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Commentary: Major lessons from minor people: Beta blockers and cytokinesis in tetralogy of Fallot

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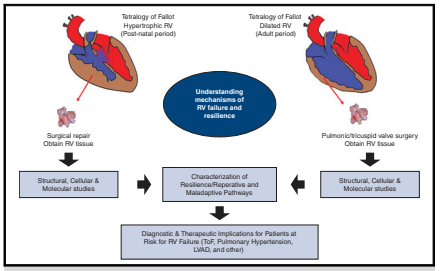

Model for advancing our understanding of mechanisms of RV failure and resilience.

Heart failure is estimated to affect more than 8 million patients in the United States. Any injury to the heart is followed by loss of cardiomyocytes. The mammalian heart has the ability to regenerate in utero following an injury. However, progressively the heart loses its regeneration capacity within the first months postnatal, with adult hearts revealing an annual regeneration capacity of no more than 1%. Even following an injury, the observed increased regeneration capacity of the heart does not compensate for the myocardial loss. The occurrence of heart failure in many cases seems like an inevitable event. Bergman[1] focuses on myocardial cytogenesis in patients with tetralogy of Fallot (ToF) with pulmonary stenosis (PS) during the early postnatal period. A study in this patient group has shown that 20% of cardiomyocytes did progress to karyokinesis (ie, division of nuclei) but failed to perform cytokinesis (ie, last stage of mitosis when the new daughter cells separate from each other).[2] Based on those findings, the proposed concept is to reduce beta-adrenergic signaling with beta blockers in an effort to promote the progression of karyokinesis to cytokinesis by upregulating *ECT2* genes. This strategy aims to provide the heart with new cardiac myocytes, improve myocardial function, and reduce the incidence of subsequent chronic heart failure. The concept of recovering myocardial function by increasing the number of myocytes is an idea that originated a long time ago.[3,4] It has been the aim of multiple preclinical and clinical studies that, in an effort to regenerate myocardium, have used various types of progenitor cells but unfortunately they have not delivered the expected results.[5]

CENTRAL MESSAGE

Tetralogy of Fallot recipients: A patient population that can teach us a lot in regard to cytokinesis, regeneration, and mechanisms of right ventricular resilience and failure.

Furthermore, a subset of patients with advanced chronic heart failure undergoing mechanical circulatory support with left ventricular assist devices can significantly improve their myocardial structure and function following several months of mechanical unloading.[6] These findings indicate that significant structural and functional improvement of a failing human heart is feasible. Basic and translational

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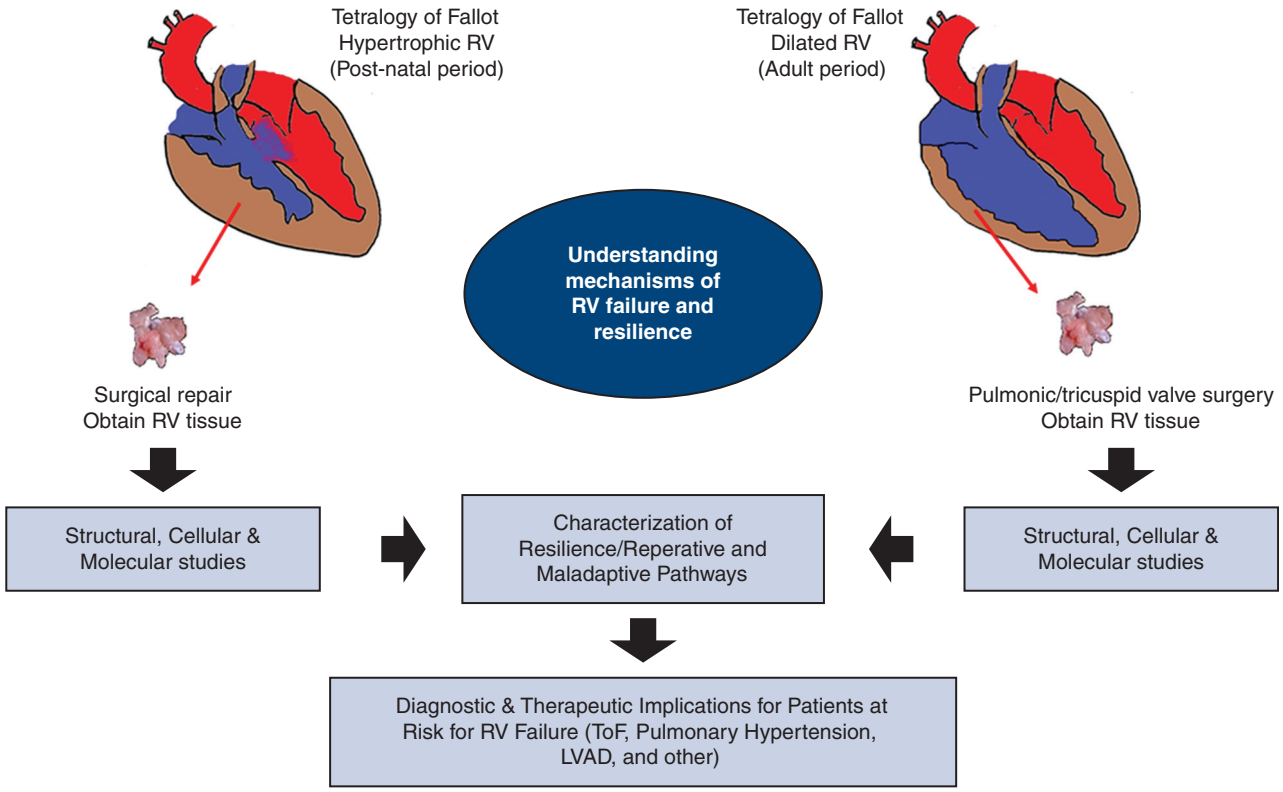

FIGURE 1. Model for advancing our understanding of mechanisms of right ventricular (*RV*) failure and resilience. *ToF*, Tetralogy of Fallot; *LVAD*, left ventricular assist device.

research aimed at uncovering the mechanisms driving the observed clinical myocardial recovery could lead to new treatments that target phylogenetically conserved pathways involved in reparative mechanisms for the left and/or right ventricles.[6] Another implication of the introduction of mechanical circulatory support as first-line therapy for clinical conditions such as acute cardiogenic shock and chronic heart failure is renewed interest in the right ventricle and how it adapts in health and disease.[7]

The ToF/PS patient population can also provide us with a unique opportunity to advance our understanding of right ventricular pathophysiological adaptations. Specifically, these patients undergo surgical correction early during their postnatal period and many of them undergo later in their life a pulmonic/tricuspid valve surgery, although at that time the right ventricle may or may not show signs of dysfunction. In the context of appropriately designed research studies, these 2 cardiothoracic surgery procedures can provide us with myocardial tissue samples at 2 consecutive time points coupled with myocardial functional phenotyping. Such studies will help us begin identifying the structural, cellular, and molecular changes that promote right ventricular resilience versus changes that drive the right ventricle to failure (Figure 1). These findings could lead to novel therapies that can be tested in ToF/PS patients but also in other patient populations with a failed or at-risk-for-failure right ventricle.

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