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Review

Revisiting skeletal myopathy and exercise training in heart failure: Emerging role of myokines

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ABSTRACT

Exercise intolerance remains a major unmet medical need in patients with heart failure (HF). Skeletal myopathy is currently considered as the major limiting factor for exercise capacity in HF patients. On the other hand, emerging evidence suggest that physical exercise can decrease morbidity and mortality in HF patients. Therefore, mechanistic insights into skeletal myopathy may uncover critical aspects for therapeutic interventions to improve exercise performance in HF. Emerging data reviewed in this article suggest that the assessment of circulating myokines (molecules synthesized and secreted by skeletal muscle in response to contraction that display autocrine, paracrine and endocrine actions) may provide new insights into the pathophysiology, phenotyping and prognostic stratification of HF-related skeletal myopathy. Further studies are required to determine whether myokines may also serve as biomarkers to personalize the modality and dose of physical training prescribed for patients with HF and exercise intolerance. In addition, the production and secretion of myokines in patients with HF may interact with systemic alterations (e.g., inflammation and metabolic disturbances), frequently present in patients with HF. Furthermore, myokines may exert beneficial or detrimental effects on cardiac structure and function, which may influence adverse cardiac remodelling and clinical outcomes in HF patients. Collectively, these data suggest that a deeper knowledge on myokines regulation and actions may lead to the identification of novel physical exercise-based therapeutic approaches for HF patients.

1. Introduction

Exercise intolerance, defined as an impairment in the capacity to perform physical exercise accompanied by symptoms of significant dyspnea and/or fatigue, is the cardinal manifestation of heart failure (HF) and is associated with reduced quality of life (QoL) and poor prognosis [1,2]. The determinants of reduced exercise capacity in patients with HF are multiple and include impaired cardiovascular and pulmonary reserve and structural and functional skeletal muscle abnormalities (i.e., skeletal myopathy), among others [1]. Additionally, most HF patients are elderly, in whom exercise intolerance secondary to skeletal muscle wasting and sarcopenia (i.e., loss of muscle mass) is part of the aging process [3]. Somewhat surprisingly, the degree of exercise intolerance and the severity of accompanying symptoms are not directly related to the degree of cardio-pulmonary weakness in HF patients, but are often related to abnormalities in skeletal musculature [4]. While many classical and novel HF drugs that reduce hospitalizations and mortality also influence exercise capacity, the magnitude of improvement is modest and variable [5]. On the other hand, preserving muscle functional capacity in patients with HF through physical exercise

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appears to be associated with a lower risk of cardiovascular and all-cause mortality [6]. However, exercise tolerance and activity levels of HF patients remain low [7].

Identifying the mechanisms by which exercise improves physical tolerance and HF prognosis in patients with HF may reinforce the therapeutic role of training and contribute to a better individualization of its prescription in this patient population. Recently, it has been proposed that the underlying mechanistic pathways of the beneficial effects of exercise in HF involve skeletal muscle hypertrophy and enhanced mitochondrial quality control, as well as reversal of histological and macroscopic adverse cardiac remodelling [8]. In this conceptual framework, we will review several issues related to a complementary and emerging view of skeletal myopathy as an active player in in the pathophysiology and clinical evolution of HF through the dysregulation of myokines. The myokines, term coined in 2003 [9], belong to a group of factors secreted into circulation by many tissues in response to exercise and known as "exerkines" [10,11]. In particular, myokines are cytokines, small proteins (5–20 KDa), or other proteoglycan peptides that are synthesized, expressed and released by muscle fibers (among other organs) in response to contraction and exert local autocrine and paracrine effects, and distal endocrine effects on a number of organs, including the heart [12]. We discuss the potential roles of dysregulated myokine secretion in patients with HF and skeletal myopathy, paying special attention to its effects not only on skeletal muscle, but also on the heart. On the other hand, we discuss how personalized exercise training may improve exercise capacity and other clinical aspects in HF patients, with myokine regulation being one of the pathophysiological mechanisms involved in the beneficial effects of exercise.

2. Skeletal myopathy in heart failure

2.1. General aspects

At the tissue and biochemical level skeletal myopathy in HF is characterized by major structural and metabolic alterations: the former can include loss of skeletal muscle bulk due to the reduced number and/or size of myocytes, shifts in fiber type with an increase in easily fatigable type IIb fibers, and capillary rarefaction, inflammation and fibrosis; the latter are characterized by a decrease in the effective mitochondria number and/or function, concomitant with a decrease in oxidative capacity and protein synthesis, and an increase in proteolysis, as well as with changes in fatty acid and glucose oxidation [8,13]. Interestingly, initial evidence from independent studies indicated that some, but not all, skeletal muscle alterations are similar between HF with reduced ejection fraction (HFrEF) and with preserved EF (HFpEF) when compared with healthy controls [13]. However, Seiler et al. [14] recently reported that molecular and cellular skeletal muscle alterations are exacerbated in HFrEF patients compared to HFpEF patients.

2.2. Major causes

Traditionally, the origin of the alterations of skeletal muscle in HF was linked to two major mechanisms: hemodynamic and metabolic alterations (Fig. 1).

Blood flow and oxygen (O_2) delivery to working muscles is reduced in HF, partly due to decreased cardiac output and partly to vasoconstriction of the small muscular arteries secondary to neurohumoral-mediated systemic endothelial dysfunction that accompanies HF [13,14]. Although O_2 extraction can be increased to account for reduced O_2 delivery, skeletal muscle maladaptation in HF may blunt diffusive O_2 transport, effectively negating this compensatory response [15]. In this regard, skeletal muscle interstitial inflammation and subsequent

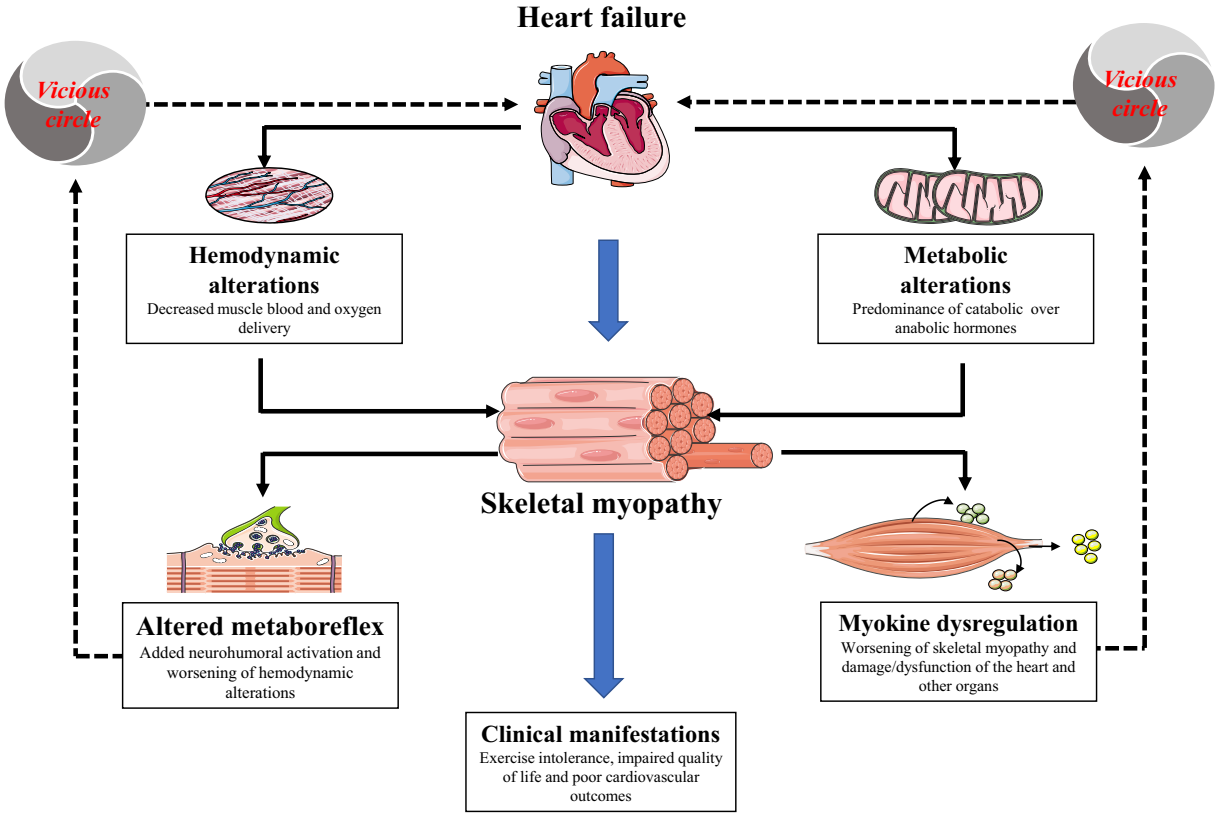

Fig. 1. Pathophysiological approach to the major mechanisms and consequences of skeletal myopathy in heart failure.

fibrosis, as well as intermuscular infiltration of adipose tissue (in patients with obesity), lead to significant limitations in O_2 diffusion and extraction [13,16,17].

HF is generally associated with systemically increased catabolism and decreased anabolism. For example, an increase in blood levels of catabolic hormones (e.g., cortisol) and a decrease in anabolic hormones (e.g., testosterone and insulin-like growth factor-1) are closely associated with progressive muscle wasting and cachexia, myopathy severity, and poor prognosis in HF [18].

2.3. Main consequences

Recent evidence suggests that, beyond its contribution to exercise intolerance in patients with HF, the skeletal muscle may also contribute to the pathophysiology of HF at two additional levels: alterations in the metaboreflex and alterations in the secretion of myokines (Fig. 1).

Patients with HF and skeletal muscle alterations show early accumulation of lactic acid during effort and a less efficient use of high-energy compounds [13]. These disturbances, in turn, trigger exaggerated metaboreflex activation with subsequent sympathetic overactivation and hemodynamic dysregulation characterized by an increase of systemic vascular resistance due to exaggerated peripheral vasoconstriction. Importantly, cardiac output is not increased due to the inability to enhance inotrophy [19]. Thus, it has been proposed that skeletal myopathy contributes to neurohumoral activation and impairment of systemic hemodynamics in HF through a hyperactivated metaboreflex [20].

The concept of skeletal muscle as a secretory organ, developed over the last two decades, partly explains how crosstalk between skeletal muscle and distant tissues occurs, and how the beneficial effects of exercise transcend the simple improved skeletal muscle functionality, to encompass systemic responses in distal organs such as the heart, kidney, brain, adipose tissue and liver [21]. There is now a wealth of data on the synthesis, kinetics of release and biological roles of myokines as mediators of muscle-organ crosstalk [12]. In fact, a recent secretome analysis of human muscle cells identified several hundred nonredundant secreted molecules, of which >300 were classified as potential myokines. Evidence accumulated in recent years suggests that circulating and tissue myokines in HF are associated with exercise tolerance, cardiac abnormalities and outcomes, and systemic effects at different levels [22]. Therefore, it has been hypothesized that myokine dysregulation might be part of skeletal myopathy in patients with HF and they emerge as potential diagnostic tools and therapeutic targets in this patient population (Graphical Abstract) [23].

3. Myokines in heart failure

3.1. Dysregulation of myokines in HF

Pioneering observations early in this century suggesting that interleukin-6 (IL-6) [24] and tumor necrosis factor-α (TNF-α) [25] behave as myokines have been confirmed in later studies [26]. Thus, the notion that skeletal muscle itself may be a source of molecules recognized to play a role in the pathophysiology of HF [27], provided novel insight on the pathogenic contribution of skeletal myopathy to the systemic maladaptations that characterize HF.

Experimental and clinical studies carried out in the following 15 years have shown that the regulation of other myokines is also impaired in HF; while some of them are upregulated (e.g., myostatin, IL-6, IL-8, osteonectin, growth differentiation factor-11 [GDF-11], follistatin-related protein 1 [FSTL1]), other are downregulated (e.g., irisin, IL-15, brain-derived neurotrophic factor [BDNF], decorin, myonectin and fibroblast growth factor-21 [FGF-21]) (reviewed in 21). Myokine profiles are variably associated with the severity of skeletal myopathy, adverse cardiac remodelling, and poor clinical outcomes [22]. In addition, the effects of myokines, either detrimental or beneficial, may be molecule-dependent [22]. As an illustrative example, a more detailed discussion of available data on myostatin and irisin in HF may cast some light on the potential roles of myokines in this condition.

Myostatin (also called growth differentiation factor-8) is a cytokine belonging to the transforming growth factor-β (TGF-β) superfamily [28]. Myostatin is a negative regulator of muscle mass, inhibiting muscle synthesis and augmenting muscle catabolism [29]. The activation of myostatin triggers the transcription of catabolic target genes, impairs the activation of satellite cells and myogenic factors, and stimulates the ubiquitin–proteasome system. Myostatin is mainly expressed in skeletal muscle, although basal expression is also detectable in the heart [30]. Myostatin gene and protein expression in skeletal muscle biopsies is higher in patients with HFrEF than in healthy controls [31,32], and higher in patients with HFpEF than in patients with HFrEF (Fig. 2) [32]. Moreover, the expression of myostatin [33,34] and that of its receptor ActRIIB [34] in left ventricular (LV) samples was higher in patients with advanced HF than in healthy subjects, although no correlations were found between myocardial myostatin and clinical parameters. Genetic elimination of myostatin [35] or blockade of the myostatin receptor [36] diminishes cardiomyoyte death and myocardial interstitial fibrosis, preserves LV function and increases survival in mice with HF, whereas overexpression of myostatin in cardiomyocytes induces the opposite effects [37]. There is also evidence that myocardial myostatin is increased in the failing mouse heart and that it is secreted into the circulation, where it can exerts systemic effects including inhibition of skeletal muscle growth [38].

On the other hand, exercise induces the muscle expression of the transcriptional coactivator peroxisome proliferator-activated receptor γ co-activator 1 α (PGC-1α), which in turn stimulates the expression of the transmembrane glycoprotein fibronectin type III domain-containing 5 (FNDC5) [39]. Irisin is a proteolytic product of FNDC5, and is secreted by skeletal muscle in response to exercise. Irisin plays an important role in fat metabolism and has been shown to induce the trans-differentiation of white adipose tissue into brown adipose tissue (termed browning), which increases energy expenditure and improves insulin resistance [39,40]. Interestingly, patients with HFrEF with a low aerobic performance (peak $VO_2 \leq 14$ mL/kg/min and VE/VCO_2 slope ≥ 34) exhibit a reduced FNDC5 and PGC-1α expression in skeletal muscle compared with patients with a high aerobic performance (Fig. 2) [41]. These clinical findings are supported by experimental data showing abnormally reduced FNDC5 and PGC-1α expression in skeletal muscle from rats with HFrEF secondary to ischemic cardiomyopathy [42]. Irisin can also be produced by the heart [43]. Compared with wild-type animals, *Fndc5* gene deletion resulted in exacerbation of LV hypertrophy, dysfunction and fibrosis, whereas *Fndc5* gene overexpression resulted in attenuation of these phenotypes [44]. In addition, administration of exogenous irisin mitigated LV hypertrophy, dysfunction and fibrosis in diabetic rodents when compared with non-treated animals [45,46]. Administration of irisin also improved LV function, decreased cardiomyocyte apoptosis, and protected mitochondria in rats submitted to cardiac ischemia and reperfusion [47].

As the field of the "myokinome" expands, studies performed in the last years have found that some molecules already known from a long-time or others recently identified also behave also as myokines and may be potentially involved in the pathophysiology of skeletal myopathy, cardiac remodelling and the progression of comorbidities that characterize HF. This is the case for apelin, musclin and several non-coding RNAs. Apelin is a peptide hormone that by activating its G-protein coupled receptor (ApelinR) exerts many biological functions and whose production is induced by muscle contraction [48]. A number of studies have demonstrated that apelin improves skeletal muscle mass and function, exerts cardioprotective effects and promotes energy expenditure [49]. In the ventricular tissue of patients with advanced HFrEF, increased [50] or unchanged apelin levels have been reported [51], while ApelinR levels are consistently decreased [50,51]. Reduced skeletal muscle musclin levels exaggerate, while its overexpression in

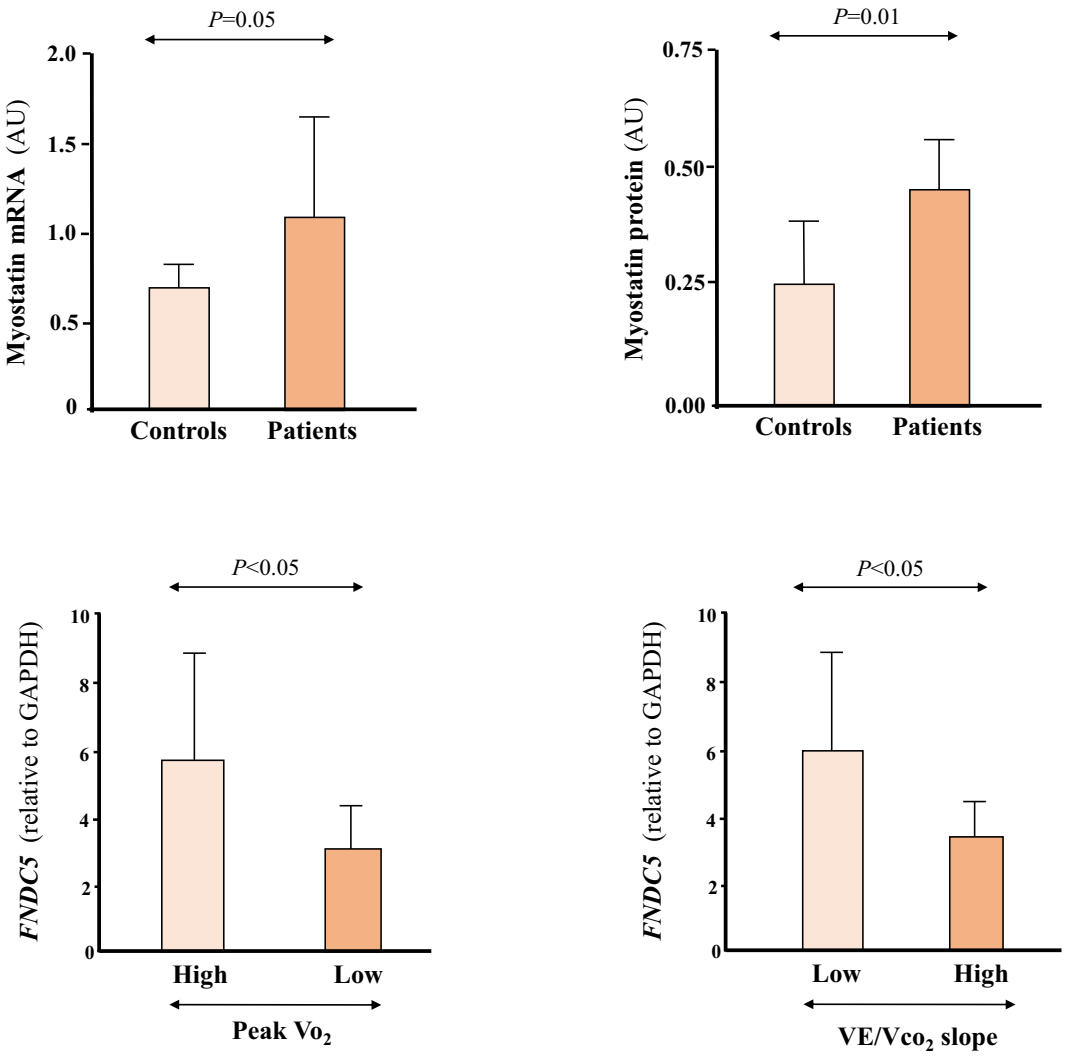

Fig. 2. Upper panels. Myostatin mRNA (left panel) and protein (right panel) expression quantified in the vastus lateralis muscle from patients with heart failure with reduced ejection fraction and age-matched healthy controls (Adapted from 31). Lower panels. Expression of the fibronectin type III domain containing 5 (*FNDC5*) gene encoding for irisin in the vastus lateralis muscle of patients with heart failure with reduced ejection fraction and low or high aerobic performance assessed using oxygen consumption (low or high peak VO_2 [$\leq$14 or >14 mL $O_2 \cdot kg^{-1} \cdot min^{-1}$, respectively] and low or high ventilatory efficiency [VE/VCO_2 slope $\geq$34 or <34, respectively]) (Adapted from 41).

muscle attenuates cardiac dysfunction and myocardial fibrosis during pressure overload [52]. Mechanistically, musclin enhances the abundance of C-type natriuretic peptide, thereby promoting cardiomyocyte contractility through protein kinase A and inhibiting fibroblast activation through protein kinase G signaling [52]. Of interest, reduced expression of *OSTN*, which encodes musclin, has been found in skeletal muscle of HF mice and HF patients [52]. On the other hand, the relevance of non-coding RNAs in muscle biology is evidenced by studies demonstrating that microRNA and long non-coding RNA profiles are dysregulated in a number of conditions associated with impaired exercise capacity [53,54]. Both microRNAs and long non-coding RNAs are sensitive to muscle contraction in response to different protocols of exercise training both in humans and animal models, which points to their potential role in the exercise-induced adaptations of skeletal muscle [53,54]. In addition, experimental data suggest that some non-coding RNAs produced in response to exercise exert direct effects on the heart. For instance, whereas microRNA-1192 protects cardiomyocytes from hypoxia via targeting caspase 3 [55], it appears that the long non-coding ExACT1 facilitates pathological LV hypertrophy [56].

In summary, from a mechanistic point of view the hypothesis emerges that myokine dysregulation may be involved in the impairment of skeletal muscle, heart and other organs in the context of HF (Graphical Abstract). However, more thorough studies, both at the cellular and pre-clinical levels, are needed to fully resolve the controversies of their exact contribution to skeletal myopathy, adverse cardiac remodelling and comorbidities in HF.

3.2. *Myokines as biomarkers in HF*

Taking into account that myokines are secreted and reach the blood stream, their potential clinical usefulness as biomarkers in HF has being suggested (Fig. 2) [57]. Indeed, supporting this notion, a study performed in a large, heterogeneous cohort of 2329 patients with HF showed that circulating IL-6 is abnormally elevated in these patients and is associated with cardiac dysfunction severity and poor clinical outcomes [58]. The prognostic value of elevated circulating IL-6 levels in HF was corroborated in a meta-analysis including 28 studies [59]. Similarly, increased levels of serum TNF-α were found in patients with severe HF presenting with cachexia, advanced adverse cardiac remodelling and pronounced exercise intolerance [60,61]. Of interest, since the stability of plasma concentrations of soluble TNF-receptors (sTNFR-1 and -2) is higher than that of TNFα itself, this may be the reason why

sTNFR-1 is a better predictor than TNFα in HF patients [61].

Regarding serum levels of myostatin three studies reported higher concentration in patients with chronic HF than in healthy controls [34,62,63], while one study reported similar levels [31] and another study reported lower levels [64]. When myostatin was abnormally increased, no differences were reported between patients with HFrEF and HFpEF [62], or between patients with ischemic HF or with non-ischemic dilated cardiomyopathy [63]. Whereas some studies reported associations between serum myostatin and severity of HF as assessed by the New York Heart Association Class (NYHA) and the plasma levels of natriuretic peptides [62,63], others did not find any association [31,34,64]. In an analysis of 288 patients with HFrEF and HFpEF and 62 healthy controls, an independent association was observed between myostatin levels and clinical outcomes, with those patients in the highest tertile of myostatin presenting the highest rates of hospitalization for HF and mortality [62]. Myostatin was also an independent predictor of survival in HF patients (Fig. 3) [62].

Serum levels of irisin are lower in patients with HFrEF than in healthy volunteers [65,66], lower in patients with HFrEF than in those with HFpEF [67], and lower in patients with HF and cachexia than in those without cachexia [68]. Correlation analyses in patients with HF showed that serum levels of irisin correlate directly with LV ejection fraction [65,69], and inversely with NYHA class [68], natriuretic peptide levels [68,69], and LV dimensions [66]. Notably, the levels of circulating irisin were negatively associated with the severity of sarcopenia in HF patients (Fig. 3) [66].

Altogether, cumulative evidence indicates that circulating levels of myokines are altered in HF and associated with features of adverse cardiac remodelling and with poor cardiac prognosis, thus reinforcing the role of skeletal myopathy in HF evolution and prognosis (Graphical abstract). Nevertheless, it is still unclear how strongly related are changes in peripheral blood concentrations of myokines in HF with skeletal myopathy since, despite their primary skeletal origin, other tissues are capable of producing and releasing them. In addition, there is limited robust evidence on the independent predictive value of myokine signatures and their added value on top of traditional circulating cardiac biomarkers.

4. Exercise in patients with heart failure

4.1. General aspects

Exercise intolerance is preceded by an accelerated decline in functional capacity, measured objectively as peak VO_2, and manifests clinically as fatigue, dyspnea, and reduced QoL [70]. Therefore, exercise is recommended (class 1, level A) for all patients who are able in order to improve exercise capacity, QoL, and reduce HF hospitalizations [71,72]. A supervised, exercise-based, cardiac rehabilitation programme should be also considered (class 2b, level c [71] or class 2b, level b-nr [72]) in patients with more severe disease, frailty, or with comorbidities.

To advance HF therapy in terms of improving clinical outcomes, muscle strength, functional capacity and QoL, implementing novel strategies based on emerging knowledge and person-centered therapy, including individualized and tailored telemedicine and technology-based programs seems necessary [73,74]. In this conceptual framework myokines may add a new dimension to the design of personalized exercise training in HF patients (Graphical Abstract).

4.2. Effects of exercise on myokines in HF

Preliminary studies in patients with cardiovascular conditions, including HF, show that physical training-induced myokine changes are associated with improvement in exercise tolerance and cardiovascular function [75]. Exercise-derived myokines might be involved in the beneficial effects of exercise in HF through three main types of effects: 1) promoting a systemic anabolic milieu with improvement of skeletal myopathy; 2) affording direct cardiac protection; and 3) ameliorating disturbances of energy metabolism. For instance, whereas the anabolic myokine IGF-1 decreases [76] and the catabolic myokine TNF-α increases [77] in the skeletal muscle of HF patients, skeletal muscle IGF-1 increases [78] and skeletal muscle TNF-α decreases [77] with endurance exercise. High-intensity interval exercise training improved skeletal myopathy in patients with chronic heart failure, and these effects were associated with increased production of members of member of the IGF-1 family and of IGFBP-3 [79]. Direct cardioprotection can be induced by a single bout of exercise and can be maintained for months with regular exercise; the mechanisms reportedly involved include increased cardiac storage of nitric oxide and decreased oxidative stress with resulting improvement of endothelial function, activation of pro-survival kinases of the reperfusion injury salvage kinase (RISK) pathway, and improved

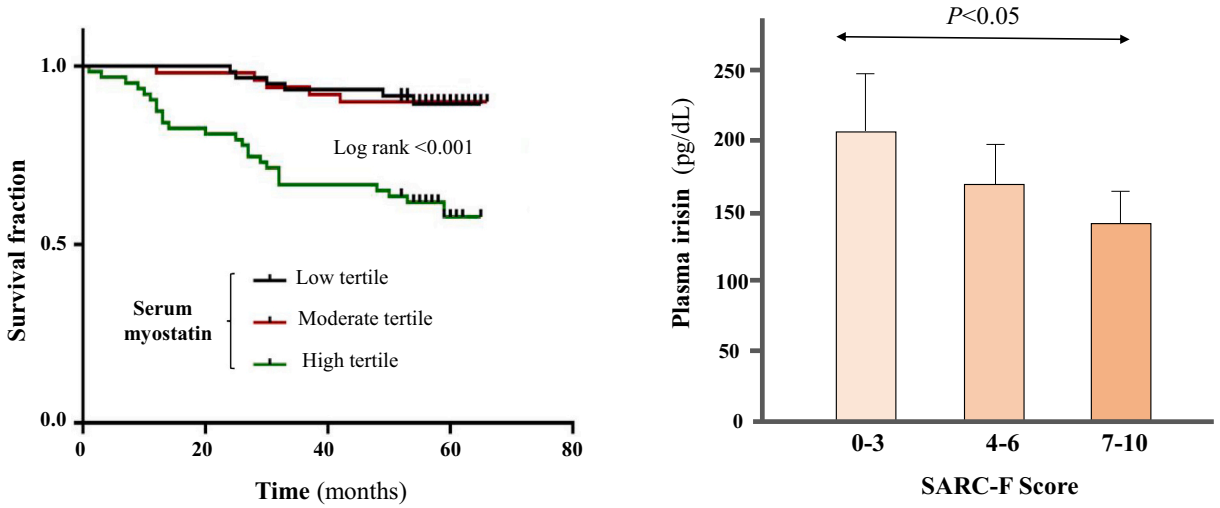

Fig. 3. Left panel. Kaplan-Meier estimates of survival in patients with heart failure (HF) according to tertiles of serum myostatin. (Adapted from 62). Right panel. Plasma irisin levels decreased in relation to the severity of sarcopenia (defined according to the SARC-F [S, Strength; A, Assistance in walking; R, Rise from a chair; C, Climb stairs; F, Falls] questionnaire scoring) in HF patients. (Adapted from 66).

calcium-retaining capacity of mitochondria [21]. Irisin [80], apelin [51] and FSTL1 [81] appear to be the myokines more involved in these cardioprotective effects. In addition, myokines mediate exercise-stimulated muscle lipid oxidation and oxidative metabolism in an autocrine fashion (e.g., IL-15 and BDNF), exercise-induced hepatic neoglucogenesis and fatty acids uptake (e.g., myonectin) and white adipose tissue lipolysis and brown adipose tissue thermogenesis (e.g., irisin and FGF-21) through endocrine communication [10,82].

The regulation of myokines through exercise can be differential and is more or less specific depending on the type of exercise. For instance, myostatin is primarily inhibited by concurrent training [83], whereas irisin is mostly induced by resistance exercises as well as by heavy strength training [84], On the other hand, apelin is stimulated by endurance training [50]. Some experimental and clinical observations support that these aspects may be relevant for the prescription of physical exercise in HF.

It has been reported that, in patients with HFrEF 12-weeks of concurrent training led to reductions in skeletal muscle myostatin mRNA and protein with final values significantly lower than in the group of HF patients that continued their sedentary style of life [31]. These findings have been corroborated in a rat model of HF [85]. Although there are no published data on the effect of physical training on circulating myostatin levels, in the only published study showing lower levels in HF patients compared to controls most of patients were following an exercise training program when they were tested but none of the controls did [62].

While no data are yet available on the effects of physical training on irisin in HF patients, there is evidence on its effects in patients with overweight or obesity. In fact, Kim et al. [86] found that in overweight/obese adults circulating irisin was increased in subjects submitted to resistance training but did not change in subjects submitted to aerobic training. In addition, the authors reported a positive correlation between the change of circulating irisin and muscle mass and a negative correlation with fat mass [86]. The potential relevance of these findings in HF is given by several observations: 1) obesity is present in 80 % of patients with HFpEF [87] and frequently acts as a co-incubator for comorbidities such as diabetes mellitus, metabolic syndrome and hypertension [88]; 2) sarcopenic obesity, a clinical condition defined by the coexistence of obesity with a decline in muscle mass and related strength and functionality, is consistently reported in HFpEF patients and poses as a major limitation to exercise capacity [89]; and 3) HFpEF patients with sarcopenic obesity present with severely reduced exercise capacity due to both obesity [90] and sarcopenia [91].

5. Roadmap to enhance the potential role of myokines in HF

Important remaining issues deserve further consideration in order to establish the role of myokines in understanding and prescribing exercise training as a therapy for HF (Table 1). Regarding the robustness of available data some concerns include the lack of consistency between the acute and chronic exercise response, discrepancies between patients and animal models of exercise, and interpretation challenges due to variability in outcomes and sampling, as well in the pre-analytical processing of biomaterials under study. Importantly, we must recognize that the current proposal for a potential role of myokines in HF is based on information provided by a limited number of small clinical trials. Therefore, we make a call to action for designing large trials evaluating the aforementioned approach to assess incremental results.

Despite the acceleration in exerkine-related research since the identification of IL-6 as a myokine in 2000 [24], much remains to be done in the scientific areas of research, technology and therapeutic interventions. Specifically, a critical need exists to move beyond the 'skeletal muscle-centric' view of myokines and focus more on their roles in inter-organ communication, immune regulation, metabolic adaptation, cardiovascular fitness, and overall health in HF patients. The multiple cross-talks between myokines and other non-muscle exerkines is another aspect that needs to be studied in depth to adequately characterize the role of these molecular mediators in the beneficial effects of exercise in HF patients with associated comorbidities.

Table 1
A three-step road map for potentiating the usefulness of myokines in patients with heart failure.

1. Deepen in the fundamental knowledge on myokines
a. Clarify the muscle profile response to different programs of exercise
b. Characterize their roles in multi-organ cross-talk as part of exerkines
c. Take advantage of omic technologies to advance in discovery and validation
2. Expand and strength the available information on myokines in HF
a. Perform large clinical studies to collect more data in different HF populations
b. Optimize the methodology and the processing of samples to measure
c. Develop studies in animal models mimicking human HF
3. Incorporate myokines into novel technological developments for HF
a. Implement as parameters for remote monitoring in exercising patients
b. Incorporate as novel oral compounds in non-exercising patients
c. Standardize as data for reporting and sharing in telemedicine

HF, means heart failure.

It can be expected that through deep omics profiling (transcriptome, proteome and metabolome) of biomaterials (including extracellular vesicles as carriers of molecular signals and drivers of inter-organ crosstalk) from humans and rodents with HF before and after acute exercise as well as chronic exercise training many more myokines and exerkines will be discovered [92]. In addition to molecular discoveries, substantial clinical work remains to decipher the dosage and type of exercise needed to elicit positive HF outcomes.

There is a need to develop novel technologies, including wearable technologies and devices, to capture the quantitative and dynamic changes of myokines over variable periods of time under the effects of physical training in patients with HF. In this regard, the establishment of community standards for data reporting and sharing is mandatory to effectively advance the translation of research into therapy.

Finally, as the role of myokines and other exerkines and their biological effects are increasingly clarified, they may potentially be harnessed to mimic the benefits of exercise in individuals who are limited in their exercise capacity or to counterbalance a metabolic non-response or adverse response to exercise, as it is the case in patients with the diagnosis of advanced HF [71,72]. The past decade has witnessed growing scientific and commercial interest in the identification of bioactive oral compounds that mimic or potentiate the effects of exercise, the so-called 'exercise pills'. These compounds have, to date, typically targeted skeletal muscle in an attempt to stimulate some of the adaptations to exercise induced by endurance training. Accordingly, they fail to impart many of the broad health protecting effects of exercise that are seen in tissues and organs other than skeletal muscle [93]. Therefore, future research in the field must move beyond the current 'myocentric' paradigm.

6. Conclusions

The preliminary data discussed here suggest that the study of myokines may provide new insights into the pathophysiology of HF-related skeletal myopathy and that they may be explored as potential biomarkers for the phenotyping and prognostic stratification of this condition in patients with HF, particularly in patients with HFpEF and associated metabolic comorbidities who may especially benefit from exercise's ability to induce myokines and other exerkines [94]. In addition, it can be hypothesized that myokines might be useful for personalizing the modality and dose of physical exercise to be prescribed in these patients (see Fig. 2).

Establishing molecular links between skeletal myopathy and

improved HF management can only strengthen the implementation of precision medicine-based management of HF. In this context, myokine (and other exerkines)-guided physical exercise might contribute to a better QoL and likely an improved prognosis, and thus contribute to a better health system performance in terms of cost-effectiveness.

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Declaration of competing interest

The authors have no conflicts of interest to disclose.

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