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Original Scientific Paper

Exercise intolerance in chronic heart failure: mechanisms and therapies. Part I

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Muscular fatigue and dyspnoea on exertion are among the most common symptoms in chronic heart failure; however their origin is still poorly understood. Several studies have shown that cardiac dysfunction alone cannot fully explain their origin, but the contribution of the multiorgan failure present in this syndrome must be highlighted. In this study, divided in two parts (see part II: pp. 643–648), we aimed to summarize the existing evidence and the most controversial aspects of the complex interplay of different factors involved in symptom generation. In this first part of the review, six key factors are revised: the heart, the lung, the skeletal muscle, the hormonal changes, the O_2 delivery to the periphery, the endothelium. In the second part, the role of the excitatory reflexes and the cardiac cachexia will be presented, and finally, the potential therapeutic implications are discussed. We believe that a better knowledge of the pathophysiology of this syndrome may contribute to the management of the patients and to the improvement in their stress tolerance and quality of life. *Eur J Cardiovasc Prev Rehabil* 17:637–642 © 2010 The European Society of Cardiology

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The problem: origin of symptoms in heart failure

Chronic heart failure (CHF) is a multisystem syndrome. Although initiated by a reduction in cardiac function, it is characterized by the activation of compensatory mechanisms, which involve the whole body: haemodynamic, autonomic and neuro-humoral changes may be initially beneficial, but subsequently become detrimental and lead to perpetuation of the syndrome [1]. These, once activated, are responsible for severe changes in many vital organs and may generate symptoms. Muscular fatigue and dyspnoea are the more common symptoms in CHF; however their origin is still poorly understood [2]. Several studies have shown that changes in cardiac function cannot fully explain their origin [3]. Interventional studies have also opposed a concept of central haemodynamics as

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Table 1 Contribution of different mechanisms to exercise intolerance symptom in heart failure

Factor	Dyspnoea	Muscle fatigue
Heart	+	±
Lung	+ +	±
Muscle	±	+ + +
Hormonal changes	+	+
Oxygen delivery	±	+ +
Endothelium	+	+ +
Excitatory reflexes	+ +	+
Cardiac cachexia	±	+ + +

the sole determinant of exercise capacity in CHF: pharmacological agents, which increase cardiac output (dobutamine) and/or reduce pulmonary capillary wedge pressure (hydralazine) do not result in an immediate increase in exercise capacity. Better knowledge of the pathophysiology of this syndrome may contribute to the management of the patients and to the improvement in their stress tolerance and quality of life [4].

This position study, divided into two parts, endorsed by the 'Exercise Physiology, Sport Cardiology and Cardiac Rehabilitation' Working Group of the Italian Society of Cardiology (Italian Federation of Cardiology), summarizes the existing evidence of the complex interplay of different factors involved in symptom generation in CHF because of systolic dysfunction. The roles of the key factors are revised and therapeutic implications are discussed here. In this first part of the review, the contributions of the heart, the lung, the skeletal muscle, the hormonal changes, the O_2 delivery to the periphery and the endothelium are presented. In the second part, the roles of the excitatory reflexes and the cardiac cachexia will be presented, and finally, the potential therapeutic implications are discussed.

Table 1 summarizes the various causes of the two major CHF symptoms, dyspnoea and fatigue, and the relative contribution of the above considered factors.

The heart

Intuitively, central haemodynamics, and the heart in particular, should be the major determinants of exercise capacity. There are several items in favour of this concept. Exercise capacity (expressed as peak O_2 consumption or peakVO_2) is strictly related to cardiac output on the basis of the Fick principle

$$\begin{aligned}\text{peak}Vo_2 &= \text{Cardiac Output} \times (\text{A} - \text{V})\,O_2\,\text{diff} \\ &= \text{Stroke Volume} \times \text{Heart Rate} \\ &\quad \times (\text{A} - \text{V})\,O_2\,\text{diff}\end{aligned}$$

where (A–V), O_2 difference is arterio–venous O_2 difference, which is usually similar between normal individuals and CHF patients [5]. Thus, exercise intolerance is mainly related to heart function and its chronotropic response, both altered in CHF. In keeping with this, in CHF secondary to idiopathic cardiomyopathy, the cardiac response to low-dose dobutamine, assessed by echocardiography, is correlated with peakVO_2 [6]. This not only suggests the importance of the pump function, but also that low-dose dobutamine, which is insensitive to factors such as skeletal muscle deconditioning or poor motivation, is a valuable alternative technique to peakVO_2 determination for assessing the severity of the disease. Furthermore, many heart abnormalities, such as arrhythmias (abnormal heart rate or rhythm) or valve diseases, if severe enough, can cause shortness of breath and/or exercise intolerance.

The leading role of pump function has been challenged by several evidences of poor relationship between resting left ventricular (LV) systolic function and peakVO_2 [7]. Recently, the role of the heart has been emphasized, but that different indices of LV dysfunction (and not just ejection fraction) need to be monitored, for example, indices of longitudinal LV function assessed by tissue Doppler imaging [8]. Furthermore, LV asynchrony, rather than uniform depression of systolic ventricular function, may play a key role in determining the maximum exercise tolerance by prolonging the total isovolumic period within the cardiac cycle [9]. The important contribution of electromechanical conduction delays to symptom generation has been further confirmed [10], regardless of baseline LV systolic dysfunction severity [10]. These findings might also explain the inconsistent effect of positive inotropic agents [11], whose efficacy may be conditioned by the substratum of the myocardial disease.

Importantly, the strong relationship between diastolic abnormalities and exercise limitation should be not underscored [12,13]. Severity of effort intolerance is linked with LV filling pressure, and consequently, therapeutic interventions that lower this pressure may enhance exercise capacity.

The lung

A modified lung physiology is an important determinant of exercise intolerance, ventilation inefficiency and dyspnoea sensation in CHF [14]. Classically, the initial source of injury to the lung is an impaired LV haemodynamic because of increased LV filling pressure and consequent untoward backward injury on the pulmonary capillary bed. The consequences of these haemodynamic perturbations are two-fold: (i) changes in lung airways function and mechanical properties, (ii) development of gas exchange abnormalities because of alveolar–capillary injury and dysfunction. Both play a key role in the limitation of maximal exercise performance and may significantly affect the physiological linear ventilatory response to maximal exercise. It is also possible that a damaged endothelium (see chapter 6) may play a critical role in lung dysfunction.

An excessive ventilatory requirement during incremental workloads is typical of CHF and is conventionally identified as an increased relationship between the rise in ventilation and the rate of carbon dioxide elimination

(VE/VCO_2). The VE/VCO_2, either measured in specific exercise periods [15] or during the entire exercise (or the greatest part of exercise) as VE/VCO_2 slope, has a remarkable value for risk stratification and prognostic prediction [16]. The increased VE/VCO_2 slope is ascribable to high dead space ventilation, low CO_2 partial pressure and/or abnormal ventilatory control mechanisms, with convincing evidence presented for all these putative mechanisms. The next subheadings briefly focus on the pulmonary determinants of an augmented VE/VCO_2.

Airways function abnormalities

Mechanical lung properties of CHF patients are primarily challenged by an increased stiffness whose entity depends on the severity and duration of the disease. Major pathogenetic bases for lung stiffening are interstitial lung congestion and heart to lung pathological interaction because of cardiomegaly, vascular engorgement, increased alveolar surface tension, unequal ventilation and activation of contractile elements of the vascular wall [17]. The combination of these factors leads to the development of a typical restrictive lung pattern [18,19]. According to Wasserman, the lung restriction may occur as a function of haemodynamic derangement, suggesting a pathogenetic role of an increased wasted ventilation with those patients with higher VE/VCO_2 slope exhibiting the higher dead space to tidal volume ratio and a premature increase in respiratory rate as a compensatory mechanism. In agreement with this, some degree of reversal in pulmonary restriction and improvement in the ventilatory response to exercise were shown after ultrafiltration, and afterload reduction with dialysis with lung decongestion, emphasizing the role of fluid overload [20].

Lung diffusion abnormalities

Diffusion changes and gas exchange inefficiency occur mainly in the setting of diastolic CHF [21]. As for abnormalities in lung mechanics, pressure elevation in the pulmonary circulation is the initial source of injury to the anatomical integrity and functional properties of lung capillaries and alveolar spaces (i.e. the blood gas barrier); this can be studied by evaluating gas diffusion for carbon monoxide or nitric oxide techniques (DLCO and DLNO, respectively). A low DLCO relates with disease severity and increased pulmonary vascular resistances [22]. For a given haemoglobin (Hb) concentration, these changes are primarily driven by a reduction in alveolar membrane component (Dm) rather than changes in capillary blood volume [23]. A correlation between alveolar–arterial O_2 gradient, DLCO and peak VO_2, and between Dm and VE/VCO_2 slope were shown supporting the role of lung diffusion abnormalities [24].

The skeletal muscle

A key role of the periphery has emerged, generating the 'muscle hypothesis', where exertional dyspnoea and fatigue are resulting from skeletal muscle disorders, also because of deconditioning [25]. These disorders are responsible for the maintenance and progression of the systemic abnormalities, at neurohormonal level, leading to a vicious circle. This constitutes the physiological basis for the benefit of physical conditioning in prognosis (Fig. 1).

Intrinsic modifications in muscle composition (and not only blood flow reduction) play a major role: qualitative and quantitative changes, such as muscle wastage [26] and shift from slow (fatigue resistant) to fast (fatigue non-resistant) fibre type, reduction in mitochondrial density and enzymes are likely to be involved [27]. An imbalance between protein synthesis and degradation with resultant cachectic status (see chapter 8, part II) plays an important role in symptoms. Programmed cell death has been found both in skeletal muscle and interstitial cells [28].

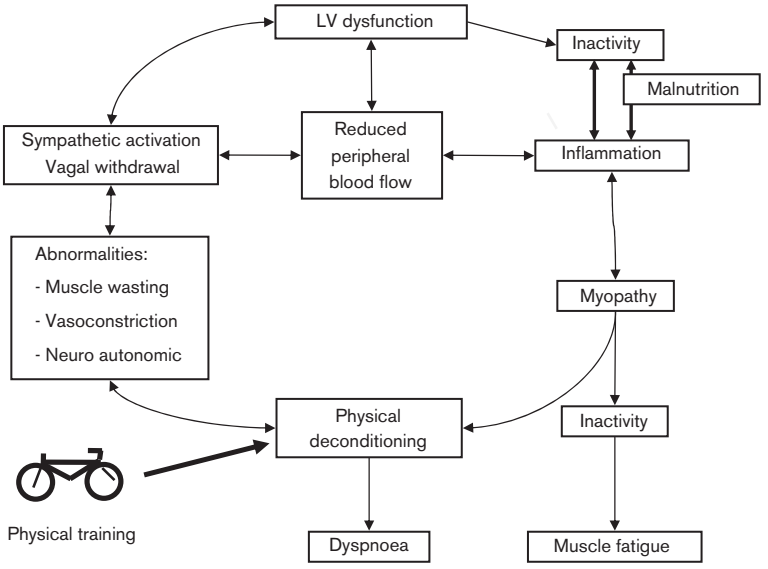
The regulation of fibre type involves the growth hormone/insulin-like growth factor-1/calcineurin/transcriptional co-activator PGC1-α cascade [29], whereas mechanisms leading to muscle wastage, protein degradation can occur through cytokine-triggered skeletal muscle apoptosis, but also through ubiquitin/proteasome and nonubiquitin-dependent pathways [30]. The systems controlling ubiquitin/proteasome activation are triggered by tumour necrosis factor α and growth hormone/insulin-like growth factor 1 [31]. Apoptosis correlates with the severity, triggered by tumour necrosis factor α: it can be induced by its second messenger sphingosine in-vitro experiments with activation of caspases 3 and 9 and mitochondrial cytochrome *c* release [32].

Furthermore, other factors contribute to muscle dysfunction. In the muscle, high levels of oxidation depressed peak force generation and slowed contraction and relaxation times [33]. A chronic inflammatory status is associated with elevation of proinflammatory cytokines: inducible NO synthase (NOS) production and oxidative stress are sufficient to activate nuclear factor-kappa B, a transcription factor for proinflammatory cytokine gene expression that contributes to muscle damage. Oxidation of sarcomeric proteins, such as myosin heavy chains, tropomyosin and actin lead to contractile impairment and muscle fatigue [34].

The hormonal changes

Neurohormonal response to heart damage may be considered a physiological compensatory response, aimed at maintaining an adequate circulatory support particularly during stress. Cardiac output is sustained through an increase in plasma volume, heart rate and contractility. These responses are elicited by activation of adrenergic drive to heart and vessels, parasympathetic withdrawal, increased renin–angiotensin–aldosterone system activation

Fig. 1



Skeletal muscle hypothesis. LV, left ventricular.

[35] associated with a vasoconstrictive endothelial response by endothelin secretion [36] and vasopressin release [37]. However, chronically maintained neuroendocrine activation becomes detrimental and leads to the overt clinical picture of CHF. Autonomic imbalance exerts a proarrhythmic and profibrotic effects, sodium-water retention with increased extravascular water and peripheral and lung oedema (leading to dypneoa). Arteriolar vasoconstriction provokes negative effect in trophism and function of skeletal muscles, renal hypoperfusion and dysfunction (leading to fatigue).

At organ level, neurohormonal activation supports the ventricular, vascular and tissue remodelling processes, associated with alterations at structural level, by ongoing cell apoptosis and necrosis, hypertrophy, fibrosis, leading to irreversible morphofunctional changes in the heart, peripheral muscles, lungs and kidney.

Plasma norepinephrine is an independent predictor of mortality [38]. Thus counteraction of the activated adrenergic nervous system and renin–angiotensin–aldosterone system constitutes the pathophysiological basis for modern pharmacological treatment using neurohormonal antagonists, namely β-blockers, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers and aldosterone antagonists.

In a significant percentage, patients with CHF may present with a 'low triiodotironine status', characterized by reduced peripheral conversion of the thyroid prohormone tetraiodotironine to the biologically active hormone triiodotironine. Low triiodotironine level contributes to the overall derangement of the neurohormonal control of circulation and recognizes a prognostic role [39]. CHF is associated with insulin resistance, characterized by both fasting and stimulated hyperinsulinaemia, which may induce altered metabolism of skeletal and heart muscle [40].

Neurohormonal activation is associated in advanced stages with immunoinflammatory flare, as indicated by higher levels of some cytokines, such as tumor necrosis α or interleukin 6, though targeted treatment has failed, up to now, to improve the patient outcome [41].

Thus, a chronic 'fly or fight' adaptation takes place. The overall predominance of sodium retention, vasoconstrictive systems on the main counter regulatory system is represented by cardiac endocrine function, that is, the ability of atrial and ventricular cardiomyocites under haemodynamic stress to produce and secrete two peptide hormones (atrial and brain natriuretic peptides) with potent natriuretic/vasodilator and antihypertrophic/apoptotic properties [42]. Their assay may guide the evaluation of efficacy of therapeutical efforts, including physical aerobic training [43].

The role of cortisol and sexual hormones is, at present, under intense evaluation. Indeed, high cortisol administration prevents endothelium damage during acute coronary syndrome and women seem to be more protected from nocturnal periodic breathing both in the presence of CHF or during high-altitude exposure.

The oxygen delivery to the periphery

Classically, O_2 delivery is measured as cardiac output times the arterial O_2 content (CaO_2). However, this is O_2 delivery to the capillary, which does not consider the O_2 flow from the capillary to the mitochondria, where O_2 partial pressure in the blood (pO_2) is around 0 mmHg.

CaO_2 depends on Hb concentration, pO_2 and the position of the oxyhaemoglobin (Hb-O_2) dissociation curve. The latter, however, has little effect on CaO_2. Indeed in the absence of hypoxia in CHF, and in normal individuals, in the systemic artery, the Hb-O_2 dissociation curve is flat on its upper part so that whatever shifts right ward or leftward (acidosis, temperature and molecules such as 2,3-diphosphoglycerate) do not have any significant effect CaO_2 [44].

In CHF cardiac output is low; its increase during exercise is blunted and patients are often anaemic: all these factors reduce CaO_2. In the systemic artery, CaO_2 increases during exercise, mainly above the anaerobic threshold, because of an increase in Hb. Exercise-induced haemo concentration is likely because of an oncotic effect of increased intracellular lactates and lactate metabolites, with a role of spleen contraction variable in the different animal species [45].

In the capillaries, with exercise, pO_2 progressively reduces from around 100 mmHg measured near the arteriolar end up to 18 mmHg at the venular end of the vessels both in normal individuals and CHF patients [46]. Indeed, in a progressively increasing workload exercise, pO_2 reduces up to the anaerobic threshold, whereas Hb-O_2 reduces throughout the test because of acidosis above the anaerobic threshold (Bohr Effect). The CHF patients, however, show a less defined temporal behaviour of pO_2 changes during exercise with an increase, at end exercise from pO_2 nadir, observed in 20% of cases. This phenomenon is likely because of a mismatch between blood perfusion and O_2 extraction in the muscle fibres. Oxygen flow from the capillary to the mitochondria depends on distance between the two, and, most importantly, on the type of tissues which O_2 flow through. It is likely that muscle fibrosis, and other chronic hypoxia-related muscle fibre changes observed in CHF negatively influence O_2 flow to the mitochondria [47].

The endothelium

Endothelial dysfunction actively affects the impaired O_2 delivery to the periphery. Endothelial dysfunction is a hallmark finding in both experimental and clinical CHF [48], and a decreased skeletal muscle vasodilatation in response to exercise seems to be an important determinant of exercise intolerance [49]. In normal individuals, during exercise a progressive peripheral arterial vasodilatation is involved in the O_2 delivery process and a significant role in the regulation of working muscle perfusion is played by flow-mediated release of endothelial vasodilating substances [50].

This flow-mediated vasodilatation is because of the attractive force of fluid flow or shear stress. The endothelium senses shear stress by means of a mechanotransducer apparatus that is not fully defined, but that involves cytoskeletal deformation and the release of endothelial agonists such as prostacyclin, endothelium-derived hyperpolarizing factor and NO [51]. Exercise is a physiological stimulus that increases shear stress in the endothelial surface and the flow-stimulated release of endothelium-derived NO plays a critical role in the response to exercise. When the NOS pathway is altered by the experimental administration of exogenous NOS antagonists, exercise-induced redistribution of blood flow to skeletal muscle is attenuated and exercise capacity is impaired [52].

In CHF patients, abnormalities in endothelial synthesis of NO increased synthesis of endotelin-1 and changes in prostaglandin metabolism significantly contribute in the impaired muscle blood flow distribution during exercise. NOS inhibition significantly reduced the forearm vasodilatation response to handgrip exercise in normal individuals, but did not change the response in patients with CHF suggesting that flow-induced NO-mediated vasodilatation during exercise is blunted in these patients [53]. In most CHF patients endothelial-mediated flow-dependent vasodilatation may be reduced as a consequence of physical deconditioning and the mechanistic evidence may be unmasked by studying the effects of exercise training on the endothelial function and exercise performance.

Selected local forearm training by repetitive handgrip exercise is capable of significantly improving the brachial artery endothelial response [54]. Regular long-term physical exercise improves both basal endothelial NO formation and agonist-mediated endothelium-dependent vasodilatation of the skeletal muscle microvasculature of the lower limb [55].

The correction of the endothelium dysfunction was associated with a significant increase in exercise capacity. Interestingly, even in stable optimally treated patients receiving resynchronization therapy, a session of exercise training improved the brachial artery flow-mediated endothelial response and peakVO_2 [56]. Whether after physical training a lack of changes in endothelial function may help to identify patients with a worse clinical outcome remains an open and relevant question.

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