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RESEARCH REVIEW

The Right Heart and Its Distinct Mechanisms of Development, Function, and Failure[1]

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Congestive heart failure is the most common cause of hospitalization in the United States for people over the age of sixty-five. As the population ages, the morbidity and mortality from heart failure will become more prevalent. Left heart failure has been, and continues to be, extensively studied. However, a recent report from the National Heart, Lung, and Blood Institute suggests that the right heart has been relatively under-investigated, and unfortunately, most of the basic mechanisms of intracellular signaling within the right heart still remain poorly understood. Right heart failure is now being increasingly recognized as distinctly different from left heart failure, and an important mediator of overall cardiovascular collapse. The purpose of this review, therefore, is to discuss the current understanding of right heart cellular development, physiology, and pathophysiology, as well as to review therapeutic interventions that are both currently available and under investigation.

Key Words: **right heart failure; pulmonary hypertension; endotoxic shock; transplantation; right ventricular assist device; stem cell therapy.**

INTRODUCTION

Left heart disease, including left heart failure associated with ischemia and endotoxemia, has been widely studied. In contrast, right heart disease remains relatively understudied and poorly understood. This disparity has been recognized, and in a recent executive summary, the National Heart, Lung, and Blood Institute concluded that right heart failure is distinctly different from left heart failure, and is a prevalent mechanism of cardiovascular collapse [1].

Many advances have been made in the understanding of left heart disease, including characterization of left ventricular anatomy and its response to acute cardiac events. Furthermore, functional studies of the left heart concerning ischemia and reperfusion [2], transplantation [3–5], and endotoxemia [6] have provided a vast array of data for further understanding left heart disease. Gender differences associated with left heart disease [7], intracellular signaling cascades [2], and stem cell studies [8, 9] have also contributed to the advancement of this field.

Despite these innovations, cardiovascular disease remains the leading single cause of death in the United States. The prevalence of cardiac disease in the United States is approximately 33.3%, with a lifetime risk of 1 in 3 for 40 y old men, and 1 in 2 for 40 y old women. A projected $431.8 billion will be spent on cardiovascular disease and stroke in 2007 alone, with $33.2 billion being spent solely on heart failure [10]. Strategies for prevention and treatment cannot be overemphasized.

Until recently, right heart disease has been relatively understudied and underappreciated. The purpose of this review, therefore, is to provide a brief overview of the current understanding of right heart cellular development, physiology, and pathophysiology, as well as to review therapeutic interventions that are both currently available and under investigation.

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Stem cell therapy as a novel means of right heart therapy will also be examined. It is our hope that this review will point out the current lack of knowledge of right heart disease, and stimulate investigators to undertake scientific studies that focus on right heart disease and its therapy.

RIGHT VENTRICULAR CELLULAR DEVELOPMENT AND STRUCTURE

The right and left ventricles are distinctly different from each other in terms of development and anatomy. Recent studies have suggested that the heart forms from two distinctly different cell populations that separate from a common progenitor [11–13]. These progenitor cell populations are referred to as *heart fields*. The primary heart field contributes to the left ventricle (LV) and atria, while the secondary heart field contributes to the right ventricle (RV) and outflow tract. Cells from these heart fields are distinguished by specific cellular markers and transcription factors. Primary heart field cells are marked by the T-box transcription factor *Tbx5* and the bHLH transcription factor *Hand1*. Secondary heart field cells are distinguished by the presence of *Hand2*, the LIM-homeodomain transcription factor *Isl1*, and *Fgf10*. Furthermore, other cardiac genes, such as the homeobox gene *Nkx2-5*, are expressed in both heart fields, but rely on distinctly different regulatory elements for expression [14]. Different cellular markers and potentially different intracellular signaling cascades may allow right and left cardiac myocytes to respond differently in terms of functional recovery after a noxious insult.

It is also conceivable that the differences in cardiac progenitor cell origin may contribute to the structural, functional, and geometric differences between the right and left heart. The right ventricle is crescent shaped in cross-section, as compared to the elliptically shaped concentric left ventricle. Structurally, the right ventricle is thin walled, and its mass is only about 1/6 that of the left ventricle. It performs approximately 1/4 the cardiac stroke work, and must overcome the pulmonary vascular resistance which is 1/10 that of the systemic circulation [15]. The right ventricle also has a lower volume to surface area ratio, thereby making it a highly compliant chamber.

The interaction of actin and myosin complexes allows for force generation and contraction within the ventricles. The mammalian heart contains two myosin heavy chain isoforms, namely β-myosin heavy chain (expressed mainly in the ventricles), and α-myosin heavy chain (expressed mainly in the atria) [16]. Each heavy chain associates with two myosin light chains, and together, they form a single hexameric unit [17]. Multiple isoforms of these units exist, and certain isoforms have been localized to the right or left heart. For example, in *lacZ* transgenic reporting models, various genes including those coding for desmin and the ventricular specific myosin light chain MLC2V, show expression in the right ventricle and outflow tract rather than the left ventricle [18]. In the presence of cardiac stress, myosin light chains have the ability to change to isoforms that maintain lower ATPase activity and a higher economy of force production [17]. Localization of isoforms to the right or left heart may therefore allow the ventricles to adapt to specific insults, such as ischemia or volume and pressure overload.

Actin thin filaments also play a role in heart disease, although isoform localization to the right or left ventricle has not been well described. α-skeletal, α-smooth, and α-cardiac isoforms exist in cardiac tissue, with the skeletal isoform replacing the majority of the smooth isoform in adulthood [19]. Several studies have demonstrated increased α-actin mRNA transcripts in cardiac tissue after being exposed to different degrees of pressure overload [20, 21]. However, total actin content does not increase after injury, and therefore, some postulate that either actin translation is less efficient, or actin turnover is greatly increased after injury. Inadequate actin protein expression after injury may account, at least in part, for the impaired contractility and decreased ejection fraction of the ventricles after a serious cardiac insult.

RIGHT VENTRICULAR PHYSIOLOGY AND PATHOPHYSIOLOGY

The primary function of the right ventricle is to deliver deoxygenated blood to the lungs for gas exchange. The right ventricle effectively serves as a reservoir for blood returning to the heart via the right atrium, thereby optimizing venous return and providing sustained low-pressure perfusion through the lungs. To this end, the RV ejects blood somewhat continuously from the right atria to the lungs. On the contrary, the left ventricle generates high pressure pulsatile flow through arterial vessels with low compliance.

The right ventricle is anatomically adapted for the generation of sustained low-pressure perfusion. It is comprised of two anatomically and functionally different cavities, namely the sinus and the conus. The sinus generates pressure during systole and the conus regulates this pressure [15, 22–27]. The resulting effect of RV contraction is pressure generation in the sinus with a peristaltic motion that starts at the apex and moves toward the conus. The right ventricle is very compliant; thus, the peak pressure is reduced but prolonged. This physiological effect sustains ejection into the pulmonary system until the right ventricle is completely emptied.

The right and left ventricles interact throughout contraction as evidenced by previous studies on ventricular mechanics. Pressure-volume studies provided ev-