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

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 changes in cardiac function cannot fully explain their origin. Interventional studies have also opposed a concept of central haemodynamics as performing the primary role in symptom generation. 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 O₂ 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.

Keywords: chronic heart failure, exercise testing, exercise tolerance, quality of life, rehabilitation
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 O2 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 O2 consumption or peakVO2) is strictly related to cardiac output on the basis of the Fick principle

\[ \text{peakVO}_2 = \text{Cardiac Output} \times (A - V) O_2 \text{ diff} \]
\[ = \text{Stroke Volume} \times \text{Heart Rate} \times (A - V) O_2 \text{ diff} \]

where \((A-V)\), O2 difference is arterio-venous O2 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 peakVO2 [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 peakVO2 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 peakVO2 [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 twofold: (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.
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
[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 dyspnoea). 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 triiodothyronine status’, characterized by reduced peripheral conversion of the thyroid prohormone tetraiodotironine to the biologically active hormone triiodotironine. Low triiodothyronine 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 5 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 cardiomyocytes under haemodynamic stress to produce and secrete two peptide hormones (atrial and brain natriuretic peptides) with potent natriuretic/vasodilator and anti-hypertrophic/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, O₂ delivery is measured as cardiac output times the arterial O₂ content (CaO₂). However, this is O₂ delivery to the capillary, which does not consider the O₂ flow from the capillary to the mitochondria, where O₂ partial pressure in the blood (pO₂) is around 0 mmHg.
CaO₂ depends on Hb concentration, pO₂ and the position of the oxyhaemoglobin (Hb-O₂) dissociation curve. The latter, however, has little effect on CaO₂. Indeed in the absence of hypoxia in CHF, and in normal individuals, in the systemic artery, the Hb-O₂ dissociation curve is flat on its upper part so that whatever shifts rightward or leftward (acidosis, temperature and molecules such as 2,3-diphosphoglycerate) do not have any significant effect CaO₂ [44].

In CHF cardiac output is low; its increase during exercise is blunted and patients are often anaemic: all these factors reduce CaO₂. In the systemic artery, CaO₂ increases during exercise, mainly above the anaerobic threshold, because of an increase in Hb. Exercise-induced haemoconcentration is likely because of an oncocytic 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, pO₂ 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, pO₂ reduces up to the anaerobic threshold, whereas Hb-O₂ reduces throughout the test because of acidosis above the anaerobic threshold (Bohr Effect). The CHF patients, however, show a less defined temporal behaviour of pO₂ changes during exercise with an increase, at end exercise from pO₂ nadir, observed in 20% of cases. This phenomenon is likely because of a mismatch between blood perfusion and O₂ 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 O₂ flow through. It is likely that muscle fibrosis, and other chronic hypoxia-related muscle fibre changes observed in CHF negatively influence O₂ flow to the mitochondria [47].

The endothelium

Endothelial dysfunction actively affects the impaired O₂ 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 O₂ delivery process and a significant role in the regulation of working muscle perfusion is played by flow-mediated 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 endothelial response [54]. Regular long-term physical exercise improves both basal endothelial NO formation and agonist-mediated endothelium-dependent vasodilatation of the muscular artery endothelial response [54]. 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]. 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.

References


