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The symptoms of heart failure

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Abstract

Chronic heart failure (CHF) and acutely decompensated heart failure (ADHF) are the most frequent hospital diagnoses in industrialized countries. The clinical presentation of heart failure is dominated by two symptoms: dyspnea and fatigue. These symptoms dictate patients' physical capacity and quality of life. Popular clinical classifications of CHF are based on exercise tolerance, ie, on dyspnea after effort and includes the most popular one proposed many decades ago by the New York Heart Association (NYHA). Traditionally, the reduced exercise capacity of HF patients is attributed to the malfunctioning cardiac pump. More recently, "peripheral" factors have been identified that may contribute to the limited exercise capacity associated with CHF. Morphological and functional abnormalities found in both skeletal muscle and respiratory muscles, including muscle atrophy, fiber type changes, reduced mitochondrial enzymes, decreased mitochondrial volume density, and alterations at the vascular/skeletal muscle interface (greater sympathetic vasoconstrictor tone, decreased capillarity, and smaller capillary diameter) may all contribute to dyspnea and fatigue, in addition to or independently from "central" derangements. ■ *Heart Metab*. 2014;64:8–12

Keywords: dyspnea; exercise; heart failure; skeletal musculature

While resting quietly, a normal man breathes with effortless ease, his frequency is below 16 breaths per minute and his tidal volume is less than 600 mL. Even when exercise brings breathing to the conscious level, the sensation is not unpleasant. If, however, airflow is impeded or if ventilation is restricted, awareness of breathing becomes a sensation of distress. Such distress is usually referred to as dyspnea, from the Greek words dys (hard) and pnoe (breathing). Thus, in its broadest context, dyspnea denotes an unpleasant awareness of breathing, ranging from mild discomfort to agony.

Dyspnea has been defined by the American Thoracic Society as "A subjective experience of breathing discomfort that consists of qualitatively distinct sensations that vary in intensity." Other definitions describe it as "difficulty in breathing," "disordered or inadequate breathing," "uncomfortable awareness of breathing," or as the experience of "breathlessness" (which may be either acute or chronic).

Dyspnea though commonly associated with disorders of the cardiac and/or respiratory system, may derive from disorders of other systems such as the central nervous system, the musculoskeletal system, the endocrine system, the hematologic system, and psychiatric disorders. DiagnosisPro, an online medical expert system, listed 497 distinct causes in October 2010. On a pathophysiological basis, the causes of dyspnea can be divided into: (i) an increased awareness of normal breathing such as during an anxiety attack; (ii) an increase in the work of breathing; and (iii) an abnormality in the ventilatory system.

Abbreviations

CHF: chronic heart failure; **HF:** heart failure; **HFREF:** heart failure with reduced ejection fraction; **IMT:** inspiratory muscle training; **NYHA:** New York Heart Association; **RBC:** red blood cell

Dyspnea and fatigue

Like pain, respiratory discomfort cannot be measured directly, although a number of indices have been proposed to predict when discomfort will appear. Three of the most popular have been the breathing reserve, the walking ventilation, and the dyspnea index. All three relate minute volume of ventilation (MVV) with the maximum breathing capacity (MBC), but none of these methods has entered into clinical practice.

Despite the detailed knowledge of normal respiration, the precise mechanism producing the sensation of breathlessness remains an enigma. The respiratory center in the pons and medulla is sensitive to changes in carbon dioxide tension and hydrogen ion concentration in the blood. The carotid and aortic chemoceptors respond principally to blood oxygen content. The intercostal nerves transmit information about muscles and joints of the chest wall, and the phrenic nerve about the diaphragm.

Most investigators agree that three main components contribute to dyspnea: afferent signals, efferent signals, and central information processing. It is believed the central processing in the brain compares the afferent and efferent signals; and dyspnea results when a "mismatch" occurs between the two: such as when the need for ventilation (afferent signaling) is not being met by physical breathing (efferent signaling).

Dyspnea is not only the most common symptom of heart failure (HF), but is also the dominating diagnostic and prognostic feature of HF. It is first observed only during activity. As heart failure advances, dyspnea appears with progressively less strenuous exercise. Ultimately, breathlessness may be present when the patient is at rest. Thus, the only difference between exertional dyspnea in a normal subject and in cardiac patients is the degree of activity necessary to trigger the symptom. Cardiac dyspnea is observed most frequently in patients with elevated left atrial pressure and elevated capillary and venous pulmonary pressures. In such conditions, the passage of fluids from the vascular to the extravascular compartments may exceed the drainage capability of the lymphatic circulation, leading to increased extravascular lung water and interstitial edema. Moreover, chronic venous pulmonary hypertension leads to fibrotic changes in the lung parenchyma and blood vessels, which results in decreased lung compliance and bronchoconstriction. This, in turn, increases the work of the respiratory muscles and the energy cost of respiration.

In HF patients, the excessive work of the respiratory muscles translates into an increased oxygen cost of breathing. This is coupled with reduced oxygen delivery to these same muscles as a consequence of the reduced cardiac output. Hence, inadequate oxygenation of the respiratory muscles may contribute to the sensation of shortness of breath.

Orthopnea, ie, dyspnea in the recumbent position, is also characteristic of those forms of HF with elevated pulmonary venous and capillary pressures, and is usually a symptom of more advanced HF than exertional dyspnea. Orthopnea is attributed to the redistribution of fluids from the lower limbs to the lungs, which is facilitated by the force of gravity acting on vascular beds in the recumbent position. A similar mechanism is suggested for paroxysmal (nocturnal) dyspnea, which is a severe shortness of breath occurring at night, due to the reabsorption of edema from dependent portions of the body. Often the patient awakens with the feeling of suffocation.

The most popular index to grade the functional capabilities of a patient with HF is the classification proposed by the New York Heart Association (NYHA) many decades ago *(Table I)*. This classification is based on the exercise tolerance of the individual patient and has intrinsic limitations, due to the subjective nature of symptoms, to the variability of symptoms either spontaneously or as a result of treatment, to the relative independence from left ventricular function/dysfunction etc, but remains very popular and is still largely used in clinical practice.

Current HF therapy is effective in reducing pulmonary congestion and improving dyspnea in patients with systolic heart failure—patients with heart failure with reduced ejection fraction (HFREF). As a consequence, these complaints may be supplanted by the feelings of fatigue and weakness. The actual physiological mechanism of the fatigue associated with heart failure is not known, but it is commonly attributed to inadequate cardiac output. However,

Heart Metab. (2014) 64:8–12

Class	Functional Capacity
I	Patients without limitation of physical activity
II	Patients with a slight limitation of physical capacity, in which ordinary physical activity leads to fatigue, palpitations, dyspnea, or angina pain; they are comfortable at rest
III	Patients with marked limitation of physical activity, in which less than ordinary activity results in fatigue, palpitation, dyspnea, or angina pain; they are comfortable at rest
IV	Patients who are not only unable to carry on any physical activity without discomfort, but who also have symptoms of heart failure or the angina syndrome even at rest; the patient's discomfort increases if any physical activity is undertaken

Table I *Adaptation of the New York Heart Association functional classification table of heart failure. Source: American Heart Association, Inc.*

alternative mechanisms may contribute to fatigue, including side effects of recommended therapy, such as potassium depletion due to diuretics and/or hypotension due to β-blockers.

Heart transplantation generally results in a dramatic improvement in exertional dyspnea. Whether this alleviation of dyspnea is related to improved lung compliance, increased perfusion of respiratory or leg musculature, or greater respiratory muscle strength is unclear. To investigate which of these mechanisms underlies the subjective improvement in dyspnea after transplantation, the work of breathing, accessory respiratory muscle oxygenation, and respiratory muscle strength were measured in transplant recipients, patients with heart failure, and normal subjects at rest and during exercise. Surprisingly, work of breathing and respiratory strength were not significantly different after transplantation. However, regional perfusion of respiratory musculature was normalized, suggesting that the improvement in this symptom is related to improved perfusion.

A study published in 1982 by Weber et al[1] proposed a new index of HF severity, based on peak oxygen consumption (peak $\dot{V}O_2$). Many subsequent studies have documented a strong relationship between peak $\dot{V}O_2$ and mortality in chronic HF patients. Today, a peak $\dot{V}O_2$<14 mL/kg/min is the major criterion for referral for possible heart transplantation.[2] A significant improvement in symptoms and survival has been reported with a pharmacologic blockade of the renin-angiotensin and β-adrenergic systems in HFREF patients, however, there is no significant benefit in patients with heart failure with preserved ejection fraction (HFPEF), who comprise more than 50% of the entire HF population. In either group, such drug therapy has little impact on exercise capacity.[3,4] In contrast, aerobic training programs increase peak $\dot{V}O_2$ by 15% to 25% in chronic HF patients, similar to the degree of improvement observed in normal individuals after such training.[5]

It is important to understand the factors that limit peak $\dot{V}O_2$ in this disorder because both quality of life and longevity are strongly influenced by aerobic capacity. Peak $\dot{V}O_2$ is determined by the product of cardiac output (CO) (ie, the central component) and arteriovenous oxygen difference ($[a\text{-}v]O_2$) (ie, the peripheral component) during exhaustive aerobic exercise.

Although both peak CO and $(a\text{-}v)O_2$ are reduced in chronic HF, the dominant deficit is in peak CO.[5,6] Peak CO/m^2 ranged from a mean of 7.8 L/min/m^2 in Class B patients (peak $\dot{V}O_2$=16 to 20/mL/kg/min) to 3.0 L/min/m^2 in Class D patients (peak $\dot{V}O_2$=10/mL/kg/min).[1] A modest reduction in peak heart rate contributes to the reduced CO, but the primary limitation to increasing CO during exercise is the blunted ability of the failing heart to augment stroke volume due to a reduced contractile reserve.[5,6]

In addition to cardiac contractile dysfunction, noncardiac mechanisms may limit exercise capacity in HF patients. Mass and strength of the skeletal musculature is reduced in this condition, with decreased oxidative type I fibers, mitochondrial volume density, and oxidative enzyme activity.[5,7,8] Structural and functional skeletal muscle changes along with impaired blood flow help to explain the blunted augmentation of $(a\text{-}v)O_2$ during aerobic exercise.[9]

Increased pulmonary dead space and greater pulmonary lactate production cause excessive lung ventilation for the work performed in HF patients. The magnitude of this excess ventilation during exercise, quantified by the ventilation/carbon dioxide production slope ($\dot{V}E/\dot{V}CO_2$), correlates with HF severity and predicts outcomes, independent of peak $\dot{V}O_2$.[10,11] This exaggerated ventilatory response, which is associated with increased lung stiffness and possibly augmented airway resistance, contributes to the sensation of excessive respiratory effort during exercise; that is dyspnea, in patients with chronic HF.

An additional potential ventilatory limitation to exercise in chronic HF is weakness of the respiratory muscles themselves, as suggested by reduced maximal inspiratory pressure (PImax), compared with healthy controls that were also a strong independent predictor of 1-year mortality.[12] Although the precise etiology of this respiratory muscle dysfunction in HF is unclear, diaphragm biopsies have demonstrated a variety of histological abnormalities, including type I fiber atrophy similar to that observed in limb skeletal muscle. Inspiratory muscle training (IMT), 30 min daily, resulted in a 115% increase in PImax, a 17% increase in treadmill peak $\dot{V}O_2$, a 19% increase in a 6-min walk, and a 14% reduction in $\dot{V}_E/\dot{V}CO_2$ slope, whereas these variables were unchanged in the control group.[13]

Quality of life, as assessed by the Minnesota Living With Heart Failure questionnaire, also improved after IMT, and this effect was partially maintained at a 1-year follow-up. A 4-week IMT program induced hypertrophy of the diaphragm and improved both resting and exercise limb blood flow during inspiratory muscle loading as well as longer time to fatigue during handgrip exercise.[14]

Prior studies in normal individuals[15,16] have shown that the work of breathing incurred during maximal aerobic exercise causes vasoconstriction in leg muscles, compromising leg blood flow. This response, labeled the inspiratory muscle metaboreflex, seems to be mediated by the activation of type IV phrenic afferent fibers by accumulated metabolites, causing an increase in sympathetic outflow.[17] This reflex is exaggerated in chronic HF patients, further compromising limb blood flow, but this adverse response is markedly attenuated by IMT.[14]

However, we should remember that two prior randomized controlled trials of IMT have failed to improve exercise capacity or dyspnea in similar patient samples.[18,19,20] Finally, acutely unloading the work of breathing by substituting helium for nitrogen in the inhaled gas mixture failed to increase peak treadmill $\dot{V}O_2$, although exercise duration was lengthened.[21] These negative studies are consistent with the diagnostic algorithm that separates cardiac from pulmonary causes of exertional dyspnea on the basis of a reduced ventilatory reserve capacity during peak exercise in pulmonary, but not cardiac patients.[22]

Several open questions remain concerning the role of IMT in chronic HF.[23] How can we identify patients who are likely to benefit from IMT? Should inspiratory muscle strength be determined in all HF patients? What are the optimal session frequency, intensity, and duration, and the optimal program length for IMT? Are the benefits of IMT on exercise capacity and quality of life additive to those of conventional aerobic training programs? Perhaps most importantly, does IMT affect morbidity and mortality of chronic HF?

Conclusions

Exercise intolerance is widely recognized as a defining symptom in patients with chronic heart failure (CHF), limiting physical activity and impairing quality of life.[8] Traditionally, this reduced exercise capacity has been commonly attributed to the malfunctioning cardiac pump. However, attention has turned toward "peripheral" factors that might also contribute to the limited exercise capacity associated with CHF. In HF patients, both skeletal muscle and respiratory muscles present with a variety of specific alterations (muscle atrophy, fiber type changes, reduced mitochondrial enzymes, decreased mitochondrial volume density). The vascular/skeletal muscle interface also present with major derangements (greater sympathetic vasoconstrictor tone, decreased capillarity, and smaller capillary diameter). However, the contribution of these skeletal muscle changes to limited exercise capacity in CHF is currently not fully acknowledged. Even under conditions where cardiac function is not limiting, both skeletal muscle blood flow—and, therefore, convective O_2 transport—and diffusion of O_2 from blood to muscle are compromised. These limitations to maximal exercise in patients with CHF support a significant peripheral difference between control subjects and patients.

The plethora of structural and functional (neurohumoral, inflammatory, reflex) consequences of CHF coalesce at the muscle microcirculation and abolish the rapid increase of capillary RBC flux, velocity, and distribution necessary to regulate the microvascular P_{O_2} and support fast $\dot{V}O_2$ kinetics.

In conclusion, muscle wasting is a frequent comorbidity among patients with chronic HF. Compared with patients without muscle wasting, patients affected by muscle wasting have lower muscle strength, worse exercise capacity in treadmill performance and walking exercise tests, and reduced left ventricular ejection

Heart Metab. (2014) 64:8–12

fraction. Larger studies are required to pave the way for developing tailored therapies for this important subgroup of patients.[24] ■

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