

Heart Failure-Induced Myopathy: The Predictive Role of Altered Myokines' Profile

Alexander E. Berezin¹, MD, PhD; Alexander A. Berezin², MD

1 Senior Consultant of Therapeutic Unit, Internal Medicine Department, State Medical University of Zaporozhye, 26, Mayakovsky av., Zaporozhye, Ukraine;

2 Internal Medicine Department, Medical Academy of Postgraduate Education, Zaporozhye, Ukraine.

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Correspondence to: Alexander E. Berezin, Professor, MD, PhD, Senior Consultant of Therapeutic Unit, Internal Medicine Department, State Medical University of Zaporozhye, 26, Mayakovsky av., Zaporozhye, Ukraine.

Email: aeberezin@gmail.com; dr_berezin@mail.ru

Telephone: +380612894585

ORCID: 0000-0002-0660-9082

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ABSTRACT

The editorial is depicted the role of altered myokines profile in heart failure (HF) patients in prediction of HF-related myopathy and unfavorable clinical events. The development and progression of the HF is closely associated with the occurrence of myopathy, which leads to fatigue, low tolerability to physical exercise and increased risk of mortality. Myokines are predominantly produced by skeletal myocytes and regulate energy homeostasis, reparation, and perfusion of both skeletal muscles and myocardium. Recent clinical studies have

shown that the altered profile of these myokines is strongly associated with the transformation of single-skeletal muscle fiber myosin heavy chain isoforms, impaired muscle energy metabolism and regeneration of skeletal muscles and myocardium. Although the predictive value of myokines appears to be optimistic for HF progression, the ability of altered myokines' profile to improve discriminative potency of contemporary predictive scores in HF requires to be wide investigated in large clinical trials.

Key words: Heart failure; Biomarkers; Myokines; Myopathy; Prediction; Outcomes

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INTRODUCTION

Heart failure (HF) remains a global medical and social problem due to its high economic burden to the health-care system, decreased quality of life of the patients and poor long-term prognosis^[1,2]. Moreover, HF is a leading cause of CV mortality and urgent hospitalization among adults and the elderly having established CV disease^[3]. Although the total number of new cases of the HF with reduced ejection fraction (HFrEF) exhibits stable rate in the last decade, the prevalence of HF with preserved ejection fraction (HFpEF) continues to remarkably growth and currently higher than that of HFrEF^[4]. Despite the difference in the presence of CV risk factors and comorbidities among patients having HFrEF and HFpEF, both phenotypes of the disease have similar outcomes^[5,6].

Fatigue, low tolerability to physical exercise, declined skeletal muscle mass, muscle weakness are most common clinical features of HF regardless of its phenotype and frequently associated with the development of the HF-related myopathy, sarcopenia and even cardiac cachexia^[7,8]. Indeed, the physical exercise intolerance as one of most disabling symptoms of specific skeletal muscle myopathy has been defined in the HFrEF and HFpEF^[9]. The HF-related skeletal

myopathy characterized by decreased the number of muscle fibers, declined muscle strength, impaired metabolism of oxidative muscle fiber types due to mitochondrial dysfunction, ongoing inflammation and oxidative stress, and altered regeneration after acute muscle injury^[10,11].

Myokines are predominantly produced by skeletal myocytes and regulate energy homeostasis, repair, and perfusion of both skeletal muscles and myocardium^[12]. In physiological condition myokines ensure the molecular adaptations of skeletal muscles to physical exercise and hemodynamic supply acting as regulator of exercise intolerance^[13]. Because myokines are also secreted by adipocytes the altered myokine profile is responsible for metabolic or hormonal derangements in skeletal muscles and adipose tissue and probably it could be a target for the therapy of HF. Therefore, some of them, such as irisin, myostatin, interleukin-6 (IL-6), were found to be powerful predictors for cardiac remodeling and mortality in myocardial infarction and HF^[13-16]. The aim of the editorial is to summarize knowledge among altered myokines profile in patients having HF and elucidate its role in prediction of HF-related myopathy and unfavorable clinical events.

MYOPATHY IN HEART FAILURE

The progression of both HFrEF and HFpEF is associated with a transformation of skeletal muscle fiber composition and metabolism by uncertain molecular mechanisms^[17]. These underlying abnormalities effect skeletal muscle energy homeostasis, structure and function through direct impairment of mitochondrial electron transport chain activity, shifted metabolic substrate utilization, increased formation of reactive oxygen species, aberrant mitochondrial dynamics, and altered ion homeostasis, microvascular inflammation and endothelial dysfunction^[18]. Yet, catabolic condition due to neurohumoral and inflammatory activation aggravates the effect of the metabolic alteration^[19]. In addition, diaphragm dysfunction and inspiratory muscle weakness also contribute to the development of exercise intolerance in HF patients^[20]. Finally, hypoxia, deep metabolic alteration and ischemia injury of muscles lead to loss of myocytes due to necrosis and apoptosis, altered myoblast differentiation, impaired repair and weak perfusion^[21]. The result of these processes are certain perturbation of specific hormonal and myokines signal pathways, which includes an imbalance in the production of aldosterone, adipocytokines, tumor necrosis factor (TNF)-alpha, myostatin, myonectin, decorin, IL-6, IL-8, IL-15, and irisin^[22]. The altered profile of these myokines is associated with the transformation of single-skeletal muscle fiber myosin heavy chain isoforms, impaired muscle energy metabolism and regeneration, which lead to the occurrence of vicious circle and progression of HF-related myopathy (Figure 1).

Finally, muscle weakness, skeletal myopathy, muscle atrophy and cachexia are the attributive factors for HF progression and they are closely associated with an increase in CV mortality, HF hospitalization, and a decrease in the quality of life and well-being^[23,24].

MYOKINES IN HF-RELATED MYOPATHY

The skeletal muscles enable to release a wide range of the biological active molecules with variable potencies called myokines, the prolife of which was found to be altered in HF patients^[25]. Although HF-related myopathy has been considered as secondary muscle injury that was associated with low capillary perfusion^[26], myokines ensure adaptive metabolic auto regulation of structure and function of both

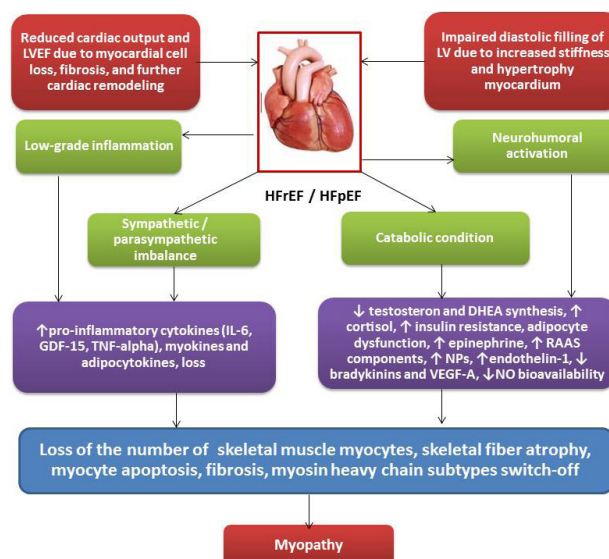


Figure 1 Principal pathophysiological mechanisms of the development of HF-related myopathy. Abbreviations: LVEF, left ventricular ejection fraction; IL, interleukin; GDF, growth differential factor; TNF, tumor necrosis factor; RAAS, renin-angiotensin-aldosterone system; NO, nitric oxide; NPs, natriuretic peptides; VEGF, vascular endothelial growth factor.

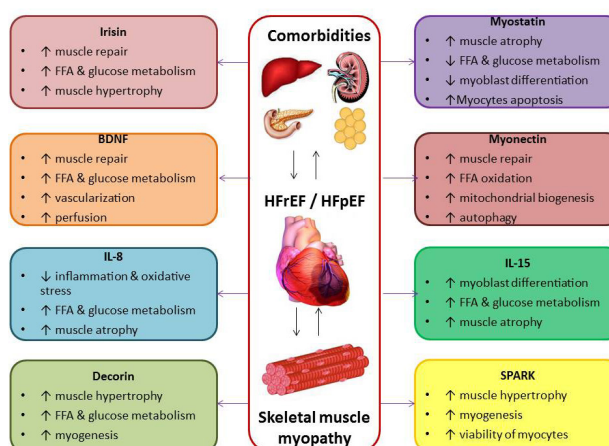


Figure 2 The effects of the myokines in HF. Abbreviations: HFrEF, heart failure with reduced ejection fraction; HFpEF, heart failure with preserved ejection fraction; FFA, free fatty acid; SPARK, secreted protein, acidic and rich in cysteine; IL, interleukin; BDNF, brain-derived neurotrophic factor.

skeletal and respiratory muscles, as well as myocardium^[27].

There is evidence for the fact that the wide spectrum of myokines provides controversial actions on skeletal muscle cells and mediates pleiotropic effects. Most of myokines are controlled by muscle contractility function, myogenesis, muscle hypertrophy, repair and consequently closely regulates exercise tolerance via intracellular signal pathways including Janus 1 and 2 kinases / 3 and 5 signal transducer and activator of transcription proteins / nuclear factor Kappa B, PI3 kinase / MAP kinase pathways^[28]. It is interesting that some potentially pro-inflammatory myokines, such as IL-15 and IL-8, simultaneously provide angiopoietic effects and support proapoptotic impact on myoblasts. It has been found interrelationship between NO-mediated cellular signaling and production of the myokines in skeletal muscle cells^[28]. However, hyperemia in skeletal muscle over physical exercise was strong associated with myokines release. The role of myokines in physiological condition and HF is reported in Table.

The occurrence of myopathy in HF accompanies by cross over changes in the spectrum of the myokines. Indeed, there were found

Table 1 The role of some myokines in physiological condition and in HF.

Myokine	Affiliation	Biological action		References
		Physiological condition	HF	
Down-regulated in HF				
Decorin	Proteoglycan	↓ accumulation of ECM, ↑ cell differentiation, proliferation, and ↓ apoptosis	↓ cardiac hypertrophy, ↑ cardiac fibrosis	[29,30]
Irisin	Muscle tissue-secreted peptide FNDC5	↑ expenditure, ↑ oxidative metabolism, ↑ myoblast differentiation, ↑ glucose uptake,	↓ tolerance to physical exercise, ↑ skeletal muscle hypotrophy	[31,32]
Myonectin	CTRP15	↑ oxidation of free fatty acid, ↑ oxidative metabolism, ↑ myoblast differentiation, ↑ glucose uptake	↑ skeletal muscle hypotrophy	[33,34]
BDNF	Neurotrophin family	↑ myoblast proliferation, ↑ neurogenesis, ↑ angiogenesis, ↑ vascular reparation	↑ tolerance to physical exercise	[35,36]
IL-15	pleiotropic cytokine with structural similarity with IL-2	Anabolic effect, ↓ oxidative stress	↑ tolerance to physical exercise, ↑ skeletal muscle mass, ↓ WAT, ↓ apoptosis of cardiac myocytes and myoblasts	[37]
Up-regulated in HF				
Myostatin	TGF-β superfamily	↑ skeletal muscle fiber-type switches, ↓ fast myosin heavy-chain expression, ↓ differentiation of myoblasts, ↑ ubiquitin-proteasomal activity in myocytes and ILGF-PKB pathway	↑ skeletal muscle hypotrophy, ↑IR, ↑ autophagy, ↑ muscle weakness, ↓ exercise tolerance	[38,39]
IL-8	cysteine-X-cysteine family of chemokines	↓ glucose disposal, ↑ IR	↓ skeletal muscle energy metabolism	[40,41]
Osteonectin	SPARC protein	Potential mediator of collagen deposition and extracellular matrix remodeling	Predictor of poor HF outcomes, ↑ cardiac contractility and reparation at early stage, ↓ cardiac myocytes survival and vascular integrity at late stage	[42]

Abbreviations: TGF-β, transforming growth factor-beta; IR, insulin resistance; ILGF-PKB, insulin-like growth factor-protein kinase B; WAT, white adipose tissue; ECM, extracellular matrix; SPARC, Secreted protein acidic and rich in cysteine.

elevated serum concentrations of myostatin and IL-8, whereas irisin and myonectin demonstrated significant decrease in their circulating levels. Finally, myokines influence not just skeletal muscles, but also myocardium and adipose tissue and ensure their autocrine metabolic regulation of energy homeostasis, hypertrophy, reparation, and as well as adaptation of skeletal muscles to physical exercise.

PREDICTIVE VALUE OF MYOKINES IN HF

Several myokines were able to predict adverse clinical outcomes in HF. Indeed, elevated serum irisin levels were independently associated with increased mortality and a risk of cardiac cachexia in acute and chronic HF patients respectively^[43,44]. Myostatin was found an independent predictor of mortality in HF patients and re-hospitalization due to HF progression^[45]. Circulating levels of BDNF were inversely associated with adverse outcomes in acute and chronic HF patients^[36,46]. In addition, SPARC proteins have demonstrated an independent association with poor long-term HF-related outcomes including death, and a risk for recurrent hospitalization due to^[47]. However, the exact molecular pathways, which link myokines with the HF outcomes remains uncertain and requires being clear elucidated in the future.

Conclusion: Myokines being autocrine / paracrine regulators of metabolic homeostasis of myocardium and skeletal muscles are involved in the pathogenesis of HF. Altered myokines' profile has been found in patients with HF_{rEF} and HF_{pEF} and was associated with poor clinical outcomes, adverse cardiac remodeling, HF-related myopathy and cardiac cachexia. Predictive value of myokines continues to investigate because preliminary findings appear to be optimistic for creation of predictive models. Large clinical trials are required to thoroughly elucidate whether altered myokines' profile is able to improve discriminative potency of contemporary predictive scores.

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