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