EDITORIAL COMMENT

Ventricular Unloading, Tissue Angiotensin II, Matrix Modulation, and Function During Left Ventricular Assist Device Support*

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Heart failure (HF) has become the major epidemic of the new millennium, and use of the left ventricular (LV) assist device (LVAD) for mechanical support in end-stage HF is increasing. Introduced as an alternative to heart transplantation, LVADs were approved by the Food and Drug Administration a decade ago to provide a bridge to transplantation in the moribund end-stage HF patient waiting for a donor heart. However, LVAD is now becoming a life-saving treatment option for patients with severe HF refractory to optimal medical therapy that includes renin-angiotensin-aldosterone system (RAAS) inhibitors, beta-adrenergic blockers, inotropes, and diuretics. The REMATCH (Randomized Evaluation of Mechanical Assistance for the treatment of Congestive Heart Failure) trial in 129 patients established the efficacy of LVAD as a new long-term myocardial replacement therapy for end-stage HF (1). Compared to medical therapy, LVAD support doubled survival at 1 year (from 25% to 52%) and tripled it at 2 years (from 8% to 23%) and improved functional status and quality of life, but there were adverse events (1). Interestingly, in the 91 inotrope-dependent REMATCH patients, LVAD doubled survival at 1 year (from 24% to 49%) and 2 years (from 11% to 28%) (2). These findings broadened the use of LVADs to include inotrope-dependent and transplant-ineligible patients. New generations of compact, implantable LVADs are being considered as alternative therapy for severe chronic and refractory HF. Although LVAD support as a bridge to recovery may be possible in some patients, LV recovery and successful LVAD explantation is the exception rather than the rule.

Traditional concepts of matrix modulation and adverse remodeling in HF. On the basis of collective knowledge (3), 4 points merit emphasis. First, cardiac remodeling is a key determinant of outcome in HF, and remodeling of the extracellular collagen matrix (ECCM) plays a critical role in adverse LV remodeling and dysfunction in chronic HF.

Second, end-stage HF is associated with adverse cardiac remodeling involving LV dilation, eccentric hypertrophy, shape change from elliptical to spherical, significant interstitial fibrosis and increase in ECCM, and LV systolic and diastolic dysfunction. Notably, altered fibroblast function, with increased production of ECCM and other proteins, such as matrix metalloproteinases (MMPs) that degrade ECCM, and impaired fibroblast/cardiomyocyte interaction contribute to LV structural remodeling and dysfunction. The main fibrillar collagens of the ECCM are types I and III, and the type I/III ratio is increased in dilated cardiomyopathy. Increased collagen type I and cross-linking associated with fibrosis cause LV stiffening and impaired contraction and relaxation, whereas newly synthesized collagen type III, being immature, contributes to LV dilation.

Third, up-regulation of the RAAS and other neurohumoral systems plays an important role in the modulation of myocardial and ECCM remodeling and progression to end-stage HF. Circulating or tissue angiotensin II (AngII), aldosterone, norepinephrine, endothelin, vasopressin, and other cytokines all contribute to adverse LV remodeling and dysfunction. However, AngII and transforming growth factor (TGF)-beta1 are among the important regulators of cardiac fibrosis.

Fourth, an imbalance between MMPs and tissue inhibitors of MMPs (TIMPs) drives adverse ECCM and LV remodeling. In HF, increased MMP-1, -2, and -9 and decreased TIMP-1, -2, and -3 have been implicated in adverse ECCM and LV remodeling, and the MMP-1/TIMP-1 or MMP-9/TIMP-3 ratio modulate ECCM turnover. LV unloading, ECCM, and function. The traditional concept is that increased load leads to increased wall stress and stretch, increased AngII, hypertrophy, and increased collagen (content, type I, and cross-linking) and stiffness, resulting in diastolic and systolic dysfunction. Conversely, decreased load would be expected to decrease AngII, hypertrophy, and collagen and stiffness and improve diastolic and systolic function.

However, there are exceptions. Cumulative evidence indicates that AngII stimulates different signaling pathways in cardiomyocytes and fibroblasts (4). Cardiomyocyte hypertrophy is primarily load-dependent, whereas fibroblast growth is primarily load-independent, and RAAS activation

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is the major stimulus for fibrosis rather than load. Not surprisingly, RAAS inhibition with angiotensin-converting enzyme (ACE) inhibitors (ACE-Is), AngII type 1 receptor antagonists, or aldosterone antagonists inhibits myocardial fibrosis and decreases ECCM.

Consistent with the “decrease load → decrease hypertrophy” paradigm, mechanical LV unloading with the LVAD normalizes the diastolic properties of hearts with end-stage HF and results in a reversal of adverse remodeling. This is evidenced by an improved LV passive end-diastolic pressure-volume relation, regression of LV hypertrophy, and a trend toward improved cardiomyocyte function, calcium cycling, and gene expression.

Despite improved LV size and myocardial mechanics, energetics, morphology, and cell signaling during LVAD use, ECCM remodeling is not reversed. This apparent disconnect or paradox is not surprising if one considers that fibroblast function is mostly load-independent. In fact, Klotz et al. (5) showed that LVAD use in 16 patients paradoxically increased LV collagen cross-linking, collagen type I/III ratio and stiffness, normalized tissue MMP-1/TIMP-1 ratio (i.e., decreased ECCM degradation), and increased tissue AngII (i.e., stimulating ECCM synthesis). Recently, Bruggink et al. (6) showed that reverse remodeling of the ECCM during LVAD use is biphasic, with an increase in collagen volume fraction over the first 200 days, a decline between 200 and 400 days, and normalization after 400 days, and these changes paralleled those in type I and type III collagen turnover.

Another apparent paradox with LVAD use is that sufficient recovery to allow explantation is rarely achieved. Whether this is due to persistent adverse ECCM remodeling and can be reversed with combination therapy is not known.

**ACE inhibition and the ECCM.** Angiotensin-converting enzyme inhibitors are widely used for chronic therapy of HF. Collective evidence indicates that ACE-Is effectively decrease ECCM and fibrosis by at least 5 mechanisms (3,7,8) (Table 1). However, partial escape of the RAAS during ACE-I therapy leads to normalization of AngII levels, partly owing to AngII production via alternative pathways, thereby providing rationale for adding AngII type 1 receptor antagonists and aldosterone antagonists.

### Table 1 Five Mechanisms for Antifibrotic Effects of ACE-Is

<table>
<thead>
<tr>
<th>Mechanism</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACE inhibition</td>
<td>decrease AngII formation (3,5)</td>
</tr>
<tr>
<td>Kininase II inhibition</td>
<td>increase bradykinin (3,5)</td>
</tr>
<tr>
<td>Alter MMP/TIMP balance</td>
<td>decrease MMP activity (3,5)</td>
</tr>
<tr>
<td>Inhibition of Ang-(1-7) metabolism</td>
<td>increase Ang-(1-7) and increase Ang I (8)</td>
</tr>
<tr>
<td>Inhibition of Ac-SDKP hydrolysis</td>
<td>∆ fibroblast proliferation, ∆ TGF-β (7)</td>
</tr>
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Reference number is provided in parentheses at the end of each entry.

**LV unloading and function: apparent paradoxes during LVAD.** In this issue of the Journal, Klotz et al. (9) report that ACE inhibition during LVAD use decreased tissue AngII, total and cross-linked collagen and LV stiffness, and normalized the MMP-1/TIMP-1 ratio in 7 end-stage HF patients relative to 15 control patients. In the right ventricle (RV), ACE-Is decreased AngII and normalized the MMP-1/TIMP-1 ratio but not collagen, mass, or size. The ACE-Is shifted the LV ex vivo end-diastolic pressure-volume relation to the left and decreased LV mass but did not improve myocardial force generation in isolated trabeculae. Although that study was small, retrospective, and observational, the finding that ACE-I therapy prevents the increase in LV tissue AngII, and that adverse ECCM and LV remodeling during prolonged LVAD use is provocative, has potential for clinical application and deserves confirmation in a larger, adequately powered trial. The findings with ACE inhibition in the RV are also provocative. The suggestion that both unloading and ACE inhibition are needed to decrease RV collagen and mass (and presumably to normalize the MMP-1/TIMP-1 ratio) in these patients is important and requires verification in other settings.

Several additional features in the study by Klotz et al. (9) deserve comment. First, the finding that increased tissue AngII is associated with increased cross-linked collagen and myocardial stiffness is consistent with the traditional concept. However, that this should occur during prolonged mechanical unloading with LVAD over a mean of 96 days is intriguing and contrary to the traditional concept. Klotz et al. (9) explains this paradox by suggesting that concomitant decrease in load and tissue AngII is essential for preventing fibrosis. This explanation needs to be reconciled with the fact that prolonged ACE inhibition may increase circulating and tissue AngII levels in patients with HF. Moreover, ACE-I–induced increase in bradykinin and normalization of the MMP-1/TIMP-1 ratio (Table 1) may contribute to reverse ECCM remodeling.

Second, although Bruggink et al. (6) also reported adverse ECCM remodeling during LVAD use, they found that LVAD has a biphasic effect on collagen volume, with an increase over the first 200 days and a decrease followed by normalization thereafter. They also noted that ACE-Is did not affect collagen volume after LVAD. This discordance suggests that larger groups of patients need to be studied for longer periods.

Third, 2 important limitations of the study by Klotz et al. (9) are that they did not measure changes in: 1) the fibrogenic cytokine TGF-β1; and 2) in vivo systolic function or diastolic function or LV remodeling by 2-dimensional (2D) echocardiography and tissue Doppler imaging or other modalities.

**Future direction.** Targeting the ECCM with combination therapy during LVAD may improve LV functional recovery and outcome in patients with end-stage HF. The concept that adjunctive therapies might improve outcome and allow successful weaning from LVADs deserves to be tested in a
large, adequately powered, multicenter, randomized clinical trial that includes serial measurements of systolic and diastolic function by 2D echocardiography/tissue Doppler imaging. Some potentially successful combination strategies that may be tested for maximizing reverse ECCM and LV remodeling and optimizing functional recovery during LVAD support are shown in Figure 1. These may well increase the likelihood of successful weaning of some patients from LVADs, as demonstrated with use of the beta$_2$-adrenergic agonist clenbuterol (10). It may also become possible to use molecular markers for identifying responders to the adjunctive pharmacotherapies.

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REFERENCES