EDITORIAL COMMENT

Cardiac biomarkers: On the track of reverse remodeling?☆

Biomarcadores cardíacos: na senda da remodelagem reversa?

Fátima Franco

*UTICA – Unidade de Tratamento de Insuficiência Cardíaca Avançada, Serviço de Cardiologia A,
Centro Hospitalar e Universitário de Coimbra, Coimbra, Portugal*

Heart failure (HF), in its different phenotypes, is a clinical syndrome with increasing prevalence that is associated with significant morbidity and mortality, as well as a high rate of rehospitalization, and has an enormous impact on national health systems in terms of both economic and human resources.[1] The incidence of HF is strongly correlated with age, rising from around 1% at the age of 65 years to around 20% at age 80. Its incidence and prevalence are expected to increase due to aging populations, lower mortality in the acute phase of coronary artery disease, increases in predisposing factors such as diabetes, hypertension and obesity, and the availability of drugs that prolong the survival of chronic patients.[2]

Over the last 30 years there have been striking advances in the treatment of HF with reduced ejection fraction (HFrEF). Medical therapy aimed at neurohormonal blockade, cardiac resynchronization (CRT) devices, implantable cardioverter-defibrillators (ICDs) and ventricular assist devices have rewritten the natural history of the syndrome, and in a significant number of patients, particularly in the early stages of the disease, at least partial reversal of ventricular remodeling can be achieved.

The concept of the heart as an endocrine organ dates back to the discovery of atrial natriuretic peptide by Bold et al. in 1983.[3] This was followed by the discovery of B-type natriuretic peptide and other molecules that were identified as potential markers in HF. The role of biomarkers in the diagnosis, stratification and prognosis of HF is now well established.[4,5] They have also played an important part in clarifying the pathophysiology and biology of the syndrome.[6] Their use is less well established for monitoring disease progression and response to therapy, since the evidence in these cases is weak. However, ever since biomarkers began to be used in HF, the goal has been natriuretic peptide-guided tailored therapy, but research to date has failed to confirm its viability.[7]

Biomarkers can be loosely classified into the following categories[8]: (1) myocardial stress/injury; (2) neurohormonal activation; (3) cardiac remodeling; and (4) comorbidities, and can thus be used to monitor different stages of the disease. Besides the natriuretic peptides and troponins, which indicate myocardial stress and/or injury and are an established tool in clinical practice, other biomarkers have recently been developed for different pathophysi-

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ological processes in HF that reflect remodeling of the myocardium and extracellular matrix. Among these are sST2 and galectin-3, both of which indicate the degree of hypertrophy and fibrosis in ventricular remodeling and have been tested in studies assessing response to therapy in HF and potential reverse remodeling.[9] Combinations of biomarkers that reflect different pathophysiological processes may have higher predictive ability for diagnosis, prognosis and follow-up, pointing to the future possibility of precisely guided therapy in HF.

Ventricular remodeling is the structural and functional changes at the myocyte and interstitial level that occur following myocardial injury and/or volume and/or pressure overload. Remodeling progresses over time in response to neurohormonal activation, volume and/or pressure overload and inflammation, and is associated with increased morbidity and mortality.[10]

In reverse remodeling, injured ventricular myocardium with a dilated and dysfunctional phenotype at least partially recovers normal function and structure. It can occur in response to therapeutic interventions that reduce or correct the neurohormonal and/or hemodynamic disturbances that caused it. Various studies have demonstrated left ventricular reverse remodeling in response to pharmacological therapy, CRT, and ventricular assistance.[11]

In the PARADIGM-HF trial, a reduction in the concentration of the biomarker sST2 between baseline and follow-up had prognostic value: sST2 was around 10% lower in patients treated with sacubitril/valsartan than in those treated with enalapril.[12] Although the reduction was modest, it was associated with clinically significant improvements in the sacubitril/valsartan group. sST2 is useful for prognostic assessment of HF patients with both reduced and preserved ejection fraction.[13]

The PROVE-HF trial (ClinicalTrials.gov identifier NCT02887183), currently under way, aims to determine changes in concentrations of biomarkers related to mechanisms of action and effects of sacubitril/valsartan therapy over a period of 12 months, and to correlate these biomarker changes with cardiac remodeling parameters and cardiovascular morbidity and mortality. The trial, due to be completed in 2019, is likely to shed light on which biomarkers are of value in monitoring therapeutic response and ventricular remodeling.

The study published by Amorim et al. in this issue of the *Journal*[14] analyzes the role of biomarkers in monitoring reverse remodeling in patients with HFrEF. Although the study population was a small group of patients with idiopathic dilated cardiomyopathy, their results are comparable to those in the literature, which indicate that reverse remodeling occurs in about a third of HFrEF patients.

The profile of patients who present remodeling includes younger age, preserved renal function and less severe remodeling as indicated by less advanced structural disease (smaller left ventricular diastolic volumes). The ability to identify potential responders to medical therapy has obvious advantages, particularly in order to avoid unnecessary implantation of devices such as ICDs.

Since cardiac biomarkers have already shown their value in the diagnosis and stratification of HFrEF, it would be interesting to discover whether they could also be used as a tool to identify patients who are likely to present reverse remodeling. The exploratory study by Amorim et al. assessed multiple biomarkers, aiming to establish correlations between these molecules and clinical and echocardiographic parameters of reverse remodeling. Performing simultaneous multiple comparisons increases the risk of false positive results and makes it difficult to draw conclusions. No correlations were in fact found between the biomarkers and reverse remodeling. The authors state that they are undertaking a study with emerging biomarkers, which may help clarify the issue. The PROVE-HF trial will certainly contribute further to our understanding of the role of biomarkers in identifying cardiac remodeling.

Conflicts of interest

The author has no conflicts of interest to declare.

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