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Markers of fibrosis, inflammation, and remodeling pathways in heart failure

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ABSTRACT

Ventricular remodeling occurs progressively in untreated patients after large myocardial infarction and in those with cardiomyopathy. The pathologic changes of increased left ventricular (LV) volume and perturbation in the LV chamber geometry involve not only the myocytes, but also the non-myocyte cells and the extracellular matrix. Inflammation, fibrosis, neuro-hormonal activation, and ongoing myocardial damage are the mechanisms underlying remodeling. The detection of an ongoing remodeling process by means of biomarkers such as cytokines, troponins, neurohormones, metalloproteinases, galectin-3, ST-2 and others, may hold a clinical value and could, to some extent, drive the therapeutical strategy in patients after a myocardial infarction or with heart failure. For this reason, there is an increasing interest in the development of new biomarkers and a great number of laboratory tests have been recently proposed, whose clinical usefulness, however, is not fully established yet.

1. Introduction

Heart failure (HF) has long been considered as an irreversible disease, willing only to receive palliative therapy. However, the idea of chronic HF as an irreversible, end-stage process has been challenged by experimental and clinical evidence that early pharmacological intervention may lead to improvement in the function and structure of the failing heart [1]. Several biohumoral markers have been proposed for the diagnosis of HF so far [2], natriuretic peptides and troponins being the most widely tested and validated in this clinical setting. Besides early diagnosis, evaluation of the ongoing remodeling process has challenged clinicians and a specific, accurate, and effective biomarker of this process is still an unmet need (Fig. 1). For this reason, there is an increasing interest in the development of novel biomarkers and a great number of laboratory tests have been recently proposed, whose clinical usefulness, however, is not fully established yet [2].

As a matter of fact, in the last international guidelines on the management of HF only 3 groups of biomarkers were taken into account: natriuretic peptides (in particular BNP and NT-proBNP both for diagnostic and prognostic purposes with class I recommendation), markers of myocardial injury (i.e., cardiac troponin I and T, with class I recommendation), and markers of myocardial fibrosis (such as galectin-3 and sST2, mainly for risk stratification with class IIb recommendation) [3] (Table 1). Of course, these recommendations are supported mainly by scientific evidences based on the results of well-designed randomized clinical trials, which demonstrated the good diagnostic and prognostic efficiency, as well as the favorable cost/benefit ratio for HF patients and community of these biomarkers [2,4,5]. However, some methodological considerations should also be taken into account, when a novel biomarker is recommended for clinical laboratory practice or large population screening. As an example, a list of some desirable characteristics for an ideal biomarker, recommended for the routine use in a clinical laboratory, are reported in Table 2.

Another aspect that should be preliminarily underscored is the heterogeneity of the HF syndrome, in terms of etiology, pathophysiology and clinical presentation: this may account for the wide differences in response to treatment and, therefore, in survival among patients who received a diagnosis of HF. As an example, HF may be associated with reduced (i.e. <40%) ejection fraction (HFrEF) or with preserved ejection fraction (HFpEF), resulting in similar symptoms and signs, but with profound differences in pathophysiology and response to treatment [3]. Patients with HFrEF have a higher risk of death than patients with HFpEF, [6], but absolute mortality is still high in the latter group. Randomized controlled trials have mainly enrolled patients with HFrEF, and it is only in these patients that efficacious therapies have been demonstrated to date [3]. In addition the diagnosis of HFpEF is challenging and generally posed after excluding other potential noncardiac causes of symptoms

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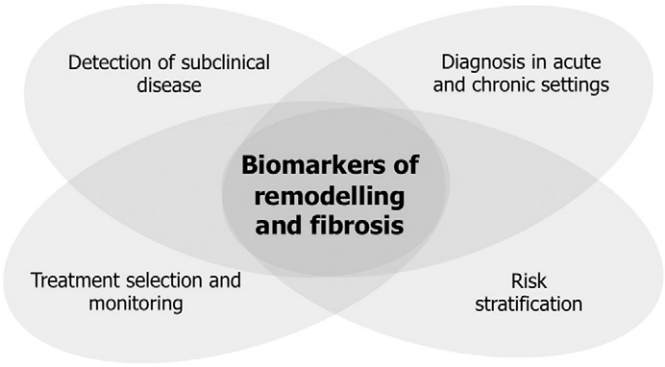

Fig. 1. Potential clinical usefulness of biomarkers of fibrosis and remodeling.

suggestive of HF. To date, efficacious therapies have not been identified for HFpEF [7,8].

The aim of this review article is to provide a general overview on the biomarkers of the different pathways involved in the remodeling process.

2. Cardiac remodeling

HF is the final result of several etiologies (ischemic heart disease accounting for roughly half of cases) and includes heterogeneous patients with diverse propensity to ventricular remodeling and clinical outcome [9]. Despite optimized medical therapy and technologically advanced device treatment, the majority of patients affected by HF experience progressive left ventricular dysfunction, worsening of symptoms and life-threatening arrhythmias. Cardiac death occurs because of arrhythmic event or pump failure, and mid and long term survival is still disappointing (9) (Fig. 2). Following the initial decline of left ventricular (LV) contractility, patients with HF can remain asymptomatic (stage B of ACCF/AHA classification) or paucisymptomatic (stage C) for years, as the result of the compensatory mechanisms sustaining cardiovascular function. However, these mechanisms promote complex structural and functional abnormalities of the myocyte and non-myocyte cells, contributing to LV enlargement and dysfunction (adverse remodeling). In particular, biomolecular remodeling [10], cardiomyocyte hypertrophy and extensive extracellular matrix production [11–13] may be promoted not only by the original noxa (i.e. necrosis, virus, toxics, autoimmunity), but also by chronic mechanical overload, myocardial ischemia due to microvascular dysfunction [14–16], and sustained activation of neurohormonal and cytokine systems [17]. From a clinical point of view, it is crucial to identify the subgroup of asymptomatic patients at higher risk, who need a more strict follow-up and an enhanced therapeutic effort, especially in the early HF stages (A and B) of disease, when the clinical status and LV function are yet poor predictors of disease evolution and clinical outcomes [18].

Myocardial remodeling in ischemic and nonischemic cardiomyopathies involves not only the myocytes, but also the non-myocyte cells and the extracellular matrix (ECM). ECM constitutes around 6% of the normal heart and includes fluid, collagen and glycoproteins. In particular, collagen is secreted by fibroblasts as procollagen into the ECM, where protease enzymes remove amino and carboxy-propeptide terminals, and is then broken down by matrix metalloproteinase enzymes, which are in turn regulated by their tissue inhibitors. In pathological conditions, the cardiac interstitium increases as a result of diffuse interstitial (microscopic) fibrosis, post-necrotic replacement (macroscopic) fibrosis, myocardial edema (as result of inflammatory processes) or pathological infiltration (e.g. amyloid). The activation of the renin–angiotensin–aldosterone system plays a central role in fibroblast activation and collagen deposition, with the transforming growth factor β (TGF β) as the downstream signal mediator. Endomyocardial biopsy still represents the current reference method for the evaluation of the remodeling process at a cellular level, although routine endomyocardial biopsy is not recommended in all cases of HF [3], but some circulating cardiac biomarkers may provide unique information regarding cardiovascular remodeling. Indeed, along the complex path from risk to fully developed HF, there are increasing numbers of injury, remodeling and neurohormonal activation substances discovered, whose assays might provide important information about HF. Some, as natriuretic peptides and troponins, are well validated and established according to evidence-based laboratory medicine principles [3–5], while several other biomarkers are still being explored for potential use in the clinical practice.

Table 1
Established biomarkers for HF management.
Adapted from 2013 ACCF/AHA Heart Failure Guidelines [3].

Biomarker	Setting	Application	Class	Evidence
BNP/NT-proBNP	Acute/chronic	Diagnosis	I	A
BNP/NT-proBNP	Acute/chronic	Risk stratification	I	A
BNP/NT-proBNP	Chronic	Guide for treatment	IIa	B
BNP/NT-proBNP	Acute	Guide for treatment	IIb	C
Troponins	Chronic	Risk stratification	I	A
Soluble ST2	Acute/chronic	Risk stratification	IIb	A/B
Galectin-3	Acute/chronic	Risk stratification	IIb	A/B

3. The pathophysiological role of cytokines in myocardial fibrosis

Inflammation mechanisms should be considered as an essential component of the normal wound healing process [19–22]. However, when the injury cannot be repaired in a short time, a chronic inflammatory response may be established. In this case, a chronic inflammatory response allows a pathological wound repair, with accumulation of permanent fibrotic tissue at the site of injury. The final result of this dysregulated inflammatory process is the impossibility for the tissue to restore the normal function.

Fibrosis can affect any organ including the lung, skin, heart, kidney and liver and it is estimated that 45% of deaths in the western world can now be attributed to diseases where fibrosis plays a major pathophysiological role [19]. In particular, the clinical syndrome of HF is characterized by a systemic inflammatory response that contributes to end organ damage in the heart and circulation and thus, can lead to progressive worsening of cardiovascular function. The inflammatory mediators in HF patients include pro-inflammatory cytokines and their cognate receptors, as well as molecules secreted/released by macrophages (such as galectin-3 and pentraxin-3-PTX3) [21]. Inflammatory biomarkers usually correlate with disease severity and prognosis across the broad spectrum of HF syndromes [21–23].

Levine et al. [23] reported for the first time that HF patients usually show elevated circulating levels of tumor necrosis factor (TNF). Further studies have then expanded this observation by demonstrating that proinflammatory cytokines and their receptors, cell adhesion molecules, and chemokines are elevated in patients with HF with a decreased ejection fraction [9]. In addition, the most important pathophysiological mechanisms underlying HF with a preserved ejection fraction are fibrosis and reduced ventricular compliance, which in turn cause the development of left ventricular diastolic dysfunction. In Tables 3 and 4 we reported a list of these inflammatory agents, more frequently suggested as possible biomarkers for HF [19–24].

Inflammation is one of the earliest events in cardiac stress situations such as pressure and/or volume overload and involves elevated levels of endothelial/vascular (VCAM) and intercellular adhesion molecules (ICAM), as well as increased production and release of inflammatory cytokines and chemokines in the tissue [18–21,23]. Cytokines and chemokines recruit activated inflammatory cells, particularly monocytes, from circulation into the cardiac tissue. Increased monocyte infiltration is seen in the early and late stages of HF [23]. Once inside the cardiac tissue, monocytes differentiate into macrophages and promote inflammation, tissue injury, and fibrosis of myocardial tissue. Activated