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Exercise intolerance and fatigue in chronic heart failure: is there a role for group III/IV afferent feedback? --Manuscript Draft--

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Abstract:	<p>Exercise intolerance and early fatigability are hallmark symptoms of chronic heart failure (CHF). While the malfunction of the heart is certainly the leading cause of CHF, the patho-physiological mechanisms of exercise intolerance in these patients are more complex, multifactorial, and only partially understood. Some evidences point towards a potential role of an exaggerated afferent feedback from group III/IV muscle afferents in the genesis of these symptoms. Overactivity of feedback from these muscle afferents may cause exercise intolerance with a double action: by inducing cardiovascular dysregulation, by reducing motor output, and by facilitating the development of central and peripheral fatigue during exercise. Importantly, physical inactivity appears to negatively affect the progression of the syndrome, while physical training can partially counteract this condition. In the present review, the role played by the group III/IV afferents feedback in the cardiovascular regulation during exercise and exercise-induced muscle fatigue of healthy people and their potential role in inducing exercise intolerance in CHF patients will be summarised.</p>

Note to Reviewers

We would like to thank both Reviewers for their thorough and considered review of our manuscript. We found all the comments to be thoughtful and constructive, and have allowed us to make some significant improvements to the manuscript. We hope these amendments are to your satisfaction. We have replied to each comment in this document (in red), and where a manuscript amendment was required, we have highlighted the changed text in yellow (added/revised words or sections) and in red (deleted) within the manuscript file. We hope you enjoy reading the revised version of the manuscript.

Reviewer #1:

This is an important and interesting review. The manuscript is very well designed and written. However, I suggest that the authors included a section about the effects of exercise training on group-III/IV receptors and/or mechano and metaboreflex.

AUTHORS: we really thank the reviewer for this useful comment. As suggested, we included a section “Exercise training as therapy for chronic heart failure patients” describing the general guidelines and effect of aerobic and resistance training on CHF as well as its potential beneficial effect on EPR.

Reviewer #2:

There are some questions to explain about the article «Exercise intolerance and fatigue in CHF:is there a role for group III/IV afferent feedback?»:

- Could you give an explanation about the relationship of this afferent feedback with the respiratory response?
- Is there any role for the diaphragmatic muscle in this afferent feedback?
- If so,have you reviewed the role of the respiratory training in this field/inspiratory muscle threshold?
- Could you give more information about the benefit of resistance training vs endurance training (continuous/intervalic)?

AUTHORS: we really thank the reviewer for these useful comments. We have included a section called “Exercise training as therapy for chronic heart failure patients” in which we described the effect of different types of training on physical capacity of CHF patient. In the same section we also included how these can reduce the exaggerated activity of peripheral muscle afferents.

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4 Luca Angius¹, Antonio Crisafulli²
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8 **Exercise intolerance and fatigue in chronic heart failure: is there a role for group III/IV**
9 **afferent feedback?**
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4 **Abstract**
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8 Exercise intolerance and early fatigability are hallmark symptoms of chronic heart failure
9 (CHF). While the malfunction of the heart is certainly the leading cause of CHF, the patho-
10 physiological mechanisms of exercise intolerance in these patients are more complex,
11 multifactorial, and only partially understood. Some evidences point towards a potential role of an
12 exaggerated afferent feedback from group III/IV **muscle afferents** in the genesis of these
13 symptoms. Overactivity of feedback from these muscle afferents may cause exercise intolerance
14 with a double action: by inducing cardiovascular dysregulation, by reducing motor output, and
15 by facilitating the development of central and peripheral fatigue during exercise. Importantly,
16 physical inactivity appears to negatively affect the progression of the syndrome, while physical
17 training can partially counteract this condition. In the present review, the role played by the
18 group III/IV afferents feedback in the cardiovascular regulation during exercise and exercise-
19 induced muscle fatigue of healthy people and their potential role in inducing exercise intolerance
20 in CHF patients will be summarised.
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33 **Keywords:** **Metabo-reflex**, Fatiguability, Circulation, Exercise pressor reflex, Sensory neurons,
34 **Muscle fatigue**.
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Introduction

Exercise intolerance and early fatigability are hallmark symptoms of chronic heart failure (CHF). These symptoms severely limit daily activities and have been traditionally considered as the consequence of the inability of the heart to meet the metabolic demand of the muscles during exercise, with the malfunction of the heart as a pump as the leading cause ¹. However, the pathophysiological mechanisms of exercise intolerance in CHF are more complex, multifactorial, and only partially investigated and understood.

At heart level, the combination of systolic and diastolic abnormalities concurs in reducing the capacity to increase cardiac output (CO). Moreover, several other abnormalities such as impairments in peripheral endothelial-dependent vasodilation, reduction in systemic oxygen delivery, reduction in pulmonary reserve, and respiratory muscle perfusion have all been observed and they potentially account for the reduced exercise capacity in this syndrome ²⁻⁵.

Changes in skeletal muscle metabolism, functioning, composition, and architecture have also been described and, in the last years, there has been mounting evidence that these changes play a pivotal role in the development of exercise intolerance and in the reduction of exercise capacity. Some clues point towards the existence of a peripheral reflex that becomes hyperactive secondary to the described skeletal muscle alterations and may contribute to the exercise intolerance and the early fatigability experienced by these patients ^{5,6}. Specifically, it has been reported that some hormonal systems (i.e. renin-angiotensin-aldosterone, vasopressin, and atrial natriuretic peptide) are over-activated and that patients show altered autonomic nervous system activity at rest and during exercise, with exaggerated sympathetic tone associated with parasympathetic withdrawal. While the exact mechanisms causing this hormonal and autonomic dysregulation are still to be fully elucidated, it appears that an exaggerated afferent feedback from group III/IV muscle afferents may be at least in part responsible for this dysregulation ^{7,8,6,5}. Importantly, physical inactivity appears to negatively affect the progression of the syndrome, while physical training can partially reverse this condition. Importantly, enhancements in exercise capacity observed after physical training appear to be the consequence of improvements in muscle and vascular function rather than in cardiac functions. Although effective in reducing mortality, classical pharmacological treatments, such as angiotensin-converting enzyme inhibitors, β -blockers, and diuretics show very limited or null effects on exercise capacity ^{3,6,9-12}.

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4 To date, most of the literature investigating the role of group III/IV muscle afferents have
5 focused on the physiology and pathophysiology of cardiovascular regulation during effort
6 exercise. Only recently a series of experiments have emphasised their role on muscle fatigue
7 development and in the inhibition of central motor drive, which negatively affect exercise
8 performance^{13,14}. Thus, overactivity of feedback from group III/IV muscle afferents may cause
9 exercise intolerance with a double action: by inducing cardiovascular dysregulation and by
10 facilitating the development of muscle fatigue. In the present narrative review, we will
11 summarise the role of the group III/IV afferents feedback in the cardiovascular regulation during
12 exercise and exercise-induced muscle fatigue of healthy people and their potential role in
13 inducing exercise intolerance in CHF patients.
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26 **Role of group III and IV muscle afferents on the cardiovascular regulation during dynamic** 27 **exercise in healthy subjects** 28 29 30 31

32 In healthy subjects, the cardiovascular adjustment to dynamic exercise is characterized by
33 an increase in heart rate (HR) and stroke volume (SV), which together enhance CO. At the same
34 time, a profound reduction in systemic vascular resistance (SVR) takes place due to metabolite-
35 induced vasodilation in the working muscle. As result, mean arterial pressure (MAP) remains
36 stable or slightly increases¹⁵⁻¹⁷. Behind these hemodynamic changes there is a fine tuning
37 operated by neural mechanisms.
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42 Specifically, at least three neural mechanisms concur in this physiological response. One
43 is a central mechanism, commonly known as “central command”. In this mechanism, the
44 cardiovascular control areas located in the brainstem are reflexively activated by regions of the
45 brain responsible for motor unit recruitment. Central command is believed to establish a basal
46 level of sympathetic activity and parasympathetic withdrawal to the cardiovascular apparatus
47 closely linked to the exercise intensity^{18,19}.
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53 This basic pattern of autonomic activity is in turn modulated by a second mechanism
54 arising from peripheral signals originating from type III/IV muscle afferents in the muscle, which
55 act as mechano- and metabo- receptors. Group III/IV nerve endings represent more than 50% of
56 the total muscle afferents and constitute the sensory arm of a reflex which is collectively termed
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4 the “exercise pressor reflex” (EPR). These muscle afferents convey information about the
5 mechanical and metabolic variations of the contracting muscle via the spinal cord to the
6 cardiovascular control centres within the brainstem^{18,20–22}. It was reported that most group III
7 afferents act mainly as “mechanoreceptors” as they respond to mechanical distortion, whereas
8 group IV afferents appear to respond to metabolites accumulation, so that they can be considered
9 as “metaboreceptors” as well as nociceptors. Several substances such as lactic acid, potassium,
10 bradykinin, arachidonic acid products, ATP, diprotonated phosphate, and adenosine are thought to
11 stimulate the metaboreceptors in the muscle^{23,24}. It should be noticed that a sub-population of
12 group III/IV nerve endings respond to both mechanical and chemical stimuli^{25,26}. Some
13 evidences suggest that mechanoreceptors can be sensitised by metabolites accumulation making
14 it difficult to isolate their pure mechano- from metabo properties^{23,27}. Group III/IV muscle
15 afferents project to the dorsal horn of the spinal cord. However, little is known about the central
16 pathways of the EPR their projections at cortical and subcortical level but it seems that the
17 *medulla oblongata* is essential for its expression^{22,28,29}.

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30 The activation of both central command and EPR leads to autonomic adjustments
31 characterised by increase in sympathetic activity and parasympathetic withdrawal. This
32 autonomic regulation is in turn modulated by the third reflex operating during exercise: the
33 baroreflex. Arterial baroreceptors are located in the carotid sinus bifurcation and aortic arch and
34 sense rapid changes in blood pressure thereby activating the baroreflex. When arterial blood
35 pressure is acutely increased or reduced, the baroreceptors are stretched or compressed, and this
36 deformation causes increment or reduction in afferent neuronal firing rate, respectively. The
37 control over blood pressure is achieved by reflexively inducing rapid adjustments in HR and
38 SVR in responses to changes in MAP^{30,31}. The baroreflex activity avoids any excessive variation
39 in blood pressure and opposes any mismatch between vascular resistance and CO^{32,32,33}.

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48 One interesting point of the functioning of these reflexes is how they interact their
49 interaction during dynamic exercise, as both the central command and the EPR can modulate the
50 activity of the baroreflex³⁴. In detail, it was reported that during exercise the operating point of
51 the baroreflex is shifted and that the stimulus response curve is relocated to a higher arterial
52 blood pressure in direct relation to exercise intensity, without any change in its sensitivity^{30,35,36}.
53 In short, the baroreflex is still operating during exercise, but the blood pressure operating point is
54 higher than rest, although it is as effectively as at rest in controlling blood pressure^{30,34,37}.

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4 It is remarkable that the target blood pressure can often be achieved despite a lack in
5 response of one of the regulated variables, thereby suggesting that these reflexes operate with a
6 high level of effectiveness and integration^{18,38,39}. For example, it has been demonstrated in
7
8 **several** human investigations dealing with EPR that when cardiac contractility cannot be
9 enhanced, the possibility to increase SV and CO is precluded. Then, the target blood pressure is
10 achieved by recruiting the SVR reserve (i.e., by inducing arteriolar vasoconstriction). Similarly,
11 if venous return is impaired and/or the reserve in cardiac preload is exploited, then the
12 recruitment of the SVR reserve is the main mechanism through which the EPR operates to adjust
13 hemodynamics⁴⁰. In short, it appears that whenever SV and CO can not properly increase (such
14 as in CHF patients), then exaggerated arteriolar constriction becomes the main mechanism
15 through which the target blood pressure is reached. Differently, in healthy subjects the preferred
16 cardiovascular adjustment during EPR is a flow-mediated (i.e. CO-mediated) mechanism
17 obtained by recruiting the inotropic and preload reserves⁴⁰.

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19 Hence, during exercise, central command, EPR, and baroreflex are all activated and
20 complex interaction occurs between these reflexes. While it is well ascertained that some
21 redundancy and neural occlusion exist between EPR and central command (i.e. their effects do
22 not sum), it is also remarkable that they can modulate the activity of the other two. As previously
23 exposed, the most studied interaction is the modulation of baroreflex operated by central
24 command and EPR. However, interaction has also been demonstrated between central command
25 and EPR. Actually, several evidences suggest that inputs from type III/IV muscle afferences
26 modulate the central command activity and exert an inhibitory effect on central motor drive⁴¹. In
27 particular, it was observed that reduction in afferent input from type III/IV **muscle afferents**
28 during exercise obtained with epidural anaesthesia resulted in an increase in central command
29 activity. These findings support the thesis that central command cannot work properly without
30 adequate feedback from peripheral muscle and that, at the same time, this feedback limits central
31 command and motor drive^{13,41}.

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55 **Role of group III and IV muscle afferents on the development of muscle fatigue during**
56 **dynamic exercise in healthy subjects**
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4 Sustained physical exercise inexorably leads to a reduced capacity to generate maximal
5 force or power. This has been commonly described as muscle fatigue ¹⁴. Most of muscle fatigue
6 has been documented to occur at or distal to the neuromuscular junction ⁴², and has been
7 commonly defined peripheral fatigue. Conversely, central fatigue refers to the inability of the
8 central nervous system to optimally recruit the muscle (e.g. a significant decrease in voluntary
9 activation) ¹⁴. Supraspinal fatigue, a subset of central fatigue, can be described as a suboptimal
10 output from the motor cortex ¹⁴. Consequently, the interaction between central and peripheral
11 fatigue leads to decrease in maximal force or power. The role and interplay of central and
12 peripheral fatigue in exercise tolerance and termination has been object of discussion for several
13 years ^{43,44}. Peripheral fatigue is measured by comparing the force of the muscle elicited by
14 electrical stimulation of the corresponding motor nerve before and after exercise ⁴⁵.
15 Quantification of central fatigue is generally performed with the superimposed twitch technique
16 ⁴⁶. More recently, transcranial magnetic stimulation (TMS) has been effectively used to study and
17 quantify supraspinal fatigue on different exercise paradigms ⁴⁷.

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30 Several experiments have been performed to understand and identify the physiological
31 mechanisms contributing to the generation of muscle fatigue ^{14,43}. A considerable amount of
32 experimental evidences supports the hypothesis that during high intensity exercise, the activity of
33 group III/IV muscle afferents might facilitate the development of central fatigue via an inhibitory
34 feedback at different sites of the motor pathway and also by influencing the level of motor unit
35 activation ^{41,48}. Injection of hypertonic saline in the muscle has been classically used as
36 experimental approach to stimulate type III/IV muscle afferents. A reduction of low-threshold
37 motor unit discharge rate during low intensity muscular contraction ^{49,50} and maximal force
38 production of knee extensor ⁵⁰ and elbow flexors muscles ⁵¹ have been found this approach.
39 Other studies reported a decrease in motor evoked potentials elicited by transcranial direct
40 stimulation TMS, thus providing evidences of an inhibitory effect at supraspinal level ⁵². The
41 reduction in maximal force production seems to be caused by decrease in voluntary activation
42 (e.g. increase in central fatigue). This hypothesis seems to be confirmed in studies where
43 voluntary activation was significantly reduced in elbow flexors muscles ⁵¹. On the other hand,
44 other studies reported an increase in spinal motoneurons excitability ⁵³. Overall, these studies
45 showed that motor unit activation can be partially regulated by peripheral reflexes elicited by
46 group III/IV muscle afferents.

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4 Post-exercise circulatory occlusion has also been employed as alternative experimental
5 approach to stimulate group III/IV muscle afferents. In regards, early investigations
6 demonstrated that maximal voluntary contraction and voluntary activation were significantly
7 reduced and did not recover until the circulation was restored ⁵⁴⁻⁵⁷. Interestingly, when the
8 fatigued muscle was kept ischemic, the decline in maximal force and voluntary activation was
9 also present in unfatigued muscle of the same limb ^{55,56}. These findings suggest the presence of
10 convergence and divergence effect at spinal level ⁵⁸, where muscle afferents from one muscle
11 may have projections to the dorsal horn receiving inputs from other adjacent muscles. Studies
12 involving TMS demonstrated that the decline maximal force production and voluntary activation
13 was also caused by an inhibitory effect at supraspinal level ^{55,56,59}.

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Pharmacological blockade has also been adopted as experimental approach to study the
role of group III/IV muscle afferents ⁴¹. This type of intervention performed prior whole-body
exercise, is able to attenuate approximately 60% of feedback from these afferents. Overall, these
investigations reported that during high intensity cycling exercise, voluntary drive (estimated by
means of electromyography), metabolites accumulation, and peripheral fatigue increased when
the feedback from exercising muscles was attenuated ⁶⁰⁻⁶². It should be considered, that in these
studies, physical performance was unchanged or impaired when afferent feedback was
attenuated, and this was probably the consequence of an impaired cardiorespiratory response
^{41,61,63}. More recently, a series of experiments involving TMS reported an increase in
corticospinal excitability when feedback from exercising muscles was attenuated ⁶⁴⁻⁶⁶. These
preliminary findings seem to confirm previous experiments showing that group III/IV muscle
afferents promote central fatigue during exercise.

Group III and IV muscle afferents and their role in cardiovascular regulation and fatigability in patients with chronic heart failure

During EPR, several abnormalities in the cardiovascular regulation have been
demonstrated in individuals suffering from CHF. To study the metaboreflex, i.e. the metabolic
part of the EPR, some human studies employed the post-exercise muscle ischemia method,
which induces metabolites accumulation thereby stimulating type III/IV muscle afferents in the

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4 muscle. During the metaboreflex activation in patients with CHF, an increase in MAP similar to
5 that observed in healthy individuals was found. However, the mechanisms underlying this
6 cardiovascular response were markedly different between patients and controls. In detail, in
7 patients suffering from CHF the rise in MAP was reached via a SVR increase, while in healthy
8 individuals this was the result of a flow increment, i.e. CO elevation ⁶⁷. This observation was
9 recently replicated also in patients suffering from heart failure with preserved ejection fraction ⁶⁸ as
10 well as in patients with coronary artery disease ⁶⁹. This abnormal hemodynamics seemed the
11 consequence of the incapacity of CHF patients to recruit the reserves in cardiac performance and
12 in cardiac pre-load in response to the metaboreflex. The exaggerated increase in SVR (i.e.
13 arteriolar constriction) compensated for the inability to increase SV. Interesting, in CHF patients
14 the MAP response was well preserved notwithstanding their lower CO in comparison with
15 healthy subjects. Hence, it appears that CHF causes a functional shift from a flow-mediated (i.e.
16 CO increase) to a vasoconstriction-mediated (i.e. SVR increase) in the mechanisms by which the
17 target blood pressure is reached during EPR. It is to be considered that this hemodynamic
18 scenario closely resembles what has been also reported in animal models of CHF ⁷⁰⁻⁷².

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32 It is to be highlighted that the described exaggerated arteriolar constriction in response to
33 metaboreflex potentially restrains muscle perfusion ⁷³, and this likely contributes to the early
34 development of fatigue and exercise intolerance shown by CHF patients. In detail, while in
35 healthy subjects metaboreflex activation maintains skeletal muscle perfusion ⁷³, this is not the
36 case in CHF, where exaggerated vasoconstriction takes place during the metaboreflex. In this
37 scenario, even the exercising muscle may become vasoconstricted ^{67,74,75} and this occurrence
38 may lead to deleterious consequences in terms of exercise tolerance and muscle tropism.

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65 It has been proposed the so called “muscle hypothesis” to explain at least in part the
exercise intolerance shown by CHF patients. In detail, it has been suggested that CHF initiates a
vicious circle where damage to the heart and disturbance in central haemodynamics trigger
compensatory mechanisms, including neurohumoral and sympathetic activation, which
persistently vasoconstricts the muscle circulation. In the longer term, this condition becomes
harmful and damages at vascular and endothelial level develop, with chronic inflammation, and
necrosis at muscular level. Various signs of myopathy, muscle mass reduction, and abnormal
metabolic and mechanical functions are actually present in CHF ^{76,77}. Importantly, these muscle
abnormalities correlate better with exercise tolerance compared to measures of left ventricular

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4 function ⁷⁴. The described muscle abnormalities in turn cause elevation in the feedback from
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6 III/IV afferents during muscle contraction, and this heightens EPR activity and dys-regulates
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8 hemodynamics, with excessive arteriolar constriction and muscle hypoperfusion. In short, in
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10 CHF central hemodynamic abnormalities in response to EPR initiates a vicious circle which, in
11
12 the longer term, causes muscle hypoperfusion, muscle wasting, and reduction in strength ^{5,78}.

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14 In support to the “muscle hypothesis” there are experimental findings in heart transplant
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16 recipients during the metaboreflex activation. In these patients exercise capacity, although
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18 improved, remains abnormally impaired after transplant compared to normal individuals. This
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20 indicates that restoring cardiac function does not fully enhance aerobic metabolism. A possible
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22 explanation for the incomplete recovery might be muscular abnormalities which developed
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24 before transplant and persist after transplant, thereby impairing exercise capacity in these
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26 patients ^{79,80}. Moreover, it has been observed that improvement in exercise capacity after heart
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28 transplant was paralleled by improvements in cardiovascular response to metaboreflex, with a
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30 gradual reduction in the metaboreflex-induced arteriolar constriction ⁷⁹. Collectively, these
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32 findings in heart transplant recipients seem to indicate that the EPR is dys-regulated in these
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34 patients before transplant and that this dys-regulation tends to ameliorate several months after
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36 transplant, in parallel with muscle metabolism and functions. This observation appears to be in
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38 line with the “muscle hypothesis” of CHF.

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40 Some authors have argued against the concept that metaboreflex is accentuated in the
41
42 CHF syndrome. Specifically, they have proposed that mechanoreceptor rather than
43
44 metaboreceptor stimulation is responsible for the abnormal haemodynamic observed in CHF
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46 during EPR activation ⁸¹⁻⁸³. It has also been proposed that metaboreflex control of sympathetic
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48 activity is attenuated in CHF and that metaboreceptors are desensitised in this syndrome ²⁸. It is
49
50 likely that the conflicting results in scientific literature on whether muscle metaboreflex is
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52 attenuated or accentuated may depend on the degree of muscle abnormalities of the CHF
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54 population, the degree of metaboreceptor desensitisation, and the mode of exercise being
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56 performed. Furthermore, authors reporting attenuated metaboreflex and accentuated
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58 mechanoreflex employed animal model of CHF (mainly rats), thus the application of these
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60 findings in humans is contentious. Moreover, evidence suggests that mechanoreceptors are
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62 sensitised by metabolites, thus rendering it difficult to differentiate the role of mechanoreflex
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64 from that of metaboreflex ²⁷. Finally, it should be considered that, in the human model, most
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4 studies dealing with metaboreflex employed the post-exercise muscle ischemia method to assess
5 metaboreflex function. This manoeuvre probably rules out any contribution of mechanoreceptors
6 since they do not operate in this setting.
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10 Whatever the mechanoreflex or the metaboreflex are responsible for the abnormal
11 elevation in EPR activity, the EPR is dysfunctional in these patients. It is interesting to note that
12 Amann and colleagues ⁸⁴ were able to demonstrate that lumbar intrathecal fentanyl reduced the
13 excessive vascular resistance during knee-extensor exercise in a CHF population, thereby
14 demonstrating a role of type III/IV muscle afferents in the abnormal hemodynamics in this
15 syndrome. More recently, Van Iterson and colleagues ⁸⁵ reported that blocking type III/IV muscle
16 afferents with intrathecal fentanyl in a population of CHF patients resulted in a faster $\dot{V}O_2$
17 kinetics. They hypothesised that the slower $\dot{V}O_2$ kinetics of CHF was the consequence of
18 peripheral and central hemodynamic maldistribution due to abnormal group III/IV muscle
19 afferents activation and that blocking these afferents could at least partially restore a normal
20 exercise response.
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24 Concerning the role played by type III/IV muscle afferents on exercise capacity, it should
25 be underscored that very few studies have been conducted in clinical population ^{84,86}. Gagnon
26 and colleagues ⁸⁶ were the first to investigate the exercise response following their
27 pharmacological blockade in COPD. Contrarily to what found in healthy population, endurance
28 time during a cycling constant work-rate was enhanced by an average of 215 seconds. According
29 to the authors, the reduced and delayed hyper-ventilatory response and lowered perceived
30 dyspnoea during exercise might provide a possible explanation for the increased exercise
31 capacity. Furthermore, a deeper loss in quadriceps muscle strength and a higher lactate level after
32 exercise with spinal anaesthesia was also found. In CHF patients, Amann and colleagues ⁸⁴ found
33 an increase in vascular conductance, peripheral blood flow (15% increase), and leg oxygen
34 delivery together with a significant reduction in MAP following intrathecal fentanyl.
35 Interestingly, the decline in maximal force production of the quadriceps following exercise was
36 attenuated by 30% compared to control condition. Taken together, these findings suggest that in
37 these kinds of clinical population, type III/IV afferents feedback might play a pivotal role to
38 reduce exercise tolerance ^{6,87,88}.
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57 One phenomenon recently proposed to explain the potential influence of group III/IV
58 afferents on the muscle fatigue development is their ability to affect cerebral blood flow and
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4 oxygenation. It has been proposed that the EPR activation lowered cerebral perfusion by
5 counteracting the normal vasodilation occurring at brain level during exercise. This would
6 increase the sense of effort and impair motor drive ⁹. However, the regulation of cerebral
7 circulation is complex, and more research is warranted to better understand the phenomenon and
8 to confirm this hypothesis.
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13 **Experimental studies proposed that afferent feedback from ventilatory muscles might be**
14 **important for exercise intolerance in CHF patients. Both animal and human model reported**
15 **histological and biochemical alterations of the diaphragm muscle in CHF ⁸⁹. Respiratory muscle**
16 **dysfunction is typically observed in CHF patients and this is often called as respiratory muscle**
17 **weakness which is caused by a substantial reduction in respiratory muscle strength (in**
18 **particularly the diaphragm) ⁹⁰. During exercise, CHF patients develop early diaphragmatic**
19 **fatigue by therefore limiting the ventilatory response and so reducing pulmonary gas exchange**
20 **and oxygen delivery. Furthermore, increased in breathlessness, exertional dyspnoea from low**
21 **exercise intensities is typically observed. Similarly, to the locomotor muscles, an exaggerated**
22 **metaboreflex from respiratory muscle has been observed ⁹¹. This mechanism, also described as**
23 **inspiratory muscle metaboreflex, is particularly important during sustained exercise as it**
24 **modulates the competition for blood flow between the locomotor and respiratory muscles ⁹². This**
25 **mismatch potentially leads to increase in the ventilatory work and may exacerbate exertional**
26 **dyspnoea and exercise intolerance. Taken together, these respiratory muscle abnormalities have**
27 **been shown to contribute to early development of fatigue in CHF patients ⁹⁰.**
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41 It should be considered that the number of studies is very limited and therefore the
42 precise role of group III/IV muscle afferents contributing to the development of muscle fatigue
43 and exercise tolerance in the clinical population is largely unknown. Nevertheless, these
44 preliminary studies provide encouraging evidences that these muscle afferents can be the target
45 of future therapeutic strategies. The major putative mechanisms responsible for the exercise
46 intolerance and early fatigue induced by type III/IV afferents feedback in CHF are shown in Fig
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Exercise training as therapy for chronic heart failure patients

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4 Aerobic exercise training is recognized as an important adjunct for improving the quality
5 of life of CHF patients. The benefits aerobic training have been discussed in previous reviews
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8^{93,94}. Aerobic training demonstrated to positively affect maximal oxygen consumption, central
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10 and peripheral hemodynamic function, peripheral vascular function and muscular function.
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12 These adaptations result in a higher workload for the same HR and perceived exertion⁹³.
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14 Continuous aerobic training of 45-60 min duration is well tolerated and recommended for CHF
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16 patients. Recently, interval/intermittent aerobic training has been shown to be more effective.
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18 This involves <5 min bouts at 90-95% of the maximal exercise capacity interspaced by >3 min
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20 of recovery⁹⁴.

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22 Resistance training has also been introduced to counteract the decline in functional
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24 alteration and muscle mass of the locomotor muscles. Previous works recommended an intensity
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26 of 30-40% of 1RM and RPE <12 for increasing local aerobic capacity, while 40-60% of 1RM
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28 and RPE <15 for increasing muscle mass. It is importance to notify that aerobic exercise remain
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30 the main training and therefore the resistance training can be considered as complement⁹⁴.

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32 Since respiratory muscle weakness is inversely correlated with exercise capacity,
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34 interventions with the potential to improve respiratory muscle strength might be able to counter
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36 this condition. Recent studies focused on the role of respiratory muscle training for the
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38 improvement of respiratory muscle strength in CHF. Several beneficial effects such as
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40 improvement in maximal inspiratory capacity, improvement in peripheral and respiratory oxygen
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42 supply, reduction in exertional dyspnoea have been reported together with improved exercise
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44 capacity and exercise tolerance with a better quality of life⁹⁸. Winkelmann et al.⁹⁹ showed that
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46 inspiratory muscle training combined with aerobic training was more beneficial than aerobic
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48 training alone in CHF patients. However, the optimal training regimen is yet to be defined.
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50 However, it seems that the benefits of respiratory muscle training appear to be intensity-
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52 dependent suggesting that high intensity training regimens is required to obtain improvement in
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54 aerobic capacity¹⁰⁰. Interestingly, a study performed by Chiappa and colleagues⁹¹ showed that
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56 inspiratory muscle training was capable to decrease limb vasculature resistance by increasing
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58 blood flow of limb muscles at rest and during exercise. One of the main results of this
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60 adaptations was the attenuation of the metaboreflex activity⁹¹. Other mechanisms might also be
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62 responsible for the increase in exercise capacity in CHF patients such as resting left ventricular
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4 function, endothelial vasodilator function and improved ventilatory response. However, other
5 mechanisms are yet to be elucidated.
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8 In animal models of CHF (rats), it was demonstrated that exercise exerts beneficial
9 effects on the exaggerated EPR, although the underlying mechanisms have not be completely
10 elucidated ^{95,96}. Observations in humans reported that exercise training could reverse the
11 exaggerated exercise-induced sympathetic activity, vasoconstriction, and ventilatory drive in
12 patients with CHF ⁹⁷. More recently, these observations have been confirmed and support the
13 concept that the exaggerated EPR activity is at least in part responsible for the sympathetic
14 overactivity in CHF patients and that this condition can be successfully counteracted by exercise
15 training ⁹⁵. However, it is to be acknowledged that the mechanisms of exercise-mediated
16 beneficial effects on EPR remain largely unknown in humans. Further studies are warranted to
17 definitively prove whether exercise training is effective in reducing the exaggerated EPR in these
18 patients.
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32 **Conclusions and future directions**

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35 In summary, the pathophysiological mechanisms of exercise intolerance and exercise
36 induced muscle fatigue in patients with CHF are complex and involve peripheral and central
37 factors. In this context, reflexes mediated by group III/IV muscle afferents appear to play an
38 important role in the phenomenon. The exaggerated afferent feedback coming from these fibres
39 potentially causes hemodynamic dysregulation, with excessive sympatho-excitation and
40 arteriolar constriction. The abnormally elevated neural feedback may also exacerbate the rate of
41 development of peripheral and central fatigue by causing a restriction in motoneuronal output.
42 Whether this exaggerated feedback arises from the activity of mechano- or metabo-receptors is
43 still a matter of debate. There is also the possibility that both receptors are involved in the
44 phenomenon. Future study specifically designed is necessary to unravel this question.
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53 Although demonstrated in few studies, exercise induced muscle fatigue in clinical
54 population can be partially attributed to a higher and/or abnormal activity of group III/IV muscle
55 afferents and also explain the reduced exercise capacity and exercise intolerance of patients
56 suffering from CHF. In light of these findings, further studies are required to elucidate the
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4 mechanisms of group III/IV muscle afferents at various sites of the motor pathway and
5 peripheral level during exercise.
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8 It is important that future investigations take into account the possible effects of
9 pharmacological therapy on the correction of the type III/IV muscle afferents hyperactivity. From
10 a clinical perspective it would be useful to verify whether blockade these receptors limits the
11 excessive sympathetic excitation and the reduced motor output observed in CHF patients. To the
12 best of our knowledge, a drug that specifically blocks these afferents has yet to be tested in
13 humans. Another further field for future research is the effect of physical training on type III/IV
14 afferents activity. Such an investigation would reveal whether a physical training program would
15 dampen the hyperactivity shown by these muscle afferents in CHF syndrome. This would have
16 the practical consequence to test whether the prescription of physical activity and the adoption of
17 an active lifestyle is an effective means to treat the exercise intolerance and to reduce fatigability
18 in these patients.
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29 30 **Author contribution**

31 LA and AC contributed to the conception or design of the work. LA and AC drafted and
32 critically revised the manuscript. LA and AC gave final approval and agree to be accountable for
33 all aspects of work ensuring integrity and accuracy.
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48 **Conflict of interest**

49 Luca Angius and Antonio Crisafulli declare that they have no conflicts of interest relevant
50 to the content of this review.
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4 **Figure caption**
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8 **Fig. 1** putative mechanisms responsible for the exercise intolerance and early fatigue induced by
9 type III/IV afferent feedback in chronic heart failure. Abnormal central abnormal hemodynamics
10 initiate a cascade which ultimately result in an increase in III/IV afferents feedback activity. It is
11 to be highlighted that physical training may potentially counteract this malfunctioning at various
12 levels, while, to date, no pharmacological intervention has been demonstrated able to correct this
13 abnormal regulation.
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Figure 1

