and was recapitulated in phenylephrine-treated neonatal cardiomyocytes, an in vitro model of hypertrophy. The phenylephrine-induced mitochondrial hyperpolarization was reversed by VIVIT, an inhibitor of the nuclear factor of activated T lymphocytes, a transcription factor regulating the expression of several mitochondrial enzymes during cardiac development and hypertrophy. The clinically used drug dichloroacetate, known to increase the mitochondria-based glucose oxidation, reversed both the phenylephrine-induced mitochondrial hyperpolarization and nuclear factor of activated T lymphocytes (NFAT) activation. In Langendorff perfusions, dichloroacetate increased rat right ventricular inotropy in hypertrophied right ventricles ($P < .01$) but not in normal right ventricles, suggesting that mitochondrial hyperpolarization in right ventricular hypertrophy might be associated with its suboptimal performance.

Conclusions: The dynamic changes in mitochondrial membrane potential during right ventricular hypertrophy are chamber-specific, associated with activation of NFAT, and can be pharmacologically reversed leading to improved contractility. This mitochondrial remodeling might provide a framework for development of novel right ventricle–specific therapies.

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Although mechanisms of left ventricular (LV) heart failure are widely documented, right ventricular (RV) failure remains understudied, despite its high clinical importance. RV dysfunction is a major cause of morbidity and mortality in many conditions, including pulmonary arterial hypertension (PAH), congenital heart disease, and lung transplant surgery.[1,2] In response to

Abbreviations and Acronyms

DAPI = 4,6-diamino-2-phenylindole
DCA = dichloroacetate
LV = left ventricle/ventricular
LVH = left ventricular hypertrophy
NFAT = nuclear factor of activated T lymphocytes
PAAT = pulmonary artery acceleration time
PAH = pulmonary arterial hypertension
RV = right ventricle/ventricular
RVH = right ventricular hypertrophy
SMC = smooth muscle cells
TMRM = tetramethyl–rhodamine methyl ester

increased afterload (as seen in PAH), the thin RV of the normal adult heart hypertrophies but eventually quickly dilates and fails. There are, however, situations in congenital heart disease wherein the RV remains hypertrophied and compensated for years despite the development of PAH. These cases are typically seen when there is no involution of the physiologic neonatal RV hypertrophy (RVH) and the fetal morphology persists through adulthood. In contrast, the normal adult LV can develop hypertrophy and remain in a compensated state in response to an increase in its afterload (systemic hypertension) for decades. The relatively early failure of the RV in pulmonary hypertension explains largely the much worse survival of patients with PAH compared with patients with systemic hypertension; at the same time, this raises the exciting possibility that something in the neonatal hypertrophied RV (normal remodeling) offers superior function and protection compared with the acquired RVH in adults with PAH (abnormal remodeling).[3] The cause of this early failure remains unknown and understudied and explains the lack of RV-specific therapies.[1,2]

We have recently described that phosphodiesterase 5 inhibitors, such as sildenafil, may be RV-specific inotropes.[4] This theory is based on the fact that phosphodiesterase type 5 is selectively expressed in the myocardium of the hypertrophied RV but not in the LV of the same animal.[4] In the search for better RV-specific therapies, as opposed to the LV, identification of differences between the two ventricles is critical. There are several studies examining the metabolism of the LV,[5,6] but there is an impressive lack of studies on the metabolism of the RV. There is some evidence for differences between the metabolism of the RV and LV, at least in hypoxic animals.[7] Potential differences in the metabolism or molecular biology between the two ventricles are not surprising given the recent discovery that the two ventricles have a different origin at early embryogenesis of the heart; whereas the RV develops from the anterior heart field, the LV develops from the early heart tube.[8] It is therefore not appropriate to extrapolate findings or conclusions from the LV to the RV. Also, the adaptation of the RV to increased afterload may be regulated by mechanisms different from those in the LV.[9] The need to specifically study RV function and failure was recently recognized by the National Institutes of Health as a priority.[1]

In the neonatal heart, the RV is physiologically hypertrophied, in response to the high pulmonary vascular resistance in utero. However, after birth, the thickness of the RV eventually becomes only a third of that of the LV, as the pulmonary vascular resistance gradually decreases.[10] The physiologic hypertrophy in the neonatal RV might be regulated by a "fetal gene program,"[11] which might be reactivated (at whole or in part) in adult disease states. Fetal and adult cardiac hypertrophy are also characterized by a predominantly glycolytic phenotype,[5,6,12] which in the LV,[13,14] vascular biology,[15] or cancer[16] is associated with a resistance to apoptosis. This has not been studied directly in the RV. The fact that metabolism and apoptosis are both directly regulated by mitochondria[17] suggests that a potential mitochondrial and metabolic remodeling might be central to the regulation of RVH.

We hypothesized that there is a chamber-specific and dynamic mitochondrial remodeling during RVH, which might be associated with its suboptimal performance; reversal of this mitochondrial remodeling might be beneficial, improving RV function. We studied mitochondrial membrane potential, a surrogate for overall mitochondrial function and metabolism,[15-19] in human and rat hearts. We used confocal microscopy and tetramethyl–rhodamine methyl ester (TMRM), a positively charged dye that localizes at the most negative organelles in the cell, the mitochondria.[17] Mitochondrial hyperpolarization or depolarization is detected and quantified by an increase or decrease in TMRM fluorescence, respectively. We show that human and rat RVH is characterized by a dynamic increase in mitochondrial membrane potential (more hyperpolarized than that observed in the normal RV and LV) and that inhibition of this by the clinically used metabolic modulator dichloroacetate (DCA, an inhibitor of the mitochondrial pyruvate dehydrogenase kinase[20]) increases inotropy in the hypertrophied RV, but not in the normal RV. Our work has significant translational potential as DCA is being used in humans with mitochondrial diseases[21] and has recently been shown to reverse mitochondrial hyperpolarization, increase glucose oxidation, and reverse disease phenotype in both cancer[16] and PAH.[15]

Methods

Complete details are available online in the E-Supplement Methods section.

Permission from the University of Alberta committees on human ethics and animal policy and welfare was attained for all experiments on human and rat tissues, respectively.

Human Heart Tissue Samples

Human samples were acquired from patients undergoing surgery for congenital heart disease or transplantation at the University of

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