Reverse Cardiac Remodeling: A Marker of Better Prognosis in Heart Failure

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Abstract

In heart failure syndrome, myocardial dysfunction causes an increase in neurohormonal activity, which is an adaptive and compensatory mechanism in response to the reduction in cardiac output. Neurohormonal activity is initially stimulated in an attempt to maintain compensation; however, when it remains increased, it contributes to the intensification of clinical manifestations and myocardial damage. Cardiac remodeling comprises changes in ventricular volume as well as the thickness and shape of the myocardial wall. With optimized treatment, such remodeling can be reversed, causing gradual improvement in cardiac function and consequently improved prognosis.

Introduction

When cardiac function reduces, neurohormonal activity increases. This important compensatory mechanism is a response to reduced cardiac output and also the main component in syndrome progression and in cardiac remodeling process. Neurohormonal activity is initially stimulated in an attempt to maintain compensation in patients; however, when it remains increased, it contributes to the worsening of clinical manifestations and myocardial damage. Similar to cardiac remodeling, the pathophysiological Frank-Starling mechanism is initially activated in an attempt to maintain compensation; nonetheless, when dilation is persistent, this mechanism results in the progression of myocardial damage and clinical manifestations of heart failure (HF) syndrome[1-5].

Ventricular remodeling is the process by which ventricular size, shape, and function are regulated by mechanical, neurohormonal, and genetic factors. It can be defined by molecular, cellular, and interstitial changes in the myocardium, resulting in alterations in the size, mass, geometry, and function of the heart as a result of a myocardial injury[5].

Its pathophysiological importance was well-demonstrated in the experimental studies with rats, conducted by the Pfeffer and Pfeffer (initially, Marc and Janice). In the myocardial infarction model, they demonstrated that mortality in rats was strongly associated with the degree of cardiac dilation and reduced ejection fraction[6,7]. Infarcted rats with greater cardiac dilation and lower ejection fraction had poorer outcomes than those with less involvement[6,7]. The postinfarction period is conventionally divided into two phases: early (up to 72 h) and late (after 72 h)[8]. Initial remodeling involves the expansion of the infarcted area, which can result in ventricular rupture or aneurysm formation[8]. In the early stage, after a moderate to large infarction, the ventricular cavity increases in size due to expansion or to stretching and thinning of the infarcted segment[8,9]. Late remodeling comprises the ventricle as a whole and is associated with time-dependent dilation, ventricle shape distortion, and ventricular wall hypertrophy, which can continue for months to years[8,9]. Pfeffer and Pfeffer[6] observed that rats with small infarctions (infarcted area < 20%) did not develop cardiac dilation and rats with moderate infarction (between 20% and 40% of infarcted area) presented progressive dilatation occurring in the noninfarcted area. The pathophysiological importance of cardiac remodeling and its role in HF prognosis have been expanded with the results of studies on ACE inhibitors in the treatment of infarcted rats. These studies have demonstrated that these drugs prevent cardiac remodeling and, in some cases, promote its reversal[7]. Rats treated with ACE inhibitors presenting dilation prevention or reverse remodeling had better prognosis than those that did not[6,7]. It was observed that the benefit of treatment was more significant in rats with moderate infarction[7].

In a subsequent study, Pfeffer et al.[10] coordinated the SAVE study; they demonstrated that the concept of remodeling also applied to humans and that treatment with ACE inhibitors modified the natural course of myocardial infarction and myocardial infarction-associated HF. Patients with myocardial infarction and ejection fraction of < 40% treated with captopril exhibited approximately 40% reduction in cardiovascular events[10].

Other studies have demonstrated that this knowledge regarding cardiac remodeling could also be applied to patients with cardiac dilatation without myocardial infarction. Data from the Framingham study clearly documented that cardiac dilation was associated with HF[11]. Patients with cardiac dilation had a 1.47-fold risk of developing heart failure compared with those without dilation[11].

The role of cardiac remodeling has been highlighted in studies on HF, confirming these findings. In this context, the Val-HeFT study demonstrated that patients with the highest ventricular volumes and lowest baseline left ventricular ejection fractions presented higher mortality[12].

Keywords

Heart Failure / therapy; Ventricular Remodeling; Stroke Volume / physiology; Prognosis.

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Reverse ventricular remodeling

Cardiac dilation is identified as an important marker of poor prognosis. Conversely, its reversal is associated with improved prognosis. Several studies have demonstrated that drugs or procedures, which modify ventricular remodeling, preventing or delaying cardiac dilation, are associated with improved outcomes. Not all drugs used in the treatment of HF influence cardiac remodeling. Animal studies in the postinfarction period have shown that beta-blockers, aldosterone blockers, and renin–angiotensin system inhibitors prevented cardiac dilation, whereas hydralazine and digitalis did not. Thus, clinical and experimental evidence suggests that the renin–angiotensin–aldosterone system and sympathetic nervous system play an important role in the process.

ACE inhibitors, as demonstrated in the SOLVD studies, reduced the rate of cardiac dilation and, in initial forms, promoted regression in cardiac dilation[10,13,14].

Studies on angiotensin II receptor blockers demonstrated that these drugs also have a beneficial effect on ventricular remodeling. In the ELITE study, both patients receiving ACE inhibitors and those receiving angiotensin II AT1 receptor-antagonists (ARB) presented the same trend regarding ventricular remodeling, with prevention of cardiac dilation. There were no differences in response between the ACE inhibitor and ARB treatments analyzed in that study[14].

Cardiac dilation is not reversed in all patients with HF and ventricular dysfunction. In patients with lesser involvement, reversal is not generally observed; it is more frequently identified in cases of moderate to intense involvement, with greater magnitude in the former[7,10,12,14]. Studies have shown reversal of cardiac dilation in approximately 30%–60% of the cases treated with neurohormonal blockers.

In a study of outpatients over 70 years of age, Cioffi et al.[15] observed an improvement in the ejection fraction in 36% during a mean follow-up of 17 months. Predictors for this improvement were absence of diabetes, history of hypertension, and treatment with beta-blockers; treatment with beta-blockers increased the chance of reversal by 3.4 times[15]. In the V-HeFT I and II studies, reverse remodeling was also observed both in the group treated with hydralazine and nitrate and that treated with enalapril[16]. A 5-unit increase in ejection fraction was the best predictor of mortality among the studied variables[16]. Approximately 30% of the patients had an increase in ejection fraction greater than 5 units; 50% of these presented an increase of more than 10 units.

The improvement in cardiac remodeling has also been observed. In the IMPROVE-HF registry, which examined 3,994 patients hospitalized for compensation, ejection fraction increased over 10% in 28.6% of patients[17].

Increased adrenergic activity appears to have a greater role in ventricular remodeling. Studies have demonstrated that beta-blockers promoted a more intense reversal of cardiac dilation than ACE inhibitors (Figure 1). ACE inhibitors prevent ventricular dilation and promote small increases in ejection

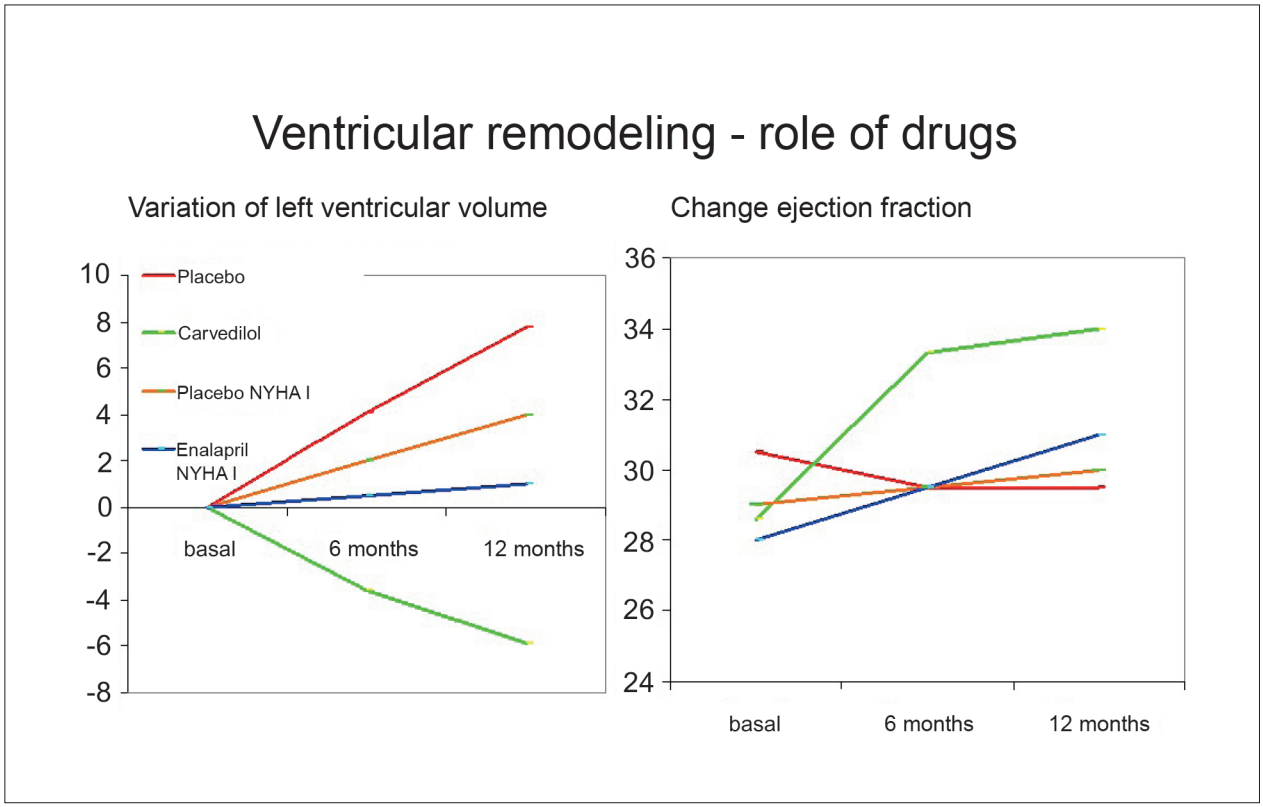

Figure 1 – *ACE inhibitors prevent cardiac dilation and beta-blockers reverse it. Coh JN et al JACC 2000; 35: 569-82.*

fraction, but reduction in ventricular diameter and increase in ejection fraction are more significant with beta-blockers[13,18].

The current literature documents that adrenergic activity actually plays an important role in ventricular remodeling, greater than that of the renin–angiotensin system, at least in the most symptomatic forms of the disease. Conversely, the adrenergic system may not be greatly stimulated in the initial phases of ventricular dysfunction because blockage of this system in asymptomatic forms of ventricular dysfunction does not result in a very significant reduction in mortality, as demonstrated in the CAPRICORN study[19].

Prognosis and remodeling

There is a growing body of evidence on the importance of reverse ventricular remodeling in HF prognosis[19-23]. Patients who present regression of ventricular dilation or increased ejection fraction after treatment have better quality of life.

At follow-up, Cioffi et al.[15] demonstrated that patients with reverse cardiac remodeling had lower mortality (3%) compared with those who did not present reversal (22%). In the V-HeFT I study, mortality in the first year of follow-up for patients who had a reduction in ejection fraction greater than 6 units, an alteration in ejection fraction ranging between −5 and 5 units, and those who had an increase in ejection fraction greater than five units was 29%, 16%, and 6%, respectively[16].

Hoshikawa et al.[18] observed that prognosis is related to the reversal of cardiac dilation. They divided their patients into three groups: those with full reverse cardiac remodeling, with LV diameter < 55 mm and Delta D fraction > 25%; those with partial reversal; and those who did not present reversal. The authors observed that all patients with no reversal of cardiac dilation died during the follow-up, which lasted an average of 5 years[18]. All patients who presented some reversal survived. In that study population, all patients were treated with neurohormonal blockers; 78% showed a reversal of cardiac dilatation and, of these, 57% showed complete reversal[18].

This same group reassessed their patients. Furthermore, Matsumura et al.[24] demonstrated the role of reverse remodeling in long-term prognosis. This study revealed that in 12 years of follow-up, all patients who had regression of cardiac dilation survived; however, those presenting increased dilation died or required transplantation. In this population of patients with dilated cardiomyopathy, it was observed that 35.6% of patients had some reversal; 37% of these presented normal diameters and ejection fractions[24]. All patients with some reversal remained alive at the end of 12 years, demonstrating that even small reversals indicate a good response to treatment[24].

In addition to the analysis of clinical trials and small group studies, reverse cardiac remodeling was assessed in a meta-analysis involving 69,766 patients in 30 randomized trials[25], which showed a strong relationship between improved ejection fraction and reduced mortality. Overall, mortality significantly decreased by 49% in patients presenting improved ejection fraction compared with those who did not[25]. Based on the regression analysis, a 5% increase in mean ejection fraction corresponded to a relative reduction of 14% in mortality (OR, 0.86; 95% CI, 0.77–0.96; p = 0.013). For each 5% absolute increase in ejection fraction, patients who presented reversals had a 4.9-fold higher chance of not dying compared with those showing no reversal. Similar results were described for the change in left ventricular volume[25].

Treatment and reverse remodeling

Because prognosis is better in patients with reversed cardiac dysfunction, at least partially, reversal should be considered a primary treatment goal. Patients not presenting this reversal should have their treatment regimen reassessed. In the absence of reversal, they should be more carefully followed up because they are at risk for a poorer outcome. Effective treatment should reverse cardiac remodeling[26-28]. Notably, all effective drugs and procedures, such as cardiac resynchronization, promote the reversal of cardiac dilation[18,29-32]. Nonreversal may be a sign that the doses of prescribed medications are inadequate or that the disease severity is high, resulting in a failure to obtain desired response to a proposed treatment.

In the treatment of HF, dosage is extremely important. Reverse remodeling is often not observed because the treatment drugs are administered at low doses. The importance of dosage can be observed in the FAST–Carvedilol study[33]. In this study, half of patients were discharged after using this drug at a dose of 3.125 mg or 6.25 mg twice daily, whereas the dosage for the remaining was rapidly increased during hospitalization and was the highest tolerated dose during discharge. At the outpatient clinic, dosage of carvedilol was not increased by the physicians for various reasons; this was most frequently because of borderline blood pressure. Thus, the average carvedilol dose was 6.99 mg/day in the control group and 16.19 mg/day in the intervention group. At follow-up, the intervention group presented a reversal of cardiac dilation; this reduction was already evident at 3 months of treatment (Figure 2)[33]. The group treated with low doses did not present reversal. At follow-up, in the first year, the survival rate was 43.5% in the control group versus 65.2% in the intervention group. The data draw attention to the importance of dosage both in reversing cardiac dilatation and reducing mortality and show that both are probably interconnected[33].

The authors of the present study have used these guidelines in clinical practice, increasing the dosage (particularly for beta-blockers) in patients who did not present reverse cardiac remodeling, thereby achieving a reversal of the dilation not obtained with the usual dosage. In patients whose heart rate is consistently above 70 bpm during optimized treatment, ivabradine has been effective in reversing cardiac dilation[34].

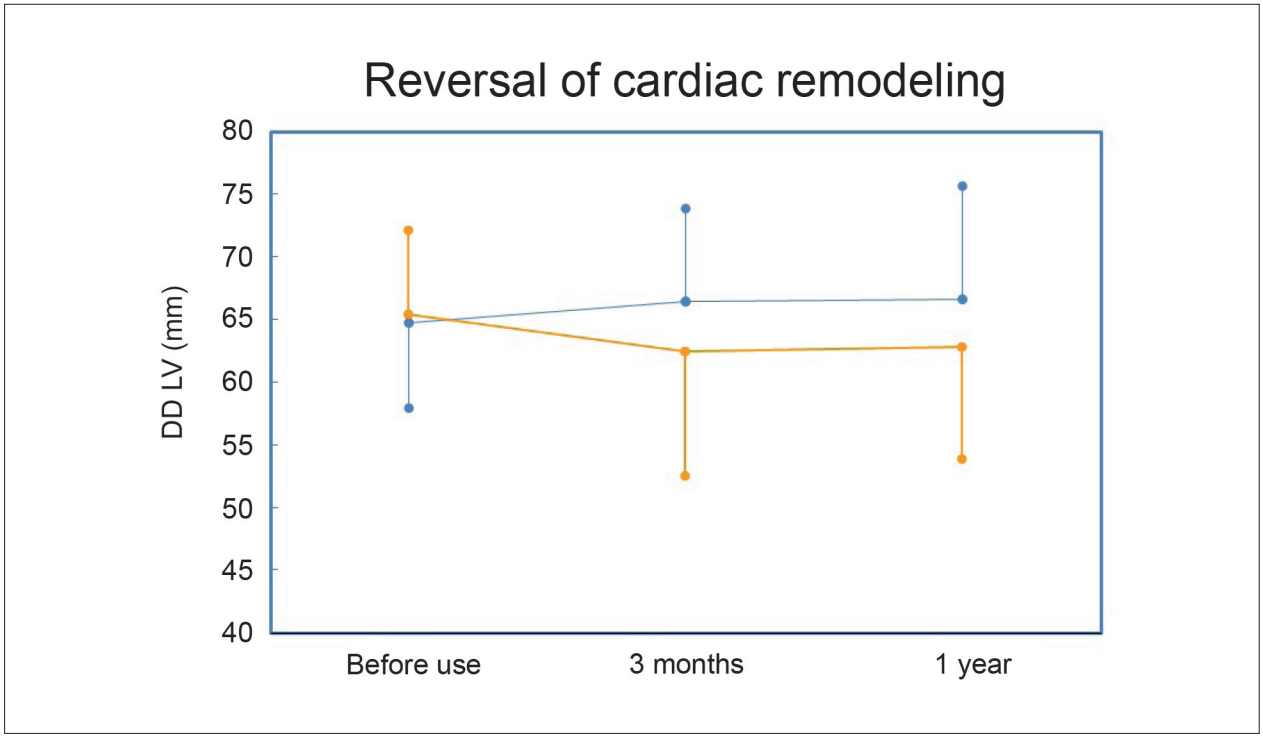

Figure 2 - *Beta-blockers used at the correct dosage reverses cardiac dilation; this reduction is already evident at 3 months of treatment. Melo D et al. JACC 2011; 57 (supl A): 17.*

Conclusion

Cardiac dilation is a marker of poorer prognosis in patients with HF. The drugs used to treat HF, particularly beta-blockers, ACE inhibitors, and ARBs, promote reverse remodeling. Patients who present reverse remodeling during treatment have better outcomes and lower mortality than those who do not present it.

Author contributions

Conception and design of the research: Reis Filho JRAR, Cardoso JN, Cardoso CMR, Pereira-Barretto, AC. Acquisition of data: Reis Filho JRAR, Cardoso JN, Cardoso CMR, Barretto AC. Analysis and interpretation of the data: Reis Filho JRAR, Cardoso JN, Cardoso CMR, Barretto AC. Writing of the manuscript: Reis Filho JRAR, Cardoso JN, Cardoso CMR, Barretto AC. Critical revision of the manuscript for intellectual content: Reis Filho JRAR, Cardoso JN, Cardoso CMR, Barretto AC.

Potential Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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Study Association

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