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EDITORIAL COMMENT

Device-Based Ventricular Reverse Remodeling

A Multimechanistic Therapeutic Strategy*

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Left ventricular (LV) mass, geometry, and architecture are prone to change in response to neurohormonal activation and physical stresses on the myocytes—a process termed *ventricular remodeling*.[1] Remodeling, which involves almost every aspect of cellular and extracellular biology, leads to progressive cavitary dilation and distortion of the normal elliptical shape of the ventricle and culminates in loss of contractility and lusitropy. Synonymous with chamber dilation due to remodeling are: 1) a rightward shift of the end-diastolic pressure-volume relationship; and 2) a reduction in the slope (i.e., end-systolic elastance [Ees]) of the end-systolic pressure-volume relationship, indicating a decline in chamber contractility. Over the years, we have come to appreciate the deleterious downstream effects of ventricular remodeling, as well as the extent to which limiting, or reversing, remodeling can lead to significant improvement in cardiovascular outcomes.[2] Thus, there have been extensive efforts dedicated toward developing therapeutic approaches that aim to reverse ventricular remodeling.

We have previously proposed 2 fundamental means by which reverse remodeling can be induced (**Figure 1**)[3]; the first is biological, and the second is physical. Biological reverse remodeling refers to the improvements in ventricular structure and function that occur in response to favorable changes in hemodynamic load or neurohormonal activation. Biological reverse remodeling can be driven by pharmacological therapies that modulate ventricular preload, afterload, or neurohormonal activity. Biological reverse remodeling can also be driven by device-based therapies that hemodynamically unload the ventricle, improve chamber contractility, or address valvular lesions (eg, aortic stenosis or mitral regurgitation). By favorably impacting hemodynamics, these biological therapies secondarily result in reductions in myocyte size, ventricular chamber size, and interstitial fibrosis. Indeed, all components of contemporary, guideline-directed optimal medical therapy for systolic heart failure (angiotensin blockers, beta-blockers, mineralocorticoid receptor antagonists, and sodium-glucose cotransporter inhibitors) share this ability to reverse remodel the LV. Generally speaking, the earlier these are applied in the disease process, the greater the degree of reverse remodeling that can be achieved. Similarly, device-based therapies such as LV assist devices, cardiac resynchronization therapy, and cardiac contractility modulation have been shown to reverse remodel the LV via direct ventricular unloading and optimization of contractility, which, secondarily, reduce neurohormonal activation.

Physical reverse remodeling, on the other hand, refers to surgical or interventional procedures that aim to directly, rather than secondarily, alter myocardial mass or ventricular geometry. The earliest of such approaches included various forms of surgical ventricular restoration, such as the Batista and Dor procedures from the 1990s, in which diseased myocardium was surgically removed or excluded, thereby restoring a more normal ventricular

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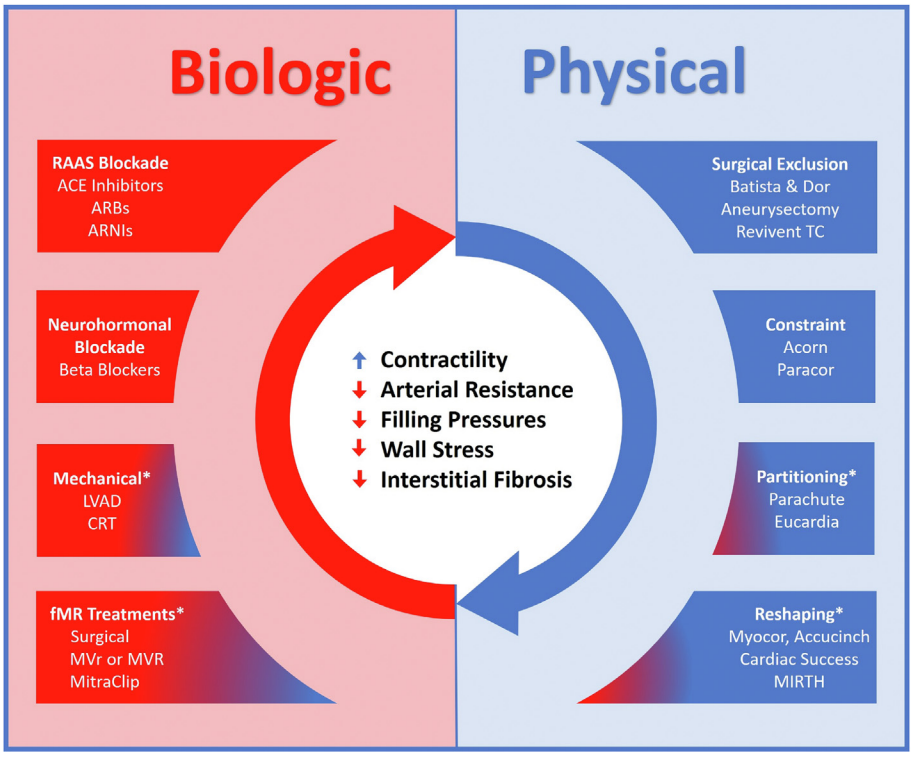
FIGURE 1 Mechanisms of Left Ventricular Reverse Remodeling



The concepts of biological and physical reverse remodeling as adapted from Brener et al.[3] Left ventricular reverse remodeling can be driven initially by biological mechanisms, as in therapies that affect the basic pathways that drive ventricular dilation. Alternatively, it may be initially driven by physical factors, as in therapies that primarily and abruptly reduce left ventricular size, geometry, or mass. The **asterisks** denote therapies that have some mechanistic overlap between physical and biological reverse remodeling. Regardless of the primary mechanism, each class of therapy has secondary effects that feed a cycle of biological and physical changes, which leads to reversal of ventricular remodeling. ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker; ARNI = angiotensin receptor–neprilysin inhibitor; CRT = cardiac resynchronization therapy; fMR = functional mitral regurgitation; LVAD = left ventricular assist device; MIRTH = Myocardial Intramural Remodeling by Transvenous Tether; MVr = mitral valve repair; MVR = mitral valve replacement; RAAS = renin-angiotensin-aldosterone system.

geometry.[4] It was learned that the impact of such procedures was highly dependent on the properties of the myocardium that was removed or excluded. Removing hypokinetic myocardium, as in the Batista procedure applied to idiopathic dilated cardiomyopathies, was detrimental, resulting in restrictive physiology and worsening of clinical outcomes. Removing akinetic myocardium, as in the Dor procedure applied to a dense infarct, was neutral both from net effects on pump function and clinical outcomes. Removing dyskinetic myocardium, as in the Dor procedure applied to an aneurysm, improves overall pump function and is believed to be associated with improved clinical outcomes. Numerous less invasive device-based LV reconstruction therapies have since emerged, which have resulted in a resurgence of interest in this approach as a treatment for heart failure. These include devices that percutaneously exclude portions of the LV, devices that constrain the entirety of the LV, or devices that reshape the LV (see Brener et al[3] for an extensive review). All of these devices remain investigational in the United States.

In this issue of *JACC: Basic to Translational Science*, Bruce et al[5] introduce a new addition to this class of therapeutic devices through a procedure called MIRTH (Myocardial Intramural Remodeling by Transvenous Tether). MIRTH involves the percutaneous implantation of a tension element circumferentially within the LV wall, which is subsequently

shortened to reduce LV diameter. Bruce et al performed MIRTH implants on 17 healthy swine and 13 swine with fibrotic myocardium secondary to ischemic cardiomyopathy. Briefly, a transvenous catheter is positioned into the coronary sinus through which a guidewire (originally intended for traversal of chronic total coronary artery occlusions) is inserted into the myocardial wall to encircle the ventricle at a predetermined basal or midventricular level. In order to navigate the guidewire within the myocardium, including scar, a novel navigational system termed EDEN (electrocardiographic radial depth navigation) was developed. By connecting the proximal guidewire to a precordial electrode, EDEN generates continuous unipolar intramyocardial electrograms that reflect relative intramyocardial depth and indicate when the MIRTH guidewire requires redirection away from the endo- or epicardial borders. Once the ventricle has been fully encircled, the guidewire is exchanged for an ultra-high-molecular-weight polyethylene braided suture to which tension is applied and the LV radius of curvature and perimeter shortened. These geometric changes are expected to reduce myocardial wall tension via Laplace's law which, in turn, could be hypothesized to induce secondary biological reverse remodeling, as has been seen with other device-based treatments.[3]

The authors are to be congratulated for developing such a novel approach using off-the-shelf equipment, designed for other purposes, and standard fluoroscopic imaging. We found it particularly remarkable that the selected guidewire can be exited from the coronary sinus into the midwall of the myocardium and advanced reliably within the myocardial midwall to encircle the chamber in a single plane. Equally impressive is the fact that the suture can be tensioned without lacerating the myocardium—a finding that was not obvious.

Beyond these technological details, several aspects of the physiological impact of the procedure were well studied. One substudy of healthy swine followed to 90 days post-MIRTH showed immediate and sustained reductions in LV systolic and diastolic diameters. However, while LV end-systolic and end-diastolic volumes declined immediately post-MIRTH by 12% and 16%, respectively, these changes did not persist at 90 days. The discrepancy between diameter- and volume-based measurements of LV size requires further exploration.

Equally interesting, LV pressure-volume loop measurements were used to study the acute dose response to varying degrees of cinching. At 9% shortening in cardiomyopathic ventricles, there was a decrease in Ees and in ventricular mechanical efficiency (the ratio of stroke work to total pressure-volume area) compared with baseline. However, at 18% shortening, there were increases in Ees, preload recruitable stroke work (another load independent measure of contractility), and mechanical efficiency. Further increases in percent shortening led to deteriorations in Ees, preload recruitable stroke work, and mechanical efficiency, with concomitant rises in LV end-diastolic pressure. Accordingly, the authors propose a 17% to 20% MIRTH circumferential shortening in cardiomyopathic ventricles as the optimum range to achieve the best improvements in myocardial performance.

Several of the study limitations were highlighted by the authors. Most notably, longer-term follow-up data on animals with heart failure treated with MIRTH are pending. The effects on volumes and contractility, as well as additional safety data, will help inform the potential clinical applicability of this form of therapy. The optimal degree of shortening requires confirmation in human hearts. One important question faced by the investigators is whether clinical studies should proceed with already available devices or whether specialized and formally tested tools should be developed. The latter would ensure proper testing of all aspects of the device and procedure to provide the maximum assurance of safety.

In our expanding era of device-based heart failure therapeutics, MIRTH emerges as a new concept that has the potential to physically reverse remodel the LV and induce additional biological reverse remodeling. Significant questions about this approach, and others under development, remain unanswered, including the long-term structural, hemodynamic, and functional impact on cardiomyopathic ventricles; whether a sustained improvement in the neurohormonal milieu can be elicited; and whether this is reflected in favorable changes at the cardiomyocyte level, akin to what has been observed with LV assist devices.[1] Finally, it will be important to evaluate the hemodynamic effects of these devices not only at rest, but also during exercise. If biological reverse remodeling does occur, increases in beta-adrenergic receptor density, with concomitant enhanced inotropic responsiveness during exercise, would be expected. Developing minimally invasive device-based therapies with these capabilities would contribute to a significant unmet need for an ever-growing heart failure population.

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