REVIEW

Myocardial Recovery and the Failing Heart: Medical, Device and Mechanical Methods

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ABSTRACT

Background: Cardiac remodeling describes the molecular, cellular, and interstitial changes that cause the ventricle to develop pathologic geometry as heart failure progresses. Reverse remodeling, or the healing of a failing heart, leads to improved mortality and quality of life.

Findings: Therapies that lead to reverse remodeling include medications such as β-blockers and angiotensin-converting enzyme inhibitors; cardiac resynchronization therapy with biventricular pacing; and mechanical support with left ventricular assist devices.

Conclusions: Further study is needed to better predict which patients will benefit most from these therapies and will then go on to experience reverse remodeling and myocardial recovery.

Key Words: cardiac remodeling, congestive heart failure, left ventricular dysfunction, myocardial recovery, reverse remodeling, ventricular assist devices

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INTRODUCTION

Reverse remodeling of the heart was first described in 1995, when 3 patients with dilated cardiomyopathy were treated with cardiomyoplasty: The latissimus dorsi muscle was mobilized and then wrapped around both ventricles to provide mechanical support.[1] Postprocedure improvements in end-systolic volume (ESV) and end-diastolic volume (EDV) prompted the question of whether this surgical procedure could be reversing the remodeling of heart failure.[1] It was already known that the remodeling of peripartum cardiomyopathy and myocarditis were reversible in some patients.[2,3] If remodeling can be reversed, can it be reversed so completely that myocardial recovery is feasible in dilated cardiomyopathy?

CARDIAC REMODELING

Left ventricular remodeling describes the molecular, cellular, and interstitial changes that manifest clinically as changes in size, shape, and function of the heart.[2] As heart failure progresses, left ventricular EDV and ESV gradually increase, ventricular walls thin, and the ventricle becomes less conical or elongated and more spherical.[4-6] The ejection fraction (EF) steadily decreases. Although early reports of pathological remodeling described the left ventricle after myocardial infarction, where the infarcted area becomes thin and dilated,[7] both ischemic and nonischemic cardiomyopathies share common mechanisms.[4,5,8]

On a cellular level, a prominent feature of the remodeling heart is cardiomyocyte hypertrophy. There are also changes in calcium handling, including impaired function of the calcium ATPase pump sarco/endoplasmic reticulum Ca2 (SERCA2a), increased calcium leak through ryanodine receptor channels resulting in decreased calcium, and reduced contractile force. Changes in the extracellular matrix include collagen formation, which leads to fibrosis, and activation of matrix metalloproteinases, which enhance matrix turnover and contribute to ventricular dilatation.[4,9]

REVERSE REMODELING

Reverse remodeling is effectively the healing of a previously failing heart, characterized by the phenotype of decreased ventricular mass and volume, decreased wall thickness, and increases in EF. Heart failure therapies that are associated with positive clinical outcomes, like improved mortality or quality of life, also have been associated with reverse remodeling. These therapies include medications, cardiac resynchronization therapy

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Table 1. Medical Therapy and Reverse Remodeling

Study	Patient population	Placebo	Drug
Enalapril in SOLVD[11]	LVEF ≤35%	N = 25 (changes at 1 y)	N = 31 (changes at 1 y)
		EDV +15	EDV -13
		136 to 151 mL/m^2	140 to 127 mL/m^2
		ESV +13	ESV -13
		103 to 116 mL/m^2	106 to 93 mL/m^2
		LVEF -1%	LVEF +4%
		25% to 24%	25% to 29%
Carvedilol[12]	NYHA II-III	N = 17 (changes at 4 mo)	N = 21 (changes at 4 mo)
	Ischemic or nonischemic	LV thickness +0.8 cm	LV thickness -0.9 cm
	LVEF <35%	1.33 to 1.41 cm	1.31 to 1.22 cm
		LV mass +39 g	LV mass -29 g
		301 to 340 g	276 to 247 g
		LVEF +1%	LVEF +10%
		19% to 20%	21 to 31%
in the Australia-New Zealand Carvedilol Trial[13]	NYHA II-III	N = 60 (changes at 1 y)	N = 63 (changes at 1 y)
	LVEF <45%	LVEDVI +10.5 mL/m^2	LVEDVI -4.6 mL/m^2
		95.7 to 106	100.2 to 95.6
		LVESVI +8.2 mL/m^2	LVESVI -7.9 mL/m^2
		68.2 to 76.4	72.9 to 65
		LVEF -1.2%	LVEF +5.5%
		30.4% to 29.2%	28.6% to 34.1%
Metoprolol XL in MERIT-HF[16]	NYHA II-IV	N = 22 (changes at 6 mo)	N = 19 (changes at 6 mo)
	LVEF ≤40%	LVEDVI +2 mL/m^2	LVEDVI -24 mL/m^2
		156 to 158	150 to 126
		LVESVI +2 mL/m^2	LVESVI -26.4 mL/m^2
		111 to 113	107 to 80.6
		LVEF +1%	LVEF +8%
		32% to 33%	29% to 37%

EDV, end-diastolic volume; ESV, end-systolic volume; LV, left ventricular; LVEDVI, left ventricular end-diastolic volume index; LVEF, left ventricular ejection fraction; LVESI, left ventricular end-systolic volume index; MERIT-HF, Metoprolol CR/XL Randomized Intervention Trial in Congestive Heart Failure; NYHA, New York Heart Association; SOLVD, Studies of Left Ventricular Dysfunction.

(CRT) with biventricular pacing, and mechanical support with left ventricular assist devices (LVADs).

MEDICATIONS AND REVERSE REMODELING

Neurohormonal antagonists have a clear mortality and morbidity benefit in the treatment of systolic heart failure. Treatment with angiotensin-converting enzyme (ACE) inhibitors, β-blockers, and angiotensin receptor blockers (ARBs) has led to improvements in myocardial dimensions and up to an 11% improvement in EF.

ACE Inhibitors and Reverse Remodeling

In the Studies of Left Ventricular Dysfunction (SOLVD) trial, 2569 patients were randomized to enalapril or placebo with a mean follow-up of 41 months.[10] A subset of 56 patients was followed with serial radionuclide ventriculograms to assess changes in ventricular volume and function. At 1 year, (see Table 1) EDV and ESV increased in the placebo group and decreased in the enalapril group. EF improved in the enalapril group.[11]

β-Blockers and Reverse Remodeling

Carvedilol improves left ventricular geometry, including reductions in wall thickness, mass, and volume, with an improvement in EF (Table 1).[12,13] Of note, the majority of patients in these β-blocker trials were already taking ACE inhibitors.

In one study, patients whose left ventricular EF improved with β-blocker therapy had changes in gene expression that reflected reverse remodeling, specifically an increase in *SERCA* ATPase mRNA and β-myosin heavy-chain mRNA and a decrease in β-myosin heavy-chain mRNA.[14]

ARBs and Reverse Remodeling

In the Valsartan Heart Failure (Val-HeFT) trial with 5010 patients with New York Heart Association class

II-IV heart failure, the left ventricular internal diastolic diameter decreased more in the valsartan group, and EF increased by 4.5% (vs an increase of 3.2%). However, the changes of reverse remodeling were only significant in patients who were already taking β-blockers or ACE inhibitors. In patients who were already taking a combination of β-blocker and ACE inhibitor, the changes in left ventricular size and EF were not different in the valsartan and placebo arms.[15]

CRT AND REVERSE REMODELING

Ventricular dyssynchrony due to intraventricular conduction delay or left bundle-branch block reduces the efficiency of ventricular contraction, and is associated with worsening heart failure and worse outcomes.[17] CRT simultaneously paces both ventricles, resulting in more effective ventricular contraction.[4,18] Restoring synchrony also decreases left ventricular mass and volume, and improves EF (Table 2). Patients who respond to CRT are more likely to have nonischemic dilated cardiomyopathy.[9]

CARDIAC SUPPORT DEVICES AND REVERSE REMODELING

The Acorn CorCap cardiac support device is a polyester mesh device fitted around the ventricles to provide circumferential diastolic support. This device reversed remodeling in animal models. Of the 50 patients who completed 5 years of follow-up, 98% were taking an ACE inhibitor or ARB and 96% were taking a β-blocker.[23] After 5 years of follow-up, the 29 patients who received the Acorn support device experienced a decrease in left ventricular EDV of 28.9 mL (10.6%) and a decrease in ESV of 21.9 mL compared with 21 patients in the control group. EF did not change.

VENTRICULAR-ASSIST DEVICES AND REVERSE REMODELING

A review of the effects of optimal medical therapy and CRT in patients with dyssynchrony clearly shows the potential for some reversibility in heart failure. Logically, use of a ventricular-assist device (VAD), which unloads the ventricle both in terms of pressure and volume, should lead to even greater reverse remodeling. VADs also improve cardiac output and perfusion.

In fact, mechanical support with a VAD may lead to decreased myocardial collagen,[24] which is consistent with decreased fibrosis, regression of myocyte hypertrophy (decreased myocyte volume, cell length, cell width, and cell length-to-thickness ratio),[25] improved myocyte contractility,[26] and changes in gene expression related to myocyte metabolism and apoptosis.[26,27] It is not clear how much of these cellular and molecular effects are due to mechanical unloading versus changes in neurohormones or circulating cytokines.

VENTRICULAR-ASSIST DEVICES AND MYOCARDIAL RECOVERY

Myocardial recovery means that normalization of the molecular, cellular, myocardial, and left ventricular geometric changes that provoked cardiac remodeling, has occurred. This would allow the heart to maintain structure and function regardless of hemodynamic or loading changes.[28] Support with VADs has permitted sufficient reverse remodeling for recovery to occur, followed by VAD explantation.

Early reports showed only small numbers of patient with LVAD recovered: 5 of 111 in one series before the more widespread use of ACE inhibitors and β-blockers.[29] In another series of patients with nonischemic cardiomyopathy and high levels of ACE inhibitor and β-blocker use, 23 patients underwent VAD explantation. In the cohort that had VADs explanted, EF increased from a mean of 16% to 46% at explantation. Of the 23 patients, 13 recovered post-explantation. They had a shorter history of heart failure and a more profound recovery during mechanical support, and continued to function without mechanical support after 2 years.[30] In another group with nonischemic cardiomyopathy, 5 of 17 patients were explanted, one after more than 2 years of mechanical support with a VAD.[31]

With VADs increasingly used as a "bridge to recovery," there is a new focus on optimizing medical therapy during mechanical support to facilitate recovery. Clenbuterol is a selective β-agonist that is used in Canada and Europe, but is not approved for use in the United States.[32,33] Clenbuterol has been shown in animal studies to reduce ventricular remodeling. The drug also causes mild hypertrophy, which minimizes the myocardial atrophy that may develop on prolonged mechanical support.

To evaluate the combination of maximal medical therapy and mechanical support, 15 patients with nonischemic cardiomyopathy were treated with aggressive medical therapy during the period of LVAD support. Once the patients were weaned off of inotropes, they were treated with lisinopril titrated to 40 mg daily, carvedilol titrated to 50 mg twice daily, spironolactone titrated to 25 mg daily, and losartan titrated to 100 mg daily. They were followed with serial echocardiograms to identify when maximal regression of the left ventricular end-diastolic diameter was reached and maintained for 2 weeks. At that time, clenbuterol was added to the medication regimen, and carvedilol was switched to the β1 selective β-blocker bisoprolol.[33] Eleven of 15 patients had sufficient myocardial recovery to undergo explantation without transplantation, and their EF increased

Table 2. CRT and Reverse Remodeling

Study	Patient population	Control	CRT
MADIT-CRT (2010)[19]	N = 1372 NYHA I-II LVEF ≤30% QRS ≥130 msec Medications 77% ACE inhibitors 93% β-blockers 32% Aldo antagonist 21% ARB	N = 623 LVEDVI -7.4 mL/m^2 LVESVI -9.1 mL/m^2 LVEF +3% LA volume index -4.7 mL/m^2	N = 749 LVEDVI -26.2 mL/m^2 LVESVI -28.7 mL/m^2 LVEF +11% LA volume index -11.9 mL/m^2
CARE-HF (2005)[20]	N = 813 NYHA III-IV LVEF ≤35% LVEDD ≥30 mm QRS ≥120 msec Medications 95% ACE inhibitors 74% β-blockers 59% Spironolactone	N = 404	N = 409 (changes at 18 mo) LVESV -26 LVEF +6.9%
CONTAK CD (2003)[21]	N = 490 NYHA II- IV LVEF ≤35% QRS ≥120 ms Medications 88% ACE inhibitors or ARBs 47% β-blockers	N = 245 (changes at 6 mo) LVEDD -0.3 mm LVESD -0.7 mm LVEF +2.8%	N = 245 (changes at 6 mo) LVEDD -3.4 mm LVESD -4.0 mm LVEF +5.1%
MIRACLE (2003)[18]	N = 323 NYHA III-IV LVEF <35% QRS >130 ms; LVEDV >55 mm Medications 94% ACE inhibitors or ARBs 59% β-blockers	N = 151 (changes at 6 mo) LVEDV + 4.7 mL LVESV +0.3 mL LVEF +0.4% LV mass +10.6 g	N = 172 (changes at 6 mo) LVEDV -27.2 mL LVESV -25.6 mL LVEF +3.6% LV mass -12.0 g
PATH-CHF (2001)[22]	N = 25 NYHA III-IV QRS >120 Medications 96% ACE inhibitors 56% β-blockers 88% Digoxin 44% Nitrates 96% Diuretics		N = 25 (changes at 6 mo) LVEDD 71 to 68 mm LVESD 63 to 58 mm LVEDV from 253 to 227 mL LVESV 202 to 174 mL LVEF 22% to 26%

ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; CARE-HF, Cardiac Resynchronization in Heart Failure Study; LA, left atrial; LV, left ventricular; LVEDD, left ventricular end-diastolic dimension; LVEDV, left ventricular end-diastolic volume; LVEF, left ventricular ejection fraction; LVESD, left ventricular end-systolic dimension; LVESV, left ventricular end-systolic volume; MADIT-CRT, Multicenter Automatic Defibrillator Implantation With Cardiac Resynchronization Therapy; MIRACLE, Multi-center InSync Randomized Clinical Evaluation; NYHA, New York Heart Association; PATH-CHF, Pacing Therapies for Congestive Heart Failure.

from 12% at baseline to 64% at explantation. Of the 11, 2 died (1 from refractory arrhythmias 24 hours after explant and 1 from lung carcinoma), and 9 survived for a mean of 59 months. Mean left ventricular EF remained normal at 64%. Recurrent heart failure occurred in 1 patient after an episode of heavy alcohol intake, whereas the other 8 remain asymptomatic with a normal functional capacity.

The same group demonstrated similar findings in 20 patients using a continuous flow VAD.[34] With a similar medication regimen (changes included carvedilol 75 mg total daily dose instead of 100 mg and digoxin),

12 of the 20 patients achieved myocardial recovery and underwent explantation of their VADs. Survival after explantation was 83.3% at 30 days and 1, 2, and 3 years.[34]

In addition to this study, rates of myocardial recovery after unloading with mechanical support remain low. In one multicenter observational study, 67 patients received LVADs over a 2-year period. Despite signs of reverse remodeling during VAD support, including improved right ventricular function, decreased left ventricular end-diastolic dimension and left ventricular mass, improved EF, only 6 patients recovered sufficiently for VAD to be explanted, a rate of 9%. Of these 6 patients, 4 presented with acute heart failure: 2 with acute myocarditis, 1 with a myocardial infarction, and 1 with new onset cardiomyopathy. Longer duration of heart failure was associated with a lower likelihood of myocardial recovery.[35] In another observational study, rate of explantation for nonischemic cardiomyopathy was 8 out of 74 (11%). Of these patients, 3 had myocarditis and 4 had peripartum cardiomyopathy. The authors noted that all of the patients who experienced recovery had already done so after only 1 or 2 months of support with VADs.[36]

MYOCARDIAL RECOVERY AND miRNAs

Micro RNAs (miRNA) are short, noncoding RNAs that regulate post-transcriptional gene expression, and play an important role in cellular processes, including cardiac remodeling and reverse remodeling.[37,38] miRNA expression in heart failure shares similarity with fetal gene expression.[38,39] Specific miRNAs that are important to cardiomyocyte hypertrophy, remodeling changes of the extracellular matrix, and to apoptosis have been identified.[40]

The study of cardiac miRNA profiles raises additional questions about timing of VAD placement.[28,41] In a study of 28 patients with dilated cardiomyopathy, lower expression of 4 specific miRNAs was seen in the patients who experienced myocardial recovery with VAD support.[41] This profile, however, may simply reflect biomarkers of heart failure severity because the miRNAs do not play a mechanistic role in reverse remodeling. If so, instead of predicting which patients are most likely to recover left ventricular function, it may instead provide insight into how to better predict patients who may benefit from earlier placement of VADs.

Similarly, another study compared the gene expression profiles of 18 patients with LVAD. Of these, 13 went on to recovery and 5 went on to transplantation. The researchers found regression of the miRNAs for brain natriuretic peptide, interleukin-1β, von Willebrand factor, a Wnt signaling antagonist (SFRP1), and induction of RGS4. Again, it is not clear whether this miRNA profile provides insight into the mechanism of recovery, or whether it is descriptive of the state of heart failure, where brain natriuretic peptide, interleukin-1β, von Willebrand factor, and SFRP1 are known to increase in heart failure, and decrease with reverse remodeling.[42]

FUTURE DIRECTIONS

Myocardial recovery is possible and has been demonstrated in small numbers of patients after mechanical support with LVADs. Currently, the tools are not available to accurately identify which patients will recover. We do know that the likelihood of recovery increases for patients with nonischemic cardiomyopathy, acute heart failure syndromes with a rapid decline, and then a rapid improvement early on with VAD support. Gene expression profiles using miRNA may one day help identify the patients whose hearts are most likely to recover with VAD support.

Aggressive medical management significantly increases the odds of myocardial recovery, including for patients with mechanical support. At the very least, β-blockers and ACE inhibitors play a critical role in reverse remodeling of the left ventricle. However, not all end-stage heart failure patients are able to tolerate the doses needed to achieve significant reverse remodeling. And outside of the clinical trial setting, medication compliance is a real issue that prevents adequate medical therapy.

As more is learned about the molecular and cellular pathways of remodeling and reverse remodeling, including miRNAs, we will gain a better understanding of myocardial recovery, which will introduce new potential therapeutic targets.

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