Reverse Remodeling

The term “reverse remodeling” was first used to describe the leftward shift in the LV end-diastolic pressure-volume curve of the failing heart following hemodynamic unloading with a ventricular assist device (LVAD) or a myocardial wrap with latissimus dorsi muscle (1, 2). An important feature of the decrease in LV size with reverse remodeling is that the change in LV geometry persisted even if the inciting therapy was abruptly stopped, suggesting that the change in properties reflected intrinsic biological changes in the LV chamber as opposed to changes in LV volume that occur simply in response to a decrease in LV filling pressure. As shown in Figure 1, reverse remodeling has been observed in a wide variety of clinical settings, even when the severity of heart failure is quite severe, including viral myocarditis, post-partum cardiomyopathy or after removal of a cytotoxic agent. There is also extensive clinical trial-based evidence supporting the potential for reverse remodeling in patients with chronic heart failure who have received device-based, and surgical interventions (reviewed in references (3) and (4)). A recurring observation in all these clinical studies/observations is that reverse remodeling is associated with an improvement in the clinical manifestations and outcomes in heart failure, raising the interesting possibility that reverse remodeling is linked mechanistically to the observed improved heart failure outcomes.
Although the precise cellular and molecular mechanisms that are responsible for the return towards normal LV size and shape during reverse remodeling are not completely understood, there is a fairly consistent biological theme with respect to the parameters that return towards baseline following pharmacological or device therapy. As shown in Table 2, there are a series of favorable changes in cardiac myocyte biology, the composition of the myocardium and the chamber properties of the LV following pharmacologic and device therapies that lead to reverse remodeling. With respect to the changes that occur in cardiac myocyte biology, clinical studies from patients undergoing LVAD implantation (5) (6-10), cardiac resynchronization therapy (11) or cardiac contractility modulation (12, 13) have consistently shown a decrease in cardiac myocyte hypertrophy. The morphological changes in cardiac myocyte size are accompanied by changes in gene expression, including reversal of the abnormal fetal gene program, genes involved in sarcomerogenesis, β-adrenergic signaling, the cytoskeleton and/or return of excitation contraction coupling genes towards expression levels observed in non-failing hearts from patients treated with beta-blockers (14, 15), ventricular assist devices (16, 17), and in cardiac resynchronization therapy (CRT) (18, 19). The decrease in cardiac myocyte cell size following LVAD support is accompanied by changes in the proteome as well, including changes in activation and/or activity levels of protein kinases linked to cell growth, including extracellular regulated kinase-1 (Erk-1) and Erk-2 and p38 (20), whereas activation/activity levels of Akt and GSK-3β (a negative regulator of hypertrophy) are unchanged (10). Treatment with beta-blockers and LVAD support results in decreased hyperphosphorylation of the ryanodine receptor (21, 22), which has been implicated in calcium leak from the SR in failing hearts, and hence contractile dysfunction. Normalization of β-adrenergic receptor density and enhanced inotropic responsiveness to isoproterenol have been
demonstrated in LVAD-supported failing hearts. (23-25) Similar findings have been observed following CRT (26). Lastly, hemodynamic unloading with LVAD support results in restoration of more normal levels of sarcomeric proteins (27), and cytoskeletal proteins and organization (28, 29). Collectively the above genomic and proteomic changes would be expected to lead to functional improvements in the failing cardiac myocyte. And indeed, there is a significant increase in contractility (maximal calcium saturated force generation) in cardiac myocytes isolated from hearts that have undergone LVAD support, when compared to myocytes isolated prior to LVAD support (30).

In addition to the changes in the biology of the adult cardiac myocyte that occur during reverse remodeling, there are a number of important changes that occur within the myocardium, including changes in the extracellular matrix, as well in microvascular density (angiogenesis). Intuitively, restoration of ECM content and organization would appear to be critical with respect to facilitating the normalization of LV structure and function following LVAD support. Unfortunately, there is very limited information on this complex topic, and what little information exists is largely phenomenological in nature. Even at the phenomenological level, there was controversy initially concerning the simple question of how total collagen content changes during LVAD support. Some groups reported a decrease in total collagen (31-33), while other groups reported an increase (34-39). One potential resolution to the controversy came with recognition that collagen content decreased in patients taking ACE-inhibitors and increased in patients not taking ACE-inhibitors (40), consistent with prior observations that tissue levels of angiotensin II, a pro-fibrotic peptide, were increased in patients supported with LVADs.

Myocardial microvasculatry density is reduced in heart failure, and has been implicated
in contractile dysfunction and cardiac remodeling in heart failure. Although morphological and functional data are relatively limited, the extant literature suggests that hemodynamic unloading leads to upregulation of angiogenesis related genes (41) and increased microvascular density (42). However, the functional significance of these findings is unclear given that coronary flow reserve remains impaired following LVAD support (43).

Finally, improvements in the LV end-diastolic pressure-volume relation (EDPVR) seen with therapies that induce reverse remodeling do not necessarily equate with improvements in all aspects of the complex structure of the ventricular chamber. For example, it has been shown that while significant improvements can be detected in the EDPVR following as little as ~30 days of support, these changes occur without any appreciable change in the ratio between chamber radius and wall thickness (r/h ratio) (44).
<table>
<thead>
<tr>
<th>Study year</th>
<th>Design</th>
<th>N</th>
<th>Adjuvant antiremodeling drug protocol</th>
<th>Protocol for monitoring cardiac function</th>
<th>Unloading duration (m)</th>
<th>Recovery overall [N (%)]</th>
<th>Recovery nonischemic [N (%)]</th>
<th>HF recurrence/follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>US multicenter, 2007(45)</td>
<td>P</td>
<td>67</td>
<td>Not standardized</td>
<td>YES</td>
<td>4.5</td>
<td>6(9)</td>
<td>5(13.5)</td>
<td>Freedom from death or Tx 100%/6 months Freedom from recurrent HF 74 and 66%/3 and 5 years, respectively Freedom from recurrent HF 100% and 89%/1 and 4 years, respectively</td>
</tr>
<tr>
<td>Berlin Group, 2008, (46, 47)</td>
<td>R</td>
<td>188</td>
<td>Not standardized</td>
<td>YES</td>
<td>4.3</td>
<td>35 (18.6)</td>
<td>35 (18.6)</td>
<td>Freedom from recurrent HF 74 and 66%/3 and 5 years, respectively Freedom from recurrent HF 100% and 89%/1 and 4 years, respectively</td>
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<tr>
<td>Harefield Group, 2006 (48)</td>
<td>P</td>
<td>15</td>
<td>Yes</td>
<td>YES</td>
<td>10.6</td>
<td>11 (73)</td>
<td>11 (73)</td>
<td>Freedom from recurrent HF 74 and 66%/3 and 5 years, respectively Freedom from recurrent HF 100% and 89%/1 and 4 years, respectively</td>
</tr>
<tr>
<td>Harefield Group, 2011 (49)</td>
<td>P</td>
<td>20</td>
<td>Yes</td>
<td>YES</td>
<td>9.5</td>
<td>12 (60)</td>
<td>12 (60)</td>
<td>Freedom from recurrent HF 83.3%/3 years Freedom from recurrent HF 100%/2 years</td>
</tr>
<tr>
<td>University of Athens-Harefield Group, (50, 51)</td>
<td>P</td>
<td>8</td>
<td>Yes</td>
<td>YES</td>
<td>6–10</td>
<td>4*(50)</td>
<td>4*(50)</td>
<td>Freedom from recurrent HF 100%/2 years</td>
</tr>
<tr>
<td>Gothenburg Group, 2006 (52)</td>
<td>P</td>
<td>18</td>
<td>Not standardized</td>
<td>YES</td>
<td>6.7</td>
<td>3 (17)</td>
<td>3 (20)</td>
<td>Freedom from recurrent HF or Tx 33%/8 years Freedom from recurrent HF 67%/1 year</td>
</tr>
<tr>
<td>Pittsburgh Group, 2003 (53)</td>
<td>R</td>
<td>18</td>
<td>Not standardized</td>
<td>YES</td>
<td>7.8</td>
<td>6 (33)</td>
<td>5 (38)</td>
<td>Freedom from recurrent HF 74 and 66%/3 and 5 years, respectively Freedom from recurrent HF 100%/8 to 29 months Freedom from recurrent HF or death 71.4%/5 years</td>
</tr>
<tr>
<td>Osaka Group, 2005 (37)</td>
<td>R</td>
<td>11</td>
<td>Not standardized</td>
<td>N/A</td>
<td>15.1</td>
<td>5 (45)</td>
<td>5 (45)</td>
<td>Freedom from recurrent HF or death 71.4%/5 years Freedom from recurrent HF 74 and 66%/3 and 5 years, respectively Freedom from recurrent HF 100%/8 to 29 months Freedom from recurrent HF or death 71.4%/5 years</td>
</tr>
<tr>
<td>Pittsburgh Group, 2010(54)</td>
<td>R</td>
<td>102</td>
<td>N/A</td>
<td>N/A</td>
<td>4.9</td>
<td>14 (13.7)</td>
<td>14 (13.7)</td>
<td>Freedom from recurrent HF or death 71.4%/5 years Freedom from recurrent HF 74 and 66%/3 and 5 years, respectively Freedom from recurrent HF 100%/8 to 29 months Freedom from recurrent HF or death 71.4%/5 years</td>
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<tr>
<td>Multicenter, 2001 (55)</td>
<td>R</td>
<td>271</td>
<td>N/A</td>
<td>N/A</td>
<td>1.9</td>
<td>22(8.1)</td>
<td>22(8.1)</td>
<td>Freedom from recurrent HF or death 77%/3.2 years Freedom from recurrent HF or death 20%/15 months</td>
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<tr>
<td>Columbia Group, 1998(56)</td>
<td>R</td>
<td>111</td>
<td>N/A</td>
<td>N/A</td>
<td>6.2</td>
<td>5(4.5)</td>
<td>4 (8)</td>
<td>Freedom from recurrent HF or death 77%/3.2 years Freedom from recurrent HF or death 20%/15 months</td>
</tr>
</tbody>
</table>

HF, heart failure; m, months; N, number; N/A, not applicable; P, prospective studies; R, retrospective studies; Tx, transplant. ‘A fifth patient fulfilled recovery criteria (5/8, 62.5%) but died of stroke just before LVAD explantation.

Modified from reference (57)
REFERENCES


44. Barbone A, Oz MC, Burkhoff D, Holmes JW. Normalized diastolic properties after left ventricular assist result from reverse remodeling of chamber geometry. Circulation 2001; 104:I229-I232.


