EDITORIAL COMMENT

Reverse remodeling: Much room for research ☆

Remodelagem reversa . . . muita margem para investigação!

Cândida Fonseca [a,b]

[a] *Unidade de Insuficiência Cardíaca, Hospital de S. Francisco Xavier, Centro Hospitalar Lisboa Ocidental E.P.E., Lisboa, Portugal*
[b] *NOVA Medical School, Faculdade de Ciências Médicas, Universidade Nova de Lisboa, Lisboa, Portugal*

Heart failure (HF) is defined clinically as a syndrome in which patients have symptoms and signs resulting from an abnormality of cardiac structure or function.[1]

Linked to such abnormalities is ventricular remodeling, a pathophysiological process common to all different types of HF in which ventricular size, shape and function are altered by mechanical, neurohormonal or genetic factors. These changes in ventricular architecture, caused by a combination of pathological myocyte hypertrophy, apoptosis, myofibroblast proliferation and interstitial fibrosis, were originally identified after myocardial infarction, but were subsequently detected in a range of acute and chronic cardiac conditions that can lead to similar alterations, including hypertension, myocarditis, and valve disease.[2–4]

All of these conditions trigger responses from neurohormonal systems including the adrenergic system and the renin-angiotensin-aldosterone system (RAAS) that, while initially protective, exacerbate and perpetuate the underlying abnormalities in cardiac structure and function if they persist, increasing the already failing heart's energy expenditure by persistently stimulating myocardial proliferation signaling pathways, with maladaptive effects on cardiac myocytes.[5]

It has become increasingly evident that various signaling pathways and mechanisms of cellular and molecular proliferation are involved in regulating cardiac architecture and the molecular composition of the myocardium and may be responsible for systolic or diastolic ventricular dysfunction. This results in one of two HF phenotypes: ventricular dilatation with systolic dysfunction caused by addition of sarcomeres in series, or ventricular hypertrophy due to sarcomere addition in parallel, probably because of activation of different pathways of cardiac proliferation.[6,7]

The importance of these neurohormonal responses, and of the need to counteract them, became clear when drugs designed to improve hemodynamics in HF with reduced left ventricular ejection fraction (LVEF) showed unexpected benefits in terms of patient survival related to their ability to modify the maladaptive effects of persistent neurohormonal

stimulation. Preventing, slowing or even reversing the process of ventricular remodeling thus became a therapeutic target in HF and LV systolic dysfunction.[8–13]

Reverse remodeling, a term denoting restoration of cardiac function and structure, became a popular concept following descriptions of cardiac recovery not only under modern HF drug therapy but also following implantation of cardiac resynchronization therapy (CRT) devices and after timely myocardial revascularization and/or valve surgery. In some cases it occurs spontaneously.

The fact that different proliferation pathways lead to different HF phenotypes, with sarcomere addition in series in systolic dysfunction and in parallel in diastolic dysfunction, may explain why drugs that improve prognosis in HF with reduced LVEF do not show the same benefit in HF with preserved LVEF.

Angiotensin-converting enzyme (ACE) inhibitors, adrenergic blockers, aldosterone antagonists, and ivabradine all reduce ventricular dilatation, improve or even normalize systolic function in HF with reduced LVEF and improve survival and quality of life in both the short and long term.[8–13] Hyperactivity of the adrenergic system appears to play a greater role in remodeling than the RAAS; studies have shown that adrenergic blockers lead to more pronounced reverse modeling than ACE inhibitors, at least in more symptomatic patients.[9]

CRT also results in reverse remodeling, reducing end-systolic and end-diastolic volumes, normalizing LV structure and improving cardiac function, a process that is associated with better prognosis.[14–16]

The effects of reverse remodeling in HF with reduced LVEF was assessed in a meta-analysis of 69 766 patients from 30 randomized trials.[17] This showed a 49% reduction in overall mortality in patients with improved LVEF compared to those without, a 5% increase in mean LVEF being associated with a 14% relative reduction in mortality (odds ratio 0.86; confidence interval 0.77–0.96; p=0.013). Every 5% absolute increase in LVEF was associated with a 4.9-fold lower probability of dying compared to those without reverse remodeling. Similar results were reported for changes in left ventricular volumes.[17]

Reverse remodeling is thus associated with better outcomes in patients with HF and reduced LVEF, and so it is crucial to understand the underlying mechanisms and to identify patient subgroups for whom this process may be particularly beneficial.[18]

There are, however, various challenges involved in the concept of reverse remodeling, including how to define it, how to identify its independent predictors, and how it correlates with prognosis in different phenotypes of HF.

The study by Amorim et al. published in this issue of the *Journal*, ''Prevalence, predictors and prognosis of ventricular reverse remodeling in idiopathic dilated cardiomyopathy'',[19] is thus of undeniable importance. LV remodeling plays a major part in the pathophysiology of idiopathic dilated cardiomyopathy (DCM), and since some patients undergo reverse remodeling under optimal therapy, it is essential to be able to identify them.

The prevalence and predictors of reverse remodeling in patients with DCM are the subject of debate. Comparison between studies is hindered by disparities in the definition of reverse remodeling and by differences in study populations, treatment and duration of follow-up. Most series are of heterogeneous populations with varying percentages of patients with reversible causes of secondary DCM, such as tachycardiomyopathy, viral myocarditis or toxicity, and report that 30–60% of DCM patients undergo reverse remodeling when treated with neurohormonal antagonists.[18,19,21] Amorim et al. studied a homogeneous population with idiopathic DCM, thus adding to the published data.

There are also methodological problems with the definition and diagnosis of reverse remodeling. While LVEF is the simplest and most effective parameter to stratify risk in daily clinical practice, recovery of LV diastolic diameter is the main physiological indicator of reverse remodeling. LV systolic diameter is a parameter that includes both LV size and systolic function. Echocardiography is the most commonly used technique both in studies and in clinical practice, although some authors assess end-diastolic diameter or volume, some end-systolic volume, and others LVEF. An increase of 15% in LVEF, used as a criterion of reverse remodeling in some studies, will have a different significance in a patient whose LVEF rises from 15% to 30% (an increase of 100%) compared to one whose LVEF rises from 30% to 45% (an increase of 50%). Amorim et al. chose a more consensual definition of reverse remodeling that combines a 10% increase in LVEF with a decrease in LV diastolic diameter, and which resulted in a prevalence of 34.5% reverse remodeling under optimal medical therapy in a median follow-up of 22.6 months, with improvements in functional class and brain natriuretic peptide levels and no mortality.[19]

The determination of variables that could predict reverse remodeling would have considerable clinical potential. It would help in assessing prognosis and in identifying DCM patients who are more likely to recover ventricular function under optimal medical therapy only, i.e. those in whom implantation of CRT devices or heart transplantation can be safely postponed, unlike those at greater risk who need to be treated more aggressively. This would be a more modern, individualized approach to care that also takes cost-effectiveness considerations into account. The European Society of Cardiology guidelines recommend a period of optimization of medical therapy (at least three months) for potential candidates for device implantation,[1] but this may need to be revised in light of the above. Simple, consensual and easily applied clinical and laboratory predictors of reverse remodeling would also be useful to identify high-risk patients, particularly in primary health care settings, enabling those who require more specialized care to be referred to an HF specialist.

In their population with idiopathic DCM, Amorim et al. clearly identified the following predictors of reverse remodeling in univariate analysis, in agreement with other published studies: less advanced disease, mild hypertension, atrial fibrillation, LV hypertrophy on ECG, absence of left bundle branch block, shorter QRS duration, higher hematocrit, lower LV diastolic diameter index, higher peak oxygen uptake efficiency, treatment with ACE inhibitors and angiotensin receptor blockers (ARBs) and use of maximal doses of ACE inhibitors/ARBs and beta-blockers.[12,19–23]

Multivariate regression analysis showed that higher doses of ACE inhibitors/ARBs were independently associated with reverse remodeling, while the presence or extent of late enhancement on cardiac magnetic resonance imaging did not predict reverse remodeling, in contrast to other published studies.[19,20,24,25] As the authors suggest, this discrepancy may have been due to the small number of patients assessed by this imaging method.

Although the authors unequivocally demonstrate that LV reverse remodeling is a predictor of good prognosis, they acknowledge that it is a heterogeneous process whose clinical implications may vary over time. Banno et al. recently reported that the incidence of events (HF rehospitalization and mortality) was three times higher in patients without reverse remodeling and that those with early (up to 400 days) remodeling had better prognosis than those with late remodeling.[26] Ruiz-Zamora et al. also reported early reverse remodeling and complete normalization of LVEF as predictors of better prognosis.[18] The process of reverse remodeling and its long-term consequences are not yet completely understood. It usually occurs within two to three years, but in some cases it may be many years after diagnosis. Some authors have identified different predictors for early and late reverse remodeling.[11,16]

We are far from fully understanding all the mechanisms of remodeling and reverse remodeling and there are still many questions that require further investigation, particularly as to which predictors are most reliable and consensual in the different forms of DCM, the usefulness of risk scores, the duration of reverse remodeling, when it occurs, and whether to continue standard therapy after normalization of LVEF. There is, in short, much room for research.

Conflicts of interest

The author has no conflicts of interest to declare.

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