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Invited critical review

# Personalized risk assessment of heart failure patients: More perspectives from transforming growth factor super-family members

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ABSTRACT

More personalized risk assessment of patients with heart failure (HF) is important to develop more tailored based care and for a better allocation of resources. The measurement of biomarkers is now part of the standards of care and is important for the sub-phenotyping of HF patients to demonstrate the activation of pathophysiological pathways engaged in the worsening of HF. The sub-phenotyping of patients can lead therefore to a more personalized selection of the treatment. Several members of the transforming growth factor β (TGF-β) super-family, such as myostatin, activin A, GDF-15 and GDF-11, are involved in cardiac remodeling and the evaluation of their circulating levels might provide new insights to the course of the disease and also to guide prognostication and therapeutic selection of HF patients.



**Contents**



## 1. Introduction

The prevalence of heart failure (HF) is still growing worldwide [1–5]. Because of its human, societal and economic impacts, HF represents a major health concern [1,2,6]. The efficient management of HF patients requires a multidisciplinary team work and efficient tools to implement more personalized approaches [1,2]. Laboratory tests and measurement of biomarkers are frequently used in cardiovascular medicine and are recognized for their added value to the diagnosis and prognosis of HF [7–10]. Among the broad list of biomarkers, natriuretic peptides are now part of the standards of care procedures and have been translated into the guidelines of European and American societies [2,11]. The integration of biomarkers from different pathophysiological pathways

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might offer more perspectives for a more personalized care and to adopt more tailored therapies for both HF patients with reduced left ventricular ejection fraction (HF-REF) and preserved left ventricular ejection fraction (HF-PEF) [12–16]. One important axis of research is focused on biomarkers related to cardiac remodeling [17–19]. The transforming growth factor β (TGF-β) super-family is cytokines which are implicated in different cellular processes such as tissue repair, remodeling or fibrosis [20,21]. The expression of different TGF-β family members is modulated in different HF models suggesting their participation in the course of the disease [22,23].

The objective of this review article is therefore to describe the potential of measuring biomarkers derived from the TGF-β super family and their contribution to a more personalized management of HF patients.

## 2. TGF-β family members and the pathogenesis of heart failure

TGF-β participates in the pathogenesis of multiple cardiovascular diseases, including hypertension, atherosclerosis, cardiac hypertrophy and HF [24]. The myocardial expression of TGF-β is up-regulated in experimental models of myocardial infarction and cardiac hypertrophy as well as in patients with dilated or hypertrophic cardiomyopathy [25]. Several mechanisms are leading to the over expression of TGF-β in HF such as mechanical stress, cytokines and neurohormones [25]. TGF-β has long been believed to be one of the most important extracellular matrix regulators [24]. In the heart, TGF-β participates in cardiac remodeling and seems to play an important role in the transition phase from myocardial infarction to HF [25]. TGF-β stimulates the accumulation of the extracellular matrix in the heart and the release of inflammatory cytokines as well as cytokines mediating cardiac fibrosis [26]. In HF, the interplay between angiotensin II and TGF-β might enhance cardiac remodeling and fibrosis and therefore the worsening of HF [21]. Interestingly, the blockade of TGF-β diminishes fibrosis in experimental models of cardiac failure [24]. The effects of TGF-β are mediated by serine/threonine kinase receptors [27–29]. The binding of ligands to their receptors induced different smad-dependent pathways [17,30,31]. The TGF-β family can be divided into four sub-families: bone morphogenic proteins, growth differentiation factors, nodal signaling ligands and transforming growth factors [17,21]. Several members of these TGF-β sub-families such as myostatin, activin A, GDF-15 and GDF-11 have been related to the pathogenesis of HF (Fig. 1).

### 2.1. Myostatin

Myostatin, also known as GDF-8, affects a variety of cellular processes but it is mostly known as a major regulator of skeletal muscle mass and was originally isolated by McPherron et al. in 1997 [32]. Myostatin is expressed in fetal and adult hearts and plays an important role in cardiac development and physiology [33]. Myostatin appears also as an important regulator of cardiac energy homeostasis [34]. Cardiac magnetic resonance imaging revealed that genetic inactivation of myostatin signaling in the adult murine heart caused cardiac hypertrophy and HF, partially recapitulating the effects of the age-dependent decline of its paralogue GDF-11 [34]. Myostatin expression is increased in congenital heart disease, and the myostatin to IGF-1 ratio increases as the ventricular function deteriorates [35]. Myostatin is also triggered in the heart in animal models of myocardial infarction and volume-overload HF and might play an important role in cardiac remodeling after injury [36,37]. Such an up-regulation of myostatin was demonstrated in cardiac tissues in humans with advanced HF [37–39]. Some neurohormones associated with heart failure also stimulate the expression of myostatin [40,41]. We previously showed that urotensin II and urocortin, two potent contributors to the pathophysiology of HF derived from fish neuroendocrinology, trigger the gene expression of myostatin, a negative regulator of cardiac growth, in primary culture of adult cardiomyocytes [42]. The myostatin over-expression in the failing myocardium is regarded as a downregulator factor possibly counteracting the action of hypertrophic stimuli [43,44]. Interestingly, during pathological loading of the heart, the myocardium produces and secretes myostatin into the circulation where it inhibits skeletal muscle growth [18]. Therefore, myostatin through local and systemic actions might contribute to cardiac remodeling and muscle wasting in HF [18].

### 2.2. Activin A

Activins elicit complex effects on cell growth and differentiation [45]. Activins as well as its binding protein, follistatin, are widely expressed,

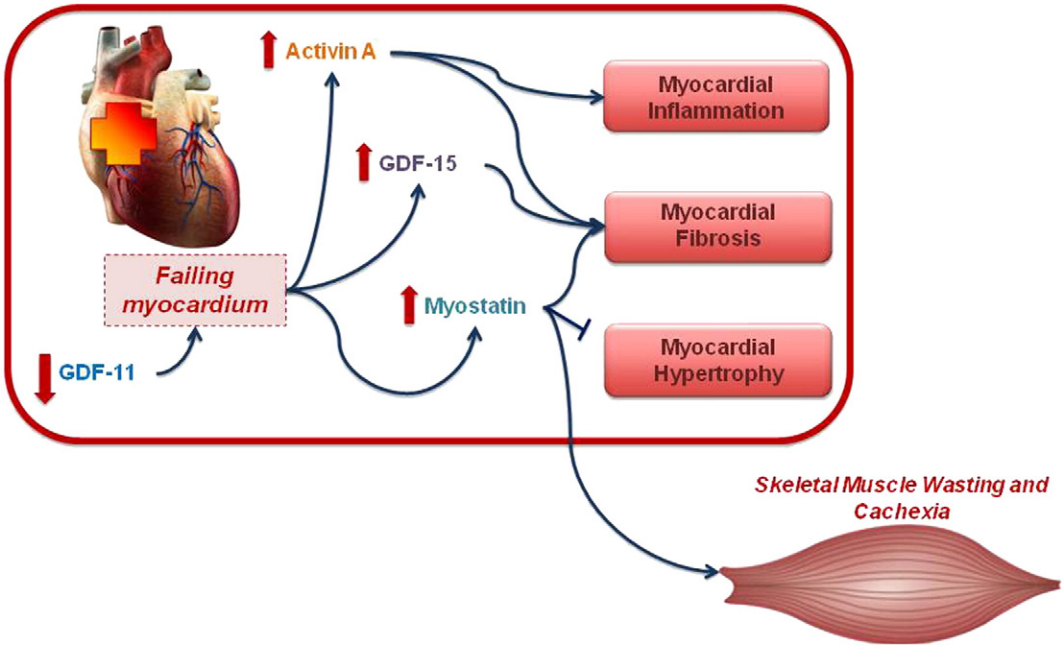


**Fig. 1.** Summary of the effects of myostatin, activin, GDF-15 and GDF-11 contributing to cardiac remodeling and skeletal muscle wasting.