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Heart failure: a cardiac or a systemic disease?

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According to the American Heart Association, heart failure may be defined as a complex clinical syndrome that can result from any structural or functional cardiac disorder that impairs the ability of the ventricle to fill with or to eject blood. Five million people are estimated to suffer from heart failure worldwide, with over 1 million hospitalizations per year. About 65 000 new cases are diagnosed every year and the estimated economic burden amounts to $40 billion/year.

The main manifestation of heart failure is fluid retention, leading to pulmonary congestion and peripheral edema, which results in dyspnea and fatigue that may limit exercise tolerance. The first hospitalization for heart failure is associated with a 4% in-hospital mortality rate. After discharge, 30% to 50% of patients die or are rehospitalized within 60 days of admission. Mortality is 20% to 30% after one year and 40% to 50% after 5 years.

This issue of *Heart and Metabolism* offers a great opportunity for a better understanding of the central and peripheral abnormalities contributing to the natural history of heart failure.

The central role of skeletal muscles on symptoms and clinical outcomes is clearly described in the article by **Mario Marzilli** and in the article by **Stephan von Haehling**. Skeletal muscle wasting, which is present in almost 20% of ambulatory patients with chronic heart failure, is associated with reductions in exercise capacity, quadriceps strength, handgrip strength, distance walked during a 6-minute corridor walk, and gait speed.

Patricia Iozzo confirms that heart failure is accompanied by defects in muscle oxidative and glucose metabolism, together with a loss in muscle mass and a remarkable intramuscular fat infiltration. These features are related to the degree of exercise intolerance and are partially restored by chronic exercise training. They are also typically present in conditions that predispose to the development of heart failure, indicating that skeletal muscle should be an early prevention target.

Romualdo Belardinelli suggests that exercise training is able to maintain peak oxygen consumption (peak $\dot{V}O_2$) at more than 60% of the $\dot{V}O_2$max in heart failure patients. He also suggests that exercise training is associated with a reduction in major cardiovascular events, including hospitalizations for chronic heart failure and cardiac mortality.

Gabriele Fragasso agrees that muscle factors limit exercise capacity independently from central hemodynamics, and suggests that pharmacological manipulation of cardiac substrate utilization with agents that directly inhibit fatty acid oxidation could improve cardiac function and, accordingly, global metabolism efficiency. Trimetazidine, a 3-ketoacyl-coenzyme A thiolase (3-KAT) inhibitor, shifts the energy substrate preference away from fatty acid metabolism and toward glucose metabolism by 3-KAT inhibitors and could be an effective adjunctive treatment in patients with heart failure.

Marco Guazzi proposes the cardiopulmonary exercise test as the gold standard for assessing the pathophysiological derangements behind heart failure. Cardiopulmonary exercise tests allow for a

global evaluation of the pulmonary, cardiovascular, muscular, and cellular oxidative systems, which are not adequately reflected thorough the measurement of individual organ-system function. Accordingly, cardiopulmonary exercise testing is now being used in a wide spectrum of clinical settings for evaluation of undiagnosed exercise intolerance. The test's popularity is increasing due to recent statements and official documents that have provided simplified easy-to-apply reports that may consistently help the practicing clinician with their interpretations and clinical directions.

Alda Huqi contributes to this issue with a stimulating analysis of the role of obesity in heart failure. Obesity is often presented as a "starting point" toward negative outcomes; conversely, when an "interventional attitude" with purposeful weight loss is adopted, the tendency can be inverted.

So, with this issue, *Heart and Metabolism* offers, once again, the readers a valuable tool to better understand a relevant clinical problem—heart failure. ■

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Heart and muscle, cut from the same striated cloth

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Abstract

In patients with heart failure, skeletal muscle appears to be almost as important as the myocardium in maintaining physical functioning and well-being. Skeletal muscle wasting is present in almost 20% of ambulatory patients with chronic heart failure. Its presence is associated with reduced exercise capacity, quadriceps strength, handgrip strength, distance walked during a 6-minute corridor walk, and gait speed. Bicycle ergometer training is very effective at reducing the intramuscular imbalance between anabolic and catabolic mediators. It is currently not known if systemic treatments can be used effectively to reduce this imbalance at a whole-body level, but the evidence from smaller trials suggests beneficial effects of essential amino acid supplementation, recombinant human growth hormone, synthetic ghrelin, and intramuscular injection of testosterone. ■ *Heart Metab*. 2014;64:4–7

Keywords: cachexia; heart failure; skeletal muscle; wasting

Muscle is key to motion. Skeletal muscle mass is directly related to peak oxygen consumption in treadmill-exercise testing and thus determines not only exercise capacity, but essentially also quality of life. Many patients with chronic heart failure (HF) are limited in their capability to exercise, and common clinical belief holds that cardiac function is the only important determinant in this regard. However, skeletal muscle appears to be almost as important as the myocardium in maintaining physical functioning and well-being in these patients. Indeed, exercise capacity is directly related to left ventricular ejection fraction, mitral regurgitation, and peak cardiac index.[1,2] On the other hand, many other factors likely influence exercise capacity in the course of heart failure: the degree of endothelial dysfunction, hemoglobin level, iron deficiency, the presence of sleep-disordered breathing, or the presence of comorbidities, just to name a few. One factor that has been largely neglected in the past decades is the status of the skeletal muscle. Over the last several years, HF research has started to focus on skeletal muscle, whose mass and function are indeed "in dire straits" as HF progresses.[3]

In order to understand the importance of skeletal muscle in patients with HF, it is important to acknowledge that this tissue undergoes permanent changes. The predominant pathway of muscle degradation is represented by the proteasome, a multisubunit protease found in all eukaryotic cell types that specifically degrades proteins marked by ubiquitin. It is not entirely clear what the mechanisms are that regulate the activity of the ubiquitin-proteasome pathway, but

Abbreviations

DEXA: dual energy x-ray absorptiometry; **HF:** heart failure

proinflammatory cytokines such as tumor necrosis factor, interleukin 1β, and interleukin 6 all stimulate its activity.[3,4] Anabolic factors like growth hormones that regulate liver insulin-like growth factor 1 expression attenuate the activity of the ubiquitin ligases. Therefore, it is not surprising that both a downregulation of the expression of anabolic players and an upregulation of catabolic players is found in HF patients presenting with reduced muscle mass and/or function *(Figure 1)*.

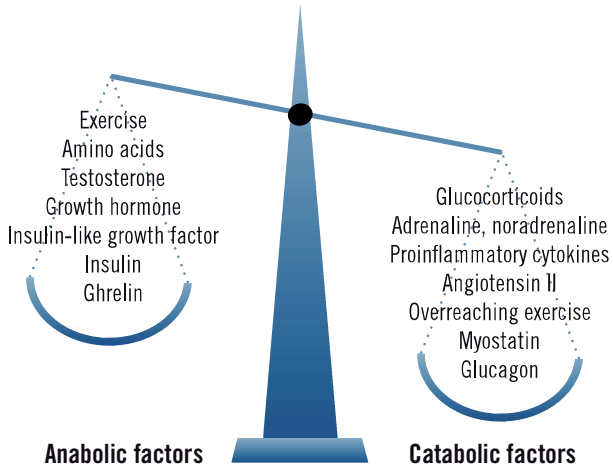

Fig. 1 *Imbalance between anabolic and catabolic factors in patients with heart failure.*

Muscle wasting, sarcopenia, cachexia, frailty—all the same?

Four main outcomes are clinically meaningful when skeletal muscle is lost: (i) anorexia; (ii) dehydration; (iii) sarcopenia; and (iv) cachexia.[5,6] Cachexia is defined as an involuntary weight loss of >5% of body weight in the presence of a chronic disease such as HF.[7] Another possible presentation is the development of sarcopenia, which is present in "a person with muscle loss whose walking speed is equal to or less than 1 m/s or who walks less than 400 m during a 6-minute walk, and who has a lean appendicular mass corrected for height squared of 2 standard deviations or more below the mean of healthy persons between 20 and 30 years of age of the same ethnic group.[8]" Even though this definition may be useful in answering research questions, it is rather cumbersome in daily clinical practice.[9] Thus, it is not surprising that a diagnosis of sarcopenia remains rare in daily clinical practice, and the fact that some workers have argued that the term sarcopenia should be restricted to "healthy aging" does not make matters easier.[10] More recently, the term "muscle wasting disease" has been proposed[11] to cover all aspects of muscle wasting in patients with chronic diseases as opposed to sarcopenia that should be diagnosed in healthy elderly subjects only. *Table I* provides an overview of some of the terms that are used in this context.

Just like with sarcopenia and/or muscle wasting disease, a diagnosis of cachexia remains rare in daily clinical practice. Apart from the difficulties in reaching a correct diagnosis, another important reason to be considered is the lack of effective treatments that are able to directly counter losing weight. Even more important is the fact that in contrast to cachexia, where the diagnosis requires not much more than a pair of scales, the correct diagnosis of muscle wasting can only be reached using sophisticated technology because patients with muscle wasting do not necessarily lose weight. Indeed, skeletal muscle can be replaced by adipose tissue or other nonfunctional tissue, and a pronounced denervation of type II fibers with the recruitment of type I fibers into surviving motor units also occurs.[12] Therefore, the diagnostic gold standard is computed tomography or magnetic

Term	Description	Reference
Cachexia	Weight loss of at least 5% of body weight within 12 months or less in the presence of chronic illness	Evans et al,[7] 2008
Frailty	Increased vulnerability for developing increased dependency and death due to diminished strength, endurance, and reduced physiologic function	Morley et al,[8] 2011
Muscle wasting disease	Muscle wasting that fulfills the criteria of sarcopenia, associated with or without frailty and/or cachexia	Anker et al,[11] 2014
Sarcopenia	Appendicular muscle mass corrected for height squared of 2 standard deviations or more below the mean of healthy persons	Morley et al,[8] 2011

Table I *Useful terms.*

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resonance imaging, as only these techniques are able to directly assess skeletal muscle mass. Researchers have largely relied on the less costly dual energy x-ray absorptiometry (DEXA) scanning that assesses fat-free mass as a proxy of skeletal muscle mass.[13]

Sarcopenia and muscle wasting in heart failure

The loss of skeletal muscle mass appears almost automatically during the normal aging process. On average, it is estimated that 5% to 13% of elderly people between the ages of 60 and 70 are affected by sarcopenia. These numbers appear independent of any chronic disease, and they increase to between 11% and 50% for those aged 80 years or over.[2,14] Other sources have estimated that 8% to 40% of elderly people above the age of 60 years are sarcopenic.[15] Sarcopenia may lead to frailty, but not all patients with sarcopenia are frail.[16]

An imbalance between anabolic and catabolic mediators in HF has already been reported 20 years ago. Since the term sarcopenia should only be restricted to healthy elderly subjects, we prefer the descriptive term of muscle wasting. Muscle wasting that fulfills the criteria of sarcopenia as described above has been reported in 19.5% of ambulatory patients with chronic HF.[17] This number is considerably higher than expected for healthy subjects of the same age group whose mean age was 67 years. HF patients with muscle wasting had significantly lower values for handgrip and quadricep strength as well as lower total peak oxygen consumption ($P<0.001$), lower exercise time ($P<0.001$), and lower left ventricular ejection fraction ($P<0.05$) than patients without muscle wasting. The distance walked during a 6-minute corridor-walk test and the gait speed during the 4-minute walk were lower in patients with muscle wasting (both $P<0.05$).[8] Interleukin 6 was significantly elevated in the serum of patients with HF and muscle wasting. Among those factors predicting lower peak oxygen consumption during a treadmill exercise test, muscle wasting remained independently predictive after adjusting for age, sex, New York Heart Association class, hemoglobin, left ventricular ejection fraction, distance walked in 6 minutes, and the number of comorbidities (odds ratio, 6.53; $P<0.01$).[8] Thus, muscle wasting can be viewed as a new comorbidity of HF that may be worth tackling in order to maintain exercise capacity and quality of life.

How to maintain muscle mass in heart failure?

Maintenance of skeletal muscle mass appears to be an interesting target in order to maintain HF patients' exercise capacity. From a pathophysiological standpoint, several anabolic or anticatabolic mechanisms have been suggested. Apart from that, skeletal muscle protein metabolism is modified by food intake.[18] Smaller clinical trials in HF have seen the beneficial use of nutritional supplementation with essential amino acids,[19] recombinant human growth hormone,[20] administration of synthetic ghrelin,[21] or intramuscular application of testosterone in both men and women.[22] Indeed, testosterone deficiency is directly related to reduced peak oxygen consumption during treadmill exercise testing in patients with HF.[23] Even electrical muscle stimulation has been used effectively to improve HF patients' exercise capacity.[24] Anticatabolic therapies have been less effective. However, the main problem with these trials is their small enrollment numbers, and therefore, the lack of reliable safety data.

The only current clinically effective treatment for muscle wasting in patients with HF is exercise training.[25] Smaller randomized trials have shown the effectiveness of progressive resistance exercise training or bicycle ergometer training, and both European[26] and North American[27] guidelines advocate exercise training in this regard. In ambulatory patients with HF, bicycle ergometer training has been shown to reduce the imbalance of intramuscular expression of anabolic and catabolic players, particularly of those that stimulate the ubiquitin-proteasome system. These effects were already observed after 4 weeks of training, even though this did not yet translate into an increase in the cross-sectional area of the quadricep muscle measured using computed tomography or into an increase in the maximal isometric force.

Conclusions

Irrespective of whether it is named sarcopenia, muscle wasting, or muscle wasting disorder, skeletal muscle wasting is present in almost 20% of outpatients with chronic HF. Its presence is associated with reduced exercise capacity, quadriceps strength, handgrip strength, distance walked during a 6-minute corridor walk, and gait speed. The prevalence of this perturbation is higher than expected for this age group, and it appears that the treatment or the prophylaxis of muscle

wasting is important to maintain the physical well-being of HF patients. Bicycle ergometer training is very effective at reducing the intramuscular imbalance between anabolic and catabolic mediators. It is currently not known if systemic treatments can be used effectively to reduce this imbalance at a whole-body level, but the evidence from smaller trials suggests beneficial effects of essential amino acids, recombinant human growth hormone, synthetic ghrelin, and intramuscular injection of testosterone. Currently, reaching a correct diagnosis of muscle wasting remains difficult because sophisticated technologies such as computed tomography, magnetic resonance imaging, or DEXA are required, but it is expected that blood biomarkers will become available that may help to identify those patients who require further testing. For the time being, physicians need to stay alert and watch out for signs in their HF patients that suggest reduced muscle mass and muscle strength. These include limitations in exercise capacity such as climbing stairs or even rising from a chair. Exercise training may be effective in these patients. ■

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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,

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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

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

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Imaging of skeletal muscle metabolism in heart failure

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Abstract

Heart failure (HF) is associated with exercise intolerance and insulin resistance. Imaging of skeletal muscle has shown that HF is accompanied by defects in muscle oxidative and glucose metabolism, together with a loss in muscle mass and remarkable intramuscular fat infiltration. These features are related to the degree of exercise intolerance and are partially restored by chronic exercise training. They are also typically present in conditions that predispose to the development of HF, indicating that skeletal muscle should be an early prevention target. ■ *Heart Metab*. 2014;64:13–17

Keywords: exercise; insulin resistance; magnetic resonance imaging; muscle composition; oxidative metabolism; positron emission tomography

Heart failure (HF) is characterized by exercise intolerance that is already present in patients with preserved ejection fraction, and is related to a reduction in peak oxygen consumption (peak $\dot{V}O_2$). Patients with HF of ischemic and nonischemic origins typically manifest insulin resistance and an elevated prevalence of type 2 diabetes.[1-5] Exercise intolerance and insulin resistance are reciprocally correlated and are both predictors of a worse prognosis. Skeletal muscle plays a dominant role in exercise performance and O_2 consumption during exercise. It is also the primary organ involved in insulin-mediated glucose disposal and in the pathogenesis of insulin resistance. This review will primarily address imaging studies of skeletal muscle perfusion, metabolism, whole-body lean/fat mass, or skeletal muscle mass and intramuscular fat, as conducted using positron emission tomography (PET) or ^{31}P magnetic resonance spectroscopy (^{31}P-MRS), and dual energy x-ray absorptiometry (DXA) or magnetic resonance imaging (MRI) in humans with HF.

Heart failure, skeletal muscle metabolism, and the response to insulin

PET imaging of perfusion and metabolism under euglycemic-insulin stimulation has documented that insulin-mediated glucose uptake in skeletal muscle declines with aging and with increasing body weight. Insulin-mediated glucose uptake was 61±8 µmol/kg muscle per minute in healthy 26-year-old subjects[6] and 37±17 µmol/kg/min in healthy 50-year-old subjects.[7] Skeletal muscle blood flow was on average 34 and 50 mL/kg/min, in young and older healthy subjects, respectively,[6,7] and oxygen consumption was 1.6 mL/kg/min in the young group.[6] We have shown that ischemic heart disease (ejection fraction [EF]=35%) was associated with skeletal muscle insulin resistance, independent of diabetes,[7] with an average glucose uptake of 23 µmol/kg/min (-40% vs age-matched controls) during insulin-stimulated conditions, and that glucose uptake was inversely related to the EF. Skeletal muscle blood flow at rest

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Abbreviations

DXA: dual energy x-ray absorptiometry; **EF:** ejection fraction; **HF:** heart failure; **MRI:** magnetic resonance imaging; **MRS:** magnetic resonance spectroscopy; **O_2:** oxygen; **PCr:** phosphocreatine; **PET:** positron emission tomography; **Pi:** inorganic phosphorus; **$\dot{V}O_2$:** oxygen consumption

was 37±14 mL/kg/min, which is not different from values observed in age-matched controls. In nondiabetic patients of similar age, but with nonischemic HF (EF=33%), Kemppainen et al[8] observed comparable values of insulin-mediated glucose uptake (22 µmol/kg/min) and blood flow (30 mL/kg/min) as well as normal values of oxygen consumption (1.7 mL/kg/min). In a subsequent study, the authors reported that insulin resistance in HF patients is not due to alterations in baseline or insulin-stimulated phosphorylation of the insulin receptor substrate (IRS)-1 and protein kinase B (Akt), or activation of phosphatidylinositide 3-kinase (PI3K), as measured in skeletal muscle biopsies.[5] Therefore, neither the delivery of insulin, glucose, or oxygen through blood flow under resting conditions, nor the above listed insulin-signaling mediators could explain the lack of insulin action to stimulate glucose utilization in skeletal muscles. Possible mechanisms may involve the sympathetic nervous system and changes in skeletal muscle mass and composition, including adjacent fat masses, as addressed below.

Heart failure and the response of skeletal muscle metabolism to submaximal exercise

Skeletal muscle glucose utilization is potently affected by exercise. PET studies have shown that an acute bout of submaximal isometric exercise can elevate skeletal muscle blood flow by >6-fold, oxygen uptake by >15-fold, and glucose uptake by 2.4-fold above the effect of insulin alone in young healthy individuals with peak $\dot{V}O_2$ of 44 mL/kg/min.[6] By using a similar study set-up in patients with nonischemic HF (peak $\dot{V}O_2$ of 20 mL/kg/min), the same authors showed that skeletal muscle blood flow was stimulated by 4.4-fold, oxygen consumption by 7.6-fold, and glucose uptake by 2.4-fold during exercise+insulin vs insulin alone.[8] Unfortunately, this study did not include a control group and comparison between the above 2 studies is limited by the marked age difference between study subjects.

Mitochondrial metabolism of skeletal muscle has been examined in HF by using ^{31}P-MRS to measure the ratio of inorganic phosphate (Pi) and phosphocreatine (PCr), with higher values indicating ATP depletion, and to estimate pH, which decreases and may cause fatigue once anaerobic glycolysis and lactate production are stimulated.[9] HF patients displayed normal Pi/PCr ratios and pH at rest, but an abnormal response during exercise with more severe fatigue, increased Pi/PCr at any given power output, and a more marked reduction in intracellular pH than observed in healthy controls. The findings suggested a depletion in PCr and impaired resynthesis of ATP, as seen in animal studies of primary HF.[10] In a subsequent study, the authors used near-infrared spectroscopy to document that skeletal muscle oxygenation seemed normal under the submaximal exercise conditions of these studies.[11] The occurrence of normal oxygenation, even with the reduction in pH, was taken to suggest that lactate was produced despite the aerobic conditions, which may occur if mitochondrial inefficiency leads to cytosolic NADH accumulation, promoting the conversion of pyruvate into lactic acid to restore oxidation of NADH to NAD.[11] In support of this interpretation, the induction of HF in animal models resulted in similar changes in high-energy phosphate metabolism and was accompanied by an increase in the NADH/NAD ratio.[10] In addition, creatine supplementation in patients with chronic HF increased skeletal muscle energy-rich phosphagens together with muscle strength and endurance.[12]

Heart failure and the response of skeletal muscle metabolism to chronic training

A 5-month training period, including supervised aerobic and resistance training in HF patients, resulted in a 27% improvement in peak $\dot{V}O_2$, a slight, but nonsignificant, reduction in NYHA functional class and heart rate, and a significant reduction in the percent body fat, but not body weight.[8] Skeletal muscle glucose uptake under both insulin and insulin+submaximal isometric–exercise stimulation was significantly increased, but no change was seen in muscle blood flow and oxygen consumption.[8] No change in muscle IRS-1 phosphorylation, Akt phosphorylation, or PI3K activation was found to explain the improvement in

insulin sensitivity.[5] This was consistent with observations in healthy middle-aged men, in whom one-week of exercise training was not coupled with PI3K or Akt activity changes.[13] This observation suggests the involvement of more distal pathways, including glucose transporter type 4 (GLUT4) membrane translocation, and/or the influence of the type of skeletal muscle fiber, as seen in insulin-resistant states[14] or forced inactivity states due to disability,[15] in which the proportion of type I fibers is reduced in parallel with insulin-mediated glucose uptake in skeletal muscle. A shift of type II glycolytic fibers into type I oxidative fibers was documented in biopsies from HF patients undergoing 6 months of exercise training.[16] However, this shift was not observed in disabled subjects undergoing electrically stimulated leg cycling, in whom skeletal muscle insulin sensitivity and expression of GLUT4, hexokinase II, and glycogen synthase were increased despite no change in fiber composition.[15]

Studies conducted with arterial-venous (a-v) substrate differences and thermodilution assessed blood flow before and after 4 to 6 months of aerobic training in 12 patients with severe chronic HF (EF=24%). These studies showed an increased leg blood flow and a-v oxygen differences at peak exercise, but not at submaximal workloads, while circulating lactate levels were markedly reduced.[17]

Studies with ^{31}P-MRS in HF patients before and after a one-month training period improved their responses to an incremental exercise test by increasing the intracellular pH, the PCr/(PCr+Pi) ratio, the PCr resynthesis rate, and the maximal rate of mitochondrial ATP synthesis in parallel with an improved contraction and duration of exercise.[18] This is in accord with bioptic evidence of greater skeletal muscle mitochondrial volume density, which may reflect the oxidative capacity and increase in functional capacity after 6 months of physical exercise in HF failure patients.[16]

Altogether, the above findings suggest that skeletal muscle abnormalities accompanying HF may depend, in part, on physical inactivity, and can be partially restored with physical training.

Skeletal muscle mass and composition

HF patients are characterized by skeletal muscle atrophy, which relates to exercise intolerance in patients with reduced or preserved ejection fraction where the percent of total and leg lean mass was reduced in parallel with peak $\dot{V}O_2$ compared with healthy controls.[19] However, the relationship linking increments in peak $\dot{V}O_2$ with total or leg lean mass,[19] calf muscle volume, or midarm area[20] was weak and poorly associated with ^{31}P-MRS findings, implicating additional mechanisms. In fact, HF patients with and without a normal ejection fraction show a reduction in type-I oxidative muscle fibers and the capillary to fiber ratio.[21] In addition, skeletal muscle in patients with HF was shown to be infiltrated by fat *(Figure 1)*.[22]

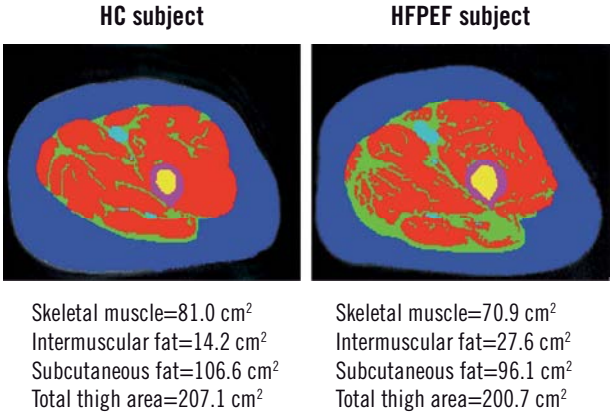

Fig. 1 *MRI axial image of the midthigh in a patient with HFPEF and in a HC subject. The red color indicates skeletal muscle, blue is subcutaneous fat, and green is intermuscular fat. The latter is substantially increased in the patient with HFPEF compared with the HC despite similar subcutaneous fat.*
Abbreviations: *HC, healthy control; HFPEF, heart failure with preserved ejection fraction; MRI, magnetic resonance imaging.*
After reference 22: *Haykowsky et al.* Am J Cardiol. *2014;113(7):1211-1216. Copyright © 2014, Elsevier Inc.*

These patients were mostly overweight and obese compared with controls, but their weight did not fully account for the difference. Intramuscular fat was suggested to limit oxygen diffusion or sequester blood flow during exercise, in accord with recent PET data documenting that a several-fold increase in perfusion occurs in leg adipose tissue while the adjacent muscle is exercising *(Figure 2)*.[23] Adipocytes interspersed between muscle fibers could also lead to an underestimation of oxidative or glucose metabolism, as they may not always be dissected from muscle in image analysis. In addition, intramuscular fat may be a proximal source of fatty acids, provoking insulin resistance, and this mechanism may be exacerbated by an overactive sympathetic tone that is frequently seen in HF. Norepinephrine has been shown to correlate with fatty acid levels, and changes in norepinephrine levels during β-blockade were inversely correlated

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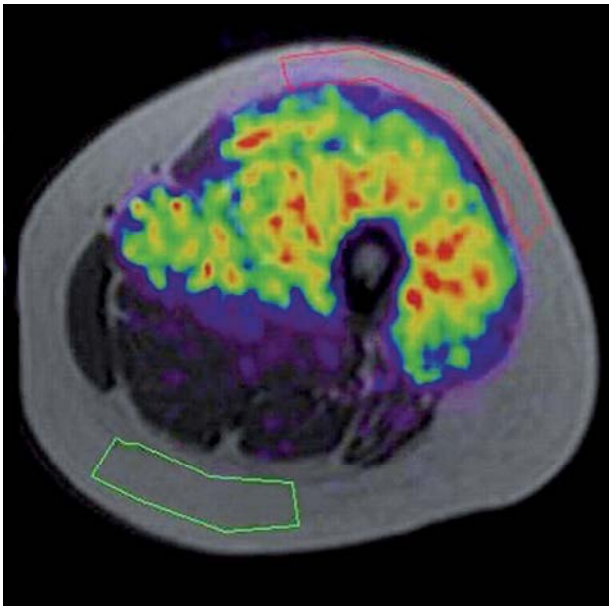

Fig. 2 *Fusion image of PET and MRI of the midthigh region. The image shows the contrast between skeletal muscle blood flow (color scale bar) in exercising anterior and resting posterior muscle groups. Subcutaneous adipose tissue blood flow adjacent to the working knee extensors (region delineated by a red line) displayed increased blood flow compared with adipose tissue adjacent to the inactive posterior hamstring muscles (region delineated by a green line).*
Abbreviations: *MRI, magnetic resonance imaging; PET, positron emission tomography.*
After reference 23: *Heinonen et al.* J Appl Physiol (1985). *2012;112(6):1059-1063. Copyright © 2012, the American Physiological Society.*

with changes in the respiratory quotient.[24] Some, but not all, β-blockers have been shown to induce a lipid-to-glucose metabolic shift[24] and enhance insulin sensitivity.[25] However, other studies did not find a correlation between insulin resistance and plasma noradrenaline.[3,26] Microneurography has been used to show that patients with ischemic cardiomyopathy had a higher resting muscle sympathetic nerve activity than patients with nonischemic dilated cardiomyopathy.[27] Sympathetic overtone and vasoconstriction may limit oxygenation and divert the available glucose into anaerobic glycolysis.

There is mutual influence between the mass and composition of skeletal muscle and HF/HF-symptoms, or between the mass and composition of skeletal muscle and skeletal muscle metabolism. Although muscle atrophy impairs exercise performance, studies on primary HF in dogs have shown that muscle atrophy can ensue as a complication.[28] Since muscles are prominent users of glucose, skeletal muscle atrophy will unavoidably reduce insulin sensitivity. On the other hand, when insulin resistance is primary due to the absence of skeletal muscle insulin receptors in mice,[29] muscle mass and force production are lost due to decreased protein synthesis without fiber type abnormalities.

Conclusion

Imaging of skeletal muscle has shown that HF is accompanied by defects in oxidative and glucose metabolism in this organ, together with a loss in muscle mass and remarkable intramuscular fat infiltration. These features are related to the degree of exercise intolerance and are partially restored by chronic exercise training. The relationship between skeletal muscle and adjacent adipose tissue may explain several of the abnormalities observed and deserves a better understanding. Although the dissection of primary mechanisms is hampered by the mutually reinforcing nature of the pathways involved, we know that muscle fat infiltration, enhanced lipolysis, insulin resistance, impaired mitochondrial function, and sympathetic overtone can occur in a variety of conditions, from normal aging and sedentariness to obesity, diabetes, coronary artery disease with normal cardiac function and others. All of these conditions predispose patients to the development of HF and the subsequent exercise intolerance. Therefore, attention to skeletal muscle health should be carefully pursued in the management of these predisposing conditions. Imaging technologies can support the earliest detection and therapeutic monitoring of skeletal muscle morphology and functional changes. ■

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Benefits of exercise training for the failing heart

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Abstract

Heart failure is the most common cause of hospitalization among adults over 65. Almost half of inpatients older than 65 years with chronic heart failure (CHF) are readmitted within 6 months of hospital discharge. Exercise training is a nonpharmacological therapy that determines important adaptations and potentiates the effects of some medications. The choice of an exercise training program should be based on the patient's preferences with the objective to maintain the program as long as possible. Recent trials have demonstrated that different exercise training programs have reached a similar result in terms of improvement in functional capacity after a few months or one or more years. The majority of exercise training programs are based on continuous mild-to-moderate aerobic activity at 40% to 70% of peak oxygen consumption (peak $\dot{V}O_2$) or peak heart rate, with an average improvement in aerobic capacity ranging from 10% to 25% after 2, 6, or 12 months. Intermittent high-intensity exercise has been recently proposed in stable CHF patients and has shown greater improvements in aerobic capacity than traditional endurance exercise programs of moderate intensity. Waltz dancing has also been used in stable CHF with a 14% improvement in peak $\dot{V}O_2$ at 8 weeks. Very recently, a 10-year exercise training program was able to maintain peak $\dot{V}O_2$ at more than 60% of the $\dot{V}O_2$max at each year of follow-up and was associated with a reduction in major cardiovascular events, including hospitalizations for CHF and cardiac mortality. The improvement in aerobic capacity has been associated with a reduction in cardiovascular events during a follow-up of 3 to 5 years, suggesting a positive effect on morbidity and mortality. ■ *Heart Metab*. 2014;64:18–22

Keywords: chronic heart failure; exercise training; outcome

In the last decade, the demonstration that exercise may improve functional capacity and quality of life in patients with chronic heart failure (CHF) has opened an interesting debate among cardiologists about the modality of exercise programs, the effects of exercise on the heart, and the clinical implications.[1-4] Although these preliminary results are encouraging, many questions are not yet answered and need to be clarified. We will briefly discuss the selection of patients, the methodology of exercise training, and the effects of exercise on coronary vessels and myocardial perfusion. Finally, we will introduce recent results on the outcome of exercise training.

Patient selection

The essential condition (sine qua non) to obtain benefits from exercise training is the patient's clinical stability. In all studies, enrolled patients did not have severe ventricular arrhythmias, unstable angina, or

Abbreviations

CHF: chronic heart failure; **HF-ACTION:** Heart Failure: A Controlled Trial Investigating Outcomes of exercise traiNing; $\dot{V}O_2$**:** oxygen consumption

signs and symptoms indicating heart failure deterioration in the last 3 months. Over this time, they were not hospitalized for worsening heart failure, nor did they need to modify the type or dosage of medications. Moreover, the majority of patients were in sinus rhythm, but atrial fibrillation did not represent a contraindication to exercise training.

Age

In a recent review, the mean age of patients studied was 59±14 years.[5] The average increase in peak oxygen consumption (peak $\dot{V}O_2$) after training was above 10% from the initial value in all decades. However, above the age of 70, the improvement in functional capacity was lower.

Sex

There were no differences in the results of physical training between women and men with the identical age and clinical picture; however, the proportion of women to men was much lower (1:4).

Medications

The combination of standard medications for heart failure with exercise did not influence the response to training programs. Patients involved in exercise training more frequently received angiotensin-converting enzyme inhibitors, nitrates, and diuretics, and less frequently received cardioselective β-blockers and antiarrhythmics.

Functional class

More than 60% of patients are in the NYHA functional class II, and 30% are in class III. Pretraining peak $\dot{V}O_2$ was between 15 and 17 mL/kg/min and was not correlated with left ventricular ejection fraction or the response to exercise training. This important issue should be taken into consideration when patients are referred for physical training. Patients with an ejection fraction <30% can have a normal functional capacity, and they can improve their peak $\dot{V}O_2$ more than 10% or 2 to 4 mL/kg/min from the initial value.

Left ventricular diastolic filling

An interesting finding is that the pattern of left ventricular diastolic filling can predict not only the response to exercise training, but also the outcome of patients with CHF.[6] Patients with an abnormal relaxation pattern (low early filling, high late filling, and prolonged deceleration time) generally have a greater increase in peak $\dot{V}O_2$ after training and a better prognosis. By contrast, patients with a restrictive left ventricular filling pattern do not improve functional capacity after training and have a worse prognosis after 3 years. A greater early diastolic filling is associated with a higher stroke volume and peak $\dot{V}O_2$ because of a lower left ventricular end-diastolic pressure and a lower transmitral gradient.

Etiology

As recently shown, almost two-thirds of patients had ischemic heart disease, 20% idiopathic dilated cardiomyopathy, and 10% valvular heart disease. Extensive coronary artery disease with left ventricular dysfunction and CHF are now considered as two new clinical indications to exercise training because potential risks of exercising are overwhelmed by a demonstration of the benefits.[1-5]

Methodology of exercise training

The results of exercise training programs are not only conditioned by patient selection, but also by the choice of the program. There is agreement in preferring aerobic exercise to isometric or eccentric exercise. The combination of an initial warm-up of calisthenics or stretching exercise with cycling on a stationary cycle ergometer is more effective in improving functional capacity than cycling alone.[5] Waltz dancing has been recently proposed as an alternative form of exercise training of moderate intensity in stable CHF, with a 14% improvement in peak $\dot{V}O_2$ at 8 weeks comparable with traditional continuous aerobic training.[7] ECG monitoring by telemetry is indicated in patients with arrhythmias or stable angina, and it is used in all patients during the initial 2 weeks of training. Blood pressure and heart

rate are measured at rest before each session, at peak exercise, and during recovery. After a warm-up phase (10 to 15 minutes), patients exercise on a stationary cycle ergometer, treadmill, or both for 30 minutes. Before and after the work phase, a short (3 to 5 minutes) loadless exercise is recommended. The intensity of the work phase is selected based on a symptom-limited–exercise test.

Since peak $\dot{V}O_2$ is a more accurate indicator of work tolerance than heart rate, it is preferable to measure gas exchange during exercise and prescribe the intensity of the exercise regimen on the heart rate corresponding to 50% to 70% of peak $\dot{V}O_2$. There is evidence that major benefits are obtained with programs of aerobic exercise at 60% to 70% of peak $\dot{V}O_2$, 3 times a week for a minimum of 8 weeks. Long-term programs are more effective than short-term programs because benefits are maintained for a longer time.[8] The results of recent randomized controlled trials have shown that two exercise sessions per week for 1 year can determine a sustained improvement in peak $\dot{V}O_2$. Supervision by a cardiologist is preferable, especially in patients with severe CHF and psychological problems. However, unsupervised home-based programs, which are more popular in northern Europe and the USA, are also effective.[5] The occurrence of untoward cardiac events is very low (<3%). The most common events are premature contractions and posttraining hypotension. Studies are concordant in reporting high compliance to training. Supervised programs, however, have a higher compliance than home-based programs (85% to 90% vs 75% to 85%).

Coronary artery adaptations

Although an improvement in functional capacity after exercise training is mainly related to peripheral adaptations,[9,10] recent studies have demonstrated myocardial and coronary vessel changes that can contribute to clinical benefits.[8,11-15] In patients with ischemic cardiomyopathy, a common finding is the coexistence of epicardial coronary artery stenoses with different amounts of necrotic, ischemic, hibernating, and normal myocardial cells. After short-term moderate exercise training, an improvement in left ventricular contractility is correlated with increases in coronary collateralization and thallium uptake.[11] Since no changes in the morphology and severity of epicardial stenoses have been demonstrated, the improved myocardial perfusion seems to be mainly explained by functional and/or structural adaptations of small coronary vessels and by improved endothelium-dependent vasorelaxation.[12] This effect has been also described in peripheral arteries after short-term programs.[16]

Another explanation may be an angiogenic effect of exercise. In the presence of a significant stenosis, intermittent bouts of exercise stimulates the expression of vascular endothelial growth factor and nitric oxide genes through a hypoxia-related mechanism.[17,18] New microvessels are generated that, in part, organize into large collaterals, and, in part, potentiate myocardial microcirculation. Adenosine concentration in the myocardial interstitium also increases after chronic exercise and can contribute to coronary collateral and vessel growth.[19,20]

A unifying hypothesis may be that exercise training improves regional myocardial perfusion through an indirect effect of opening preexisting collaterals and a direct effect of neoformation of small vessels. The former is due to functional adaptations of major coronary arteries determining a pressure difference between stenotic and normal arteries, and the latter is related to two mechanisms where one is dependent on adenosine and another that may be related to growth factors. An improvement in capillary diffusion capacity is a hypothesis that should be confirmed in humans. At present, no direct demonstration exists to show that an improvement in flow-mediated dilation of conduit arteries can improve myocardial perfusion. This is an intriguing hypothesis that needs to be demonstrated. Moreover, the clinical significance of these adaptations requires larger studies.

Outcome

A recent trial has demonstrated, for the first time, that a long-term program of supervised exercise training improved the survival of patients with CHF.[8] Trained patients, after 1214±56 days of follow-up, had a 63% reduction in cardiac mortality and a 71% lower rate of hospital readmission for heart failure than untrained controls. Cost-effective analysis pointed out that a patient's life can be prolonged, on average, by an additional 1.82 years at the low cost-effectiveness ratio of $1773 per life-year saved.[21] An independent

predictor of survival was posttraining thallium uptake, suggesting that the improvement in myocardial perfusion after exercise training is more important than the severity and the number of coronary artery stenoses.[11]

More recently, the HF-ACTION trial (Heart Failure: A Controlled Trial Investigating Outcomes of exercise traiNing), a multicenter randomized controlled trial enrolling 2331 medically stable outpatients with heart failure, demonstrated a smaller, but significant, improvement in peak $\dot{V}O_2$ at 3 months that still persisted at 12 months.[22] This improvement, however, was not associated with a reduced incidence of hard events. In contrast to our previous trial, patients that exercised with no supervision had a dropout rate of 33% at 12 months, suggesting that supervision may be crucial and may explain a better adherence to training in a long-term exercise training program. Very recently, a 10-year exercise training program was able to maintain peak $\dot{V}O_2$ at more than 60% of the $\dot{V}O_2$max at each year of the follow-up and was associated with a reduction in major cardiovascular events, including hospitalizations for CHF and cardiac mortality.[23]

Conclusions

There is mounting evidence that exercise is a non-pharmacologic form of cardiovascular therapy, which potentiates the effects of standard pharmacological interventions and determines important biological and clinical benefits in patients with chronic heart disease. Nowadays, interest is focusing on the methodology of exercise training, the mechanisms of clinical benefits, and their prognostic significance over both short-term and long-term periods. Exercise, if correctly designed and performed, can be considered an adjunctive therapeutic tool in the management of CHF as well as ischemic heart disease. The improvement in aerobic capacity has been associated with a reduction in cardiovascular events during a follow-up of 3 to 5 years, suggesting a positive effect on morbidity and mortality. Recently published guidelines recommend including exercise training in the therapeutic strategy of CHF patients; however, only a small percentage of patients are referred for exercise training. Other studies are needed in order to confirm long-term clinical benefits and the choice of the best protocol for any single patient. ■

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Effects on global metabolism by regulation of substrate utilization in heart failure

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Abstract

In patients with chronic heart failure, exertional intolerance is a major clinical problem. Muscle factors that limit exercise capacity are unrelated to central hemodynamics. While cardiac cachexia represents the most extreme form of loss of muscle mass in chronic heart failure, a more subtle form of lean body mass changes clearly exists, as is evident by the loss of skeletal muscle observed in patients with non-cachectic congestive heart failure. Previous studies have shown that pharmacological manipulation of cardiac substrate utilization with agents that directly inhibit fatty acid oxidation could improve cardiac function and, accordingly, global metabolism efficiency. The most extensively investigated agent of this group of drugs is trimetazidine, a 3-ketoacyl-coenzyme A thiolase (3-KAT) inhibitor. Clinical studies have shown that shifting the energy substrate preference away from fatty acid metabolism and toward glucose metabolism by 3-KAT inhibitors could be an effective adjunctive treatment in patients with heart failure in terms of left ventricular function and global metabolism improvement. In this article, the recent literature on the beneficial effects of this new potential use of 3-KAT inhibitors on left ventricular dysfunction and global metabolism is reviewed and discussed. ■ *Heart Metab*. 2014;64:23–27

Keywords: diabetes; global metabolism; heart failure; left ventricular function; trimetazidine

Wasting of subcutaneous fat and skeletal muscle is relatively common in heart failure (HF) and suggests an increased utilization of noncarbohydrate substrates for energy production.[1] In fact, fasting blood ketone bodies[2] as well as fat oxidation during exercise[3] have been shown to be increased in patients with HF. Insulin resistance has been found to be associated with HF[4] and the consequent impaired suppression of lipolysis could determine the development of ketosis, thereby, determining reduced metabolic efficiency. Heart and arm skeletal muscle glucose uptake is inversely related to serum free fatty acid (FFA) levels,[5] and increased FFA flux from adipose to non-adipose tissue amplifies metabolic derangements that are characteristic of the insulin resistance syndrome.[6] New findings suggest that raised FFA levels not only impair glucose uptake in heart and skeletal muscle, but also cause alterations in the metabolism of vascular endothelium leading to premature cardiovascular disease.[7]

Conversely, by increasing utilization of glucose and lactate, which are efficient fuels for aerobic respiration, the oxygen consumption efficiency of the myocardium and skeletal muscle can be improved

Abbreviations

3-KAT inhibitor: 3-ketoacyl-coenzyme A thiolase inhibitor; **ATP:** adenosine triphosphate; **ET-1:** endothelin-1; **FFA:** free fatty acid; **HF:** heart failure; **PCr:** phosphocreatine

by 16% to 26%.[8] Trimetazidine has been shown to directly inhibit fatty acid oxidation by blocking 3-ketoacyl-coenzyme A thiolase (3-KAT), the last enzyme involved in β-oxidation. Trimetazidine has been shown to affect myocardial substrate utilization by inhibiting oxidative phosphorylation and by shifting energy production from FFA to glucose oxidation.[9] Several studies have outlined the potential benefits of this agent on regional and global myocardial dysfunction. Therefore, 3-KAT inhibitors could also play a beneficial role in terms of glucose metabolism homeostasis, at both the cardiac and skeletal muscle level.

Modulation of myocardial metabolism by 3-KAT inhibitors in postischemic heart failure

By keeping in mind the concept that trimetazidine should be able to promote the utilization of glucose and nonfatty substrates by the mitochondria, attention has been focused on heart failure, where maintenance of metabolic efficiency is a crucial issue.

The effects of adding trimetazidine to the standard treatment for diabetic patients with ischemic dilated cardiomyopathy were assessed[10] on symptoms, exercise tolerance, and left ventricular function over short-term and long-term periods. In both cases, trimetazidine induced a significant beneficial effect on left ventricular function and control of symptoms compared with placebo. These results paved the way for additional studies, which have invariably confirmed the positive effects of trimetazidine in patients with postischemic left ventricular dysfunction.[11-13]

Modulation of myocardial metabolism by 3-KAT inhibitors in heart failure of different etiologies

The beneficial effect of trimetazidine on left ventricular function has been attributed to the preservation of intracellular levels of phosphocreatine (PCr) and adenosine triphosphate (ATP).[14] Previous clinical studies using ^{31}P magnetic resonance spectroscopy (^{31}P-MRS) to measure PCr/ATP ratios in the myocardium have shown that this ratio is reduced in the failing human myocardium.[15] The PCr/ATP ratio is a measure of myocardial energetics and its reduction may depend on an imbalance in myocardial oxygen supply and demand. A reduction in the total creatine pool, a phenomenon known to occur in HF, may also lead to a reduction in the PCr/ATP ratio. In patients with HF of different etiologies on full standard medical therapy, it has been observed that the trimetazidine-induced improvement in functional class and left ventricular function is associated with an improvement in the PCr/ATP ratio, which supports the hypothesis that trimetazidine preserves intracellular levels of myocardial high-energy phosphate.[16] These results appear particularly interesting, especially in view of previous evidence indicating that the PCr/ATP ratio is a significant predictor of mortality.[17]

Based on the results of this pilot study, it has also been tested whether trimetazidine, added to the usual treatment, could be beneficial in a more consistent group of patients with systolic-dysfunction heart failure of different etiologies.[18] Compared with patients on conventional therapy alone, those on trimetazidine showed improvement in functional class, exercise tolerance, quality of life, and left ventricular function *(Figure 1)*. Plasma B-type natriuretic peptide (BNP)

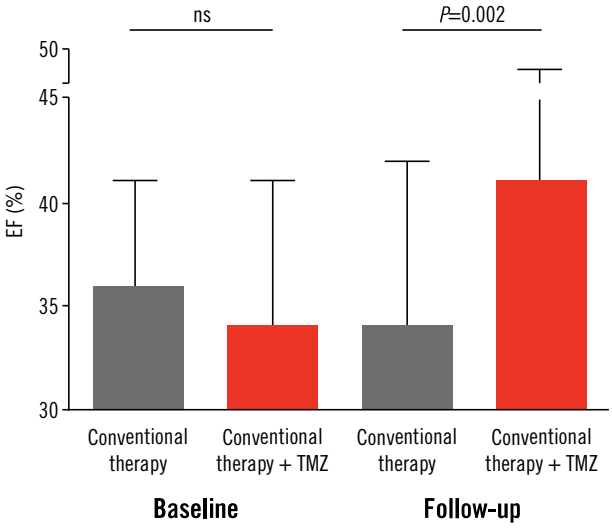

Fig. 1 *Long-term effects of trimetazidine on ejection fraction in patients with heart failure of different etiologies. Histograms (mean±1 SD) show the significant beneficial long-term effects of trimetazidine compared with conventional therapy alone.*
Abbreviations: *EF, ejection fraction; ns, not significant; SD, standard deviation; TMZ, trimetazidine.*
Based on reference 18: *Fragasso G et al.* J Am Coll Cardiol. *2006;48:992-998.*

levels were also significantly reduced in patients on trimetazidine compared with conventional therapy alone. Two recent meta-analyses and an international multicenter retrospective study have invariably confirmed these findings.[19-21]

Modulation of glucose metabolism by 3-KAT inhibitors

Patients with HF are insulin resistant. Recent studies have identified a direct relationship between endothelial dysfunction and insulin resistance.[22] When present, insulin resistance has been found to be operative in both cardiac and skeletal muscles.[23] In this context, a therapeutic option could be to induce muscles directly to reduce FFA utilization in favor of glucose oxidation. The use of a partial fatty acid inhibitor could play a very specific role. In fact, 3-KAT inhibitors should be able to promote the utilization of glucose and nonfatty substrates by the mitochondria. Apart from improving left ventricular function in cardiac patients, it has been shown recently that trimetazidine could also improve overall glucose metabolism in the same patients, indicating an attractive ancillary pharmacological property of this class of drugs.

The well-known insulin resistant state in most cardiac patients is certainly aggravated in those patients with overt diabetes. This is particularly relevant in patients with both diabetes and left ventricular dysfunction, where the availability of glucose and the ability of cardiomyocytes and skeletal muscle to metabolize glucose are grossly reduced. Since a major factor in the development and progression of HF is a reduced availability of ATP, glucose metabolism alterations could further impair the efficiency of cardiomyocytes to produce energy. By inhibiting fatty acid oxidation, trimetazidine stimulates total glucose utilization, including glycolysis and glucose oxidation. Therefore, the effects of trimetazidine on glucose metabolism could be dependent on both improved cardiac efficiency and improved peripheral glucose extraction and utilization. Finally, considering the known relation between endothelin-1 (ET-1) concentration and glucose metabolism abnormalities,[22] the observed beneficial effects of trimetazidine on glucose metabolism could also partly be ascribed to the positive effect of the drug on reducing ET-1 levels.

On this ground, forearm glucose and lipid metabolism as well as forearm release of endothelial vasodilator and vasoconstrictor factors have been evaluated during a prolonged inhibition of β-oxidation by trimetazidine in patients with postischemic left ventricular dysfunction. Trimetazidine increased both insulin-induced forearm glucose oxidation and forearm cyclic guanosine monophosphate release, while forearm ET-1 release was decreased.[24] These effects of trimetazidine at the skeletal muscle level add a new therapeutic window in the treatment of patients with heart failure and insulin resistance.

Effects of 3-KAT inhibitors on endothelial function

Trimetazidine can reduce endothelin release in cardiac patients.[13,24,25] Growth factors, vasoactive substances, and mechanical stresses are involved in the ET-1 increase in heart failure patients. Despite the known adaptive aspect of supporting contractility of the failing heart, persistent increases in cardiac ET-1 expression in the failing heart have a pathophysiological maladaptive aspect and are associated with the severity of myocardial dysfunction.[26] A causal role for ET-1 has been indicated in the vascular adaptation to skeletal muscle deconditioning, which is similar to other conditions.[27]

Trimetazidine-induced reduction in intracellular acidosis in ischemic myocardium could influence not only myocardial membranes, but also endothelial membranes.[28] By decreasing endothelial damage, trimetazidine could inhibit ET-1 release and, in turn, decrease myocardial damage. A second hypothesis is that by just decreasing the effects of chronic myocardial ischemia, trimetazidine could inhibit ET-1 release. Additionally, considering the close relationship between the endothelium and insulin sensitivity, the observed effects of trimetazidine on endothelial function could also explain the beneficial action of trimetazidine on global glucose metabolism.[24]

Effects of trimetazidine on whole-body energy metabolism in patients with heart failure

A higher resting metabolic rate has been observed in patients with HF,[29-31] which probably contributes to progressive worsening of the disease. The rate of energy expenditure is related to increased serum FFA oxidation. Both energy expenditure and serum FFA oxidation are inversely correlated with left ventricular ejection fraction and positively correlated with

concentrations of the growth hormones epinephrine and norepinephrine.[32] Norepinephrine increases whole-body oxygen consumption, circulating FFA concentrations, and FFA oxidation.[33] These changes have been attributed to stimulation of hormone-sensitive lipase in adipose tissue and stimulation of oxygen consumption independent of lipolysis by norepinephrine.[34] This data, together with close correlations between plasma norepinephrine concentrations, energy expenditure at rest, and FFA oxidation, make increased sympathetic activity the most likely explanation for alterations in fuel homeostasis in patients with HF. Therefore, intervention strategies aimed at optimizing global and cardiac metabolism could be useful for interrupting the vicious circle of reduced function at greater metabolic expenses in different cardiac conditions.[35]

In a recent study, it has been shown that 3 months of treatment with trimetazidine added to the usual treatment consistently reduces whole-body resting energy expenditure along with improved functional class, quality of life, and left ventricular function in patients with systolic HF, regardless of the etiology or the patient's diabetic status *(Figure 2)*.[36] The observation that the beneficial effect of trimetazidine on left ventricular function is also paralleled by a reduction in the whole-body rate of energy expenditure, when compared with patients on conventional treatment, underlies the possibility that the effect of trimetazidine may be mediated through a reduction in metabolic demand at the level of the peripheral tissues and, in turn, in some sort of central (cardiac) relief. Therefore, reduction in whole-body energy demand could be one of the principal mechanisms by which trimetazidine could improve symptoms, exercise tolerance, and left ventricular function in patients with heart failure.

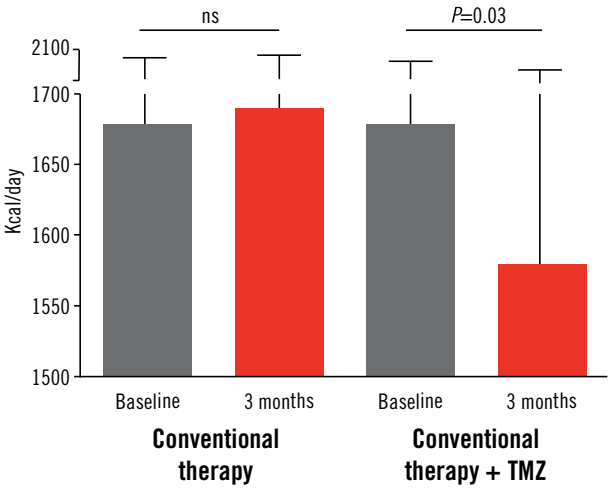

Fig. 2 *Rate of energy expenditure in heart failure patients. Rate of energy expenditure (kcal/d) measured by indirect calorimetry at baseline and a 3-month follow-up in patients with heart failure receiving conventional therapy alone (left histograms) or conventional therapy plus trimetazidine (right histograms).*
Abbreviations: *ns, not significant; TMZ, trimetazidine.*
Modified after reference 36: *Fragasso G et al.* Heart. *2011;97:1495-1500. Copyright © 2011, BMJ Publishing Group Ltd and the British Cardiovascular Society.*

Conclusions

Trimetazidine, a partial inhibitor of fatty acid oxidation, could have an important role in the therapeutic strategy of patients with heart failure and exertional intolerance. More specifically, shifting the energy substrate preference away from fatty acid metabolism and toward glucose metabolism by using trimetazidine may be an effective adjunctive treatment in patients with heart failure, especially in terms of left ventricular and skeletal muscle metabolism and function improvement. These effects seem operative in heart failure syndromes regardless of the etiopathogenetic cause and not confined to those of ischemic origin. ■

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Skeletal muscle myopathy in advanced heart failure: a case report

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Abstract

Chronic heart failure (CHF) is a progressive myocardial disease characterized by the inability of the heart to pump enough blood to meet the body's demand and by a reduced exercise tolerance. Recently, the presence of a skeletal myopathy has received much attention as the main player responsible for the reduced aerobic capacity in patients with CHF. Herein, we describe a case of a patient with advanced CHF with skeletal myopathy who underwent a cardiopulmonary test as well as dobutamine and exercise echocardiography stress tests for the determination of peak cardiac output. A blunted increase in cardiac output, attained with either dobutamine or during exercise, suggests that forward failure is still a major determinant of reduced aerobic capacity. ■ *Heart Metab*. 2014;64:28–30

Keywords: cardiac output; cardiopulmonary exercise test; echocardiography; heart failure; skeletal muscle myopathy

Chronic heart failure (CHF) is characterized by an intolerance to exercise that causes early fatigue and shortness of breath. Intuitively, cardiac output (CO) is expected to be a stronger determinant of aerobic capacity in patients with CHF. However, it is now well recognized that patients with CHF may reach a peak oxygen consumption (peak $\dot{V}O_2$) during symptom-limited exercise on a treadmill or bicycle before exhausting the capacity of the left ventricle to increase CO.[1] A number of authors suggested that peripheral skeletal muscle abnormalities prominently contribute to the exercise intolerance associated with CHF, whereas, central hemodynamic parameters, such as CO, are far less predictive of clinical symptoms and outcomes.[2-7] Herein, we describe a case of a patient with advanced CHF with skeletal myopathy who underwent cardiopulmonary exercise tests (CPXs) as well as dobutamine and exercise echocardiography stress tests for the determination of peak CO.

Case report

The patient was a 65-year-old man with a history of hypertension, type 2 diabetes, cigarette smoking, mild chronic renal failure, and sleep-related Cheyne-Stokes respiration. In January 2013, he was hospitalized for anterior ST-segment elevation myocardial infarction complicated by cardiac failure followed by cardiogenic shock, ventricular fibrillation, and cardiac arrest. After resuscitation, an intra-aortic balloon pump was inserted until the patient was clinically stabilized. At that time, the patient underwent coronary angiography, which showed a 75% stenosis of the proximal left anterior descending artery with total occlusion of the middle

Abbreviations

ACE inhibitors: angiotensin-converting enzyme inhibitors; **BNP:** brain natriuretic peptide; **CHF:** chronic heart failure; **CO:** cardiac output; **CPX:** cardiopulmonary exercise test; **EMG:** electromyography; **LV:** left ventricular

segment of the same vessel. He was then revascularized with percutaneous angioplasty and stenting of the coronary lesions. The following month, he was implanted with an automatic cardioverter-defibrillator.

In October 2013, the patient was hospitalized due to worsening decompensation symptoms, including shortness of breath at rest, orthopnea, and paroxysmal nocturnal dyspnea. Physical findings included tachycardia, S3 gallop, and diffuse pulmonary rales. An echocardiogram showed an enlarged left ventricle with global hypokinesia and apical, anterior, inferior, lateral, and septal akinesia. The patient's left ventricular (LV) ejection fraction was 0.26, the ratio of transmitral Doppler early filling velocity to tissue Doppler early diastolic mitral annular velocity (E/E') was 17.6, and resting cardiac index was 1.75 L/min/m^2. He received optimal medical therapy with aspirin, angiotensin-converting enzyme (ACE) inhibitors, β-blockers, antialdosterone antagonists, and loop diuretics. On admission, brain natriuretic peptide was 802 pg/mL and N-terminal pro-brain natriuretic peptide was 2704 pg/mL. At the time of hospital discharge, they were 418 pg/mL and 1980 pg/mL, respectively.

After stabilization of the clinical status, the patient underwent CPX, dobutamine, and exercise echocardiography stress tests. Peak $\dot{V}O_2$ was 13.0 mL/kg/min. During the stress tests, CO showed similar responses to direct inotropic stimulation as well as to exercise. A blunted increase in CO was apparent either with dobutamine (from 3.5 to 4.8 L/min) or with exercise (from 3.0 to 4.7 L/min). The total workload (40 W) and time to exhaustion were similar with CPX and exercise echocardiography. The patient underwent electromyography (EMG) to detect the electrical activity generated by skeletal muscle cells of the lower limbs. A decrease in action potential duration and a reduction in the area to amplitude ratio of the action potential were reported on the right quadriceps femoris. The responses were totally absent on the left quadriceps femoris. These findings were interpreted to be a result of a reduction in the number of motor units secondary to increased interstitial cellularity and decreased capillary density.

Discussion

This case report shows that the presence of the skeletal myopathy, as diagnosed by EMG, cannot solely explain a patient's inability to perform exercise. The blunted LV response either to inotropic stimulation or during exercise is indicative of the importance of central hemodynamics and that CO should be regarded as a key limiting factor of exercise capacity.

Skeletal myopathy refers to a clinical disorder of the skeletal muscles. Abnormalities of muscle cell structure and metabolism lead to various patterns of weakness and dysfunction. Many reports claim that alterations in skeletal muscle morphology, metabolism, blood flow, and function play a major role in exercise intolerance in patients with CHF, the so-called "skeletal muscle hypothesis." However, our findings show that, even in the presence of documented skeletal muscle myopathy, cardiac dysfunction is still a major determinant of reduced exercise tolerance in CHF.[8-12] As a matter of fact, it is remarkable that, in this patient, the CO responded similarly using either the dobutamine stress test or exercise. Since CO greatly contributes to peak $\dot{V}O_2$, this observation suggests that LV pump failure rather than muscle skeletal myopathy is the primary determinant of the reduced exercise capacity, even in the presence of documented muscle abnormalities. The role of LV systolic and diastolic parameters in predicting cardiopulmonary exercise performance has been addressed by several authors.[13-15] In the study by Scrutinio et al, the cardiac response to low-dose dobutamine, as assessed by echocardiography, correlated well with peak $\dot{V}O_2$.[13] In another study, the E/E' ratio was found to be the most powerful predictor of peak oxygen consumption.[15]

Recently, some authors have proposed an alternative view to "the skeletal muscle hypothesis" that can account for the influences played by the periphery on central hemodynamics.[16-18] It is highly probable that the inability to enhance ventricular contractility during stimulation plays a pivotal role in the inability of CHF patients to increase stroke volume. The overactivation of signals originating from skeletal muscle receptors (mechano-metaboreceptors) is an intriguing hypothesis proposed to explain the origin of symptoms and the beneficial effect of exercise training in the CHF

syndrome. The so-called metaboreflex has been reported to be hyperactive in CHF and to be responsible for a paradoxical increase in systemic vascular resistance and decrease in cardiac output whenever it is activated in these patients.

Conclusion

Although skeletal muscle abnormalities may contribute to the ability of the left ventricle to increase CO with exercise and to the early occurrence of fatigue and dyspnea, in this particular case report, the blunted cardiac response to dobutamine cannot be explained by the presence of skeletal myopathy. Impaired myocardial responses during dobutamine and exercise stress echocardiography indicate that central hemodynamics are always a primary determinant of exercise capacity in patients with CHF. It is likely that most symptoms resulted mainly from a forward cardiac failure secondary to the large myocardial infarction, in spite of the presence of documented skeletal muscle myopathy. ■

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How to interpret cardiopulmonary exercise tests

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Abstract

Exercise intolerance and related symptoms are cardinal manifestations of most cardiopulmonary disorders. Assessing the functional response with gas exchange analysis by cardiopulmonary exercise testing (CPX) is now the gold standard for thoroughly assessing the pathophysiological derangements behind these diseases. CPX provides an assessment of the integrative response involving the pulmonary, cardiovascular, muscular, and cellular oxidative systems, which are not adequately reflected thorough the measurement of individual organ system function. Accordingly, CPX is now being used in a wide spectrum of clinical settings for evaluation of undiagnosed exercise intolerance, and the test's popularity is increasing due to recent statements and official documents that have provided simplified and easy-to-apply reports that may consistently help the practicing clinician with their interpretations and clinical directions. ■ *Heart Metab*. 2014;64:31–36

Keywords: cardiopulmonary exercise; oxygen consumption; ventilation inefficiency

Applications and use of exercise testing with gas exchange analysis, added to electrocardiogram (ECG) and blood pressure monitoring, have been expanding in recent years and is now part of routine clinical diagnostic studies.[1,2]

A growing appreciation for this test has been possible due to the development of rapidly responding electronic gas analyzers to replace the more demanding chemical methods for measuring respiratory gases and to the development of flow meters that can measure instantaneous flow and volume. This has greatly decreased the technical time, and therefore, the cost to do gas exchange measurements.[2] Test-to-test repeatability and high reliance of data recorded are other significant features that have contributed to a preferred use compared with other exercise testing modalities.[3] These tests are referred to as cardiopulmonary exercise tests (CPXs) because the cardiovascular and pulmonary systems are assessed when gas exchange is measured during exercise.

The purposes for which CPXs are currently being applied attest to its growing importance in cardiopulmonary medicine. This approach is useful in terms of assessing the mechanism of exercise intolerance, evaluating disability, making activity and training recommendations, quantifying responses to therapy, and predicting outcomes. Due to these distinctive features, CPX has received a particular amount of attention in recent years; numerous studies have adopted CPX variables as end points over the last decade, and the test, with all its features, is becoming more common in daily clinical practice.[1]

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Abbreviations

ATP: adenosine triphosphate; **CPX:** cardiopulmonary exercise test; **ECG:** electrocardiogram; **HR:** heart rate; **MVV:** maximum voluntary ventilation; **RER:** respiratory exchange rate; **$\dot{V}/\dot{Q}$:** ventilation/perfusion [ratio]; **$\dot{V}_E$:** ventilation; **$\dot{V}O_2$:** oxygen consumption; **WR:** work rate

The present review addresses how to broadly interpret CPX results and how data can be interpreted in cases of disorders of the heart and the lung. Therefore, a translation from pathophysiological bases to clinical implications is provided.

Mechanisms for exercise intolerance and cardiopulmonary exercise test diagnoses

Exercise necessitates an increase in gas transport between the air and the mitochondria. This vital physiological coupling occurs due to a correct matching between several systems; primarily the pulmonary, cardiovascular, and muscular systems. Exercise intolerance is caused by any disease state that disrupts the normal gas-exchange coupling between the external and internal ventilation.

The basic requirement to sustain muscular activity is an increase in cellular respiration for the production and regeneration of adenosine triphosphate (ATP). To support the increase in cellular respiration, there is a need for an increase in O_2 and CO_2 transport between the cells and the external airways. This increase must match the rate of cellular respiration except for the following: (i) transient lags allowed by the capacitance in the transport system; (ii) O_2 stores on the venous side of the circulation; and (iii) small stores of high-energy phosphate in the form of creatine phosphate in the myocytes.

There are a series of pathophysiological questions relevant for the clinician to ask when caring for patients with exercise intolerance due to dyspnea and/or fatigue. Primarily, the clinician should determine whether the metabolic demand for the given exercise is increased (ie, obesity), and if the exercise is limited by impaired O_2 flow (eg, cardiac, pulmonary, or peripheral disease, or an anemic condition), or impaired O_2 utilization (eg, muscle glycolytic problem or mitochondrial enzyme defect). Also relevant to the pathophysiology is whether there is an abnormal degree of ventilation perfusion ($\dot{V}/\dot{Q}$) ratio mismatching (ie, cardiac and pulmonary disease). Despite the complex pathophysiological interaction between biological systems during exercise, the simplified CPX approach for diagnostic standardization of exercise intolerance uses a nine-panel graphic array exemplified in *Figure 1* (normal healthy subject).

Panel 3. Oxygen consumption ($\dot{V}O_2$) vs work rate (WR) is the panel suggested to start with because it shows the true exercise performance by displaying $\dot{V}O_2$ at peak exercise that may differ from maximum $\dot{V}O_2$ ($\dot{V}O_2$max), where the percent predicted can be determined by appropriate reference equations.[4] This panel is also useful because it describes the pattern of increase in $\dot{V}O_2$, which may often be abnormal in patients with cardiovascular disorders depending on the specific pathophysiological condition. Linearity is a prerequisite for a normal response to exercise, and, in healthy subjects, the slope of $\dot{V}O_2$ increase over O_2 uptake is 10 mL/min/W.[5] After reviewing the plots in panel 3, the others are relevant to go into the pathophysiological state of coupling of the above mentioned main organ systems.

Panel 1. Minute ventilation ($\dot{V}_E$) vs WR. This linear relationship normally recognizes three patterns with the first change in slope corresponding to the switch to a prevalent anaerobic metabolism determining an increase in $\dot{V}_E$ for the augmented CO_2 release due to lactate tamponade and a second one close to exercise termination due to the ventilator compensatory response.

Panel 2. Heart rate (HR) and $\dot{V}O_2$/HR (O_2 pulse) vs WR. O_2 pulse is a surrogate measure of stroke volume considering $\dot{V}O_2$ as cardiac output (CO=stroke volume x HR) x arteriovenous oxygen difference ([a-v]O_2). Considering the C(a-v)O_2 difference content, O_2 pulse mirrors the stroke volume.

Panel 4. $\dot{V}_E$ vs $\dot{V}CO_2$. This is a linear relationship until compensation for metabolic acidosis. The slope of the linear part is steep when the exercise physiologic dead space/tidal volume ratio (V_{DS}/V_T) is increased.

Panel 5. HR vs $\dot{V}O_2$ and $\dot{V}CO_2$ vs $\dot{V}O_2$. HR increases linearly with $\dot{V}O_2$ to the predicted maximum in normal subjects. In patients with cardiac disease or pulmonary vascular disease, the increase may lose its linearity with HR increasing progressively, but more rapidly, than $\dot{V}O_2$. Up to the anaerobic threshold, $\dot{V}CO_2$ increases linearly with $\dot{V}O_2$ with a slope of one

or slightly less than one. Then, $\dot{V}CO_2$ increases more rapidly and the steepening of the slope depends on the rate of lactic acid buffering.

Panel 6. Ventilatory equivalent for O_2 and CO_2 ($\dot{V}E/\dot{V}CO_2$ and $\dot{V}E/\dot{V}CO_2$) vs WR. $\dot{V}O_2$ decreases to a nadir at the anaerobic threshold, and $\dot{V}CO_2$ decreases to a nadir at the ventilatory compensatory point. Both values are high with pulmonary vascular occlusive disease.

Panel 7. VT vs $\dot{V}E$. The patients' vital capacity and inspiratory capacity (IC) are shown on the VT axis and measured maximum voluntary ventilation (MVV) is shown on the $\dot{V}E$ axis. With airflow limitation, maximal exercise $\dot{V}E$ approximates MVV. Thus, the breathing reserve ([MVV-$\dot{V}E$] at maximal exercise) is approximately zero. The breathing reserve cannot be predicted from resting pulmonary function measurements alone. With restrictive lung disease, VT may approximate the IC at low work rates and the respiratory rate may excessively increase.

Panel 8. Respiratory exchange ratio (RER; $\dot{V}CO_2/\dot{V}O_2$). This usually starts at approximately

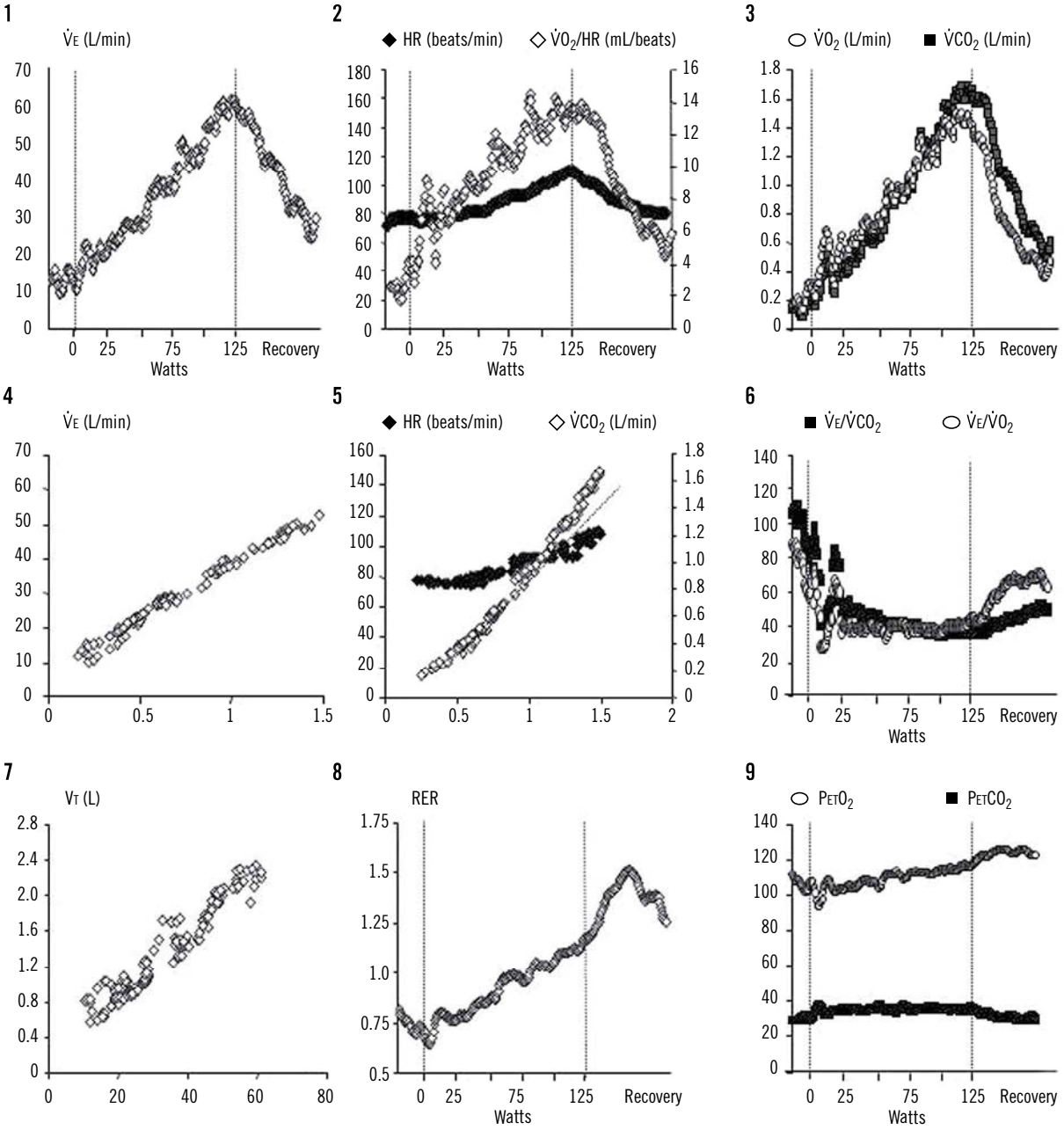

Fig. 1 *The nine-panel graphic array used in the CPX approach for diagnostic standardization of exercise intolerance uses.*
Abbreviations: *CPX, cardiopulmonary exercise testing; HR, heart rate; $\dot{V}E$, ventilation; $\dot{V}O_2$, oxygen consumption; $\dot{V}CO_2$, carbon dioxide consumption; VT, tidal volume; $P_{ET}O_2$, end-tidal oxygen tension; $P_{ET}CO_2$, end-tidal pressure of carbon dioxide.*

0.8 and increases to above 1.0, which is above the anaerobic threshold. Acute hyperventilation at rest and initial exercise stages yields a RER>1.

Panel 9. End-tidal pressure of carbon dioxide ($P_{ET}CO_2$) and end-tidal oxygen tension ($P_{ET}CO_2$) vs WR. Low $P_{ET}CO_2$ reflects either hyperventilation or a high $\dot{V}/\dot{Q}$ mismatching. The RER signals if the hyperventilation is acute. Arterial blood gases or knowledge of plasma HCO_3- differentiates chronic hyperventilation from $\dot{V}/\dot{Q}$ mismatching.

The report in specific disorders

What is useful in heart failure and coronary artery disease?

In heart failure (HF), $\dot{V}O_2$ is markedly below the predicted normal value, and a major exercise limitation is a defect in cardiac output increase. Since cardiac output increases linearly with $\dot{V}O_2$ and $C(a\text{-}v)O_2$ is approximately maximal even in advanced HF, $\dot{V}O_2$ may be generally considered a valid surrogate of cardiac output. When cardiac output fails to increase appropriately, the relationship between $\dot{V}O_2$/WR decreases as WR increases. This change may be gradual (shallow) rather than abrupt like the change in $\dot{V}O_2$/WR slope (flattening) observed when the myocardium becomes ischemic.[1] In coronary artery disease, the occurrence of $\dot{V}O_2$/WR flattening is accompanied by a reduction in the slope of the O_2 pulse increase and may offer suitable clinical information in the clinical framework of coronary artery disease. In a report comparing sensitivity and specificity of CPX criteria with standard exercise-ECG criteria for diagnosis of cardiac ischemia, CPX provided a much higher sensitivity (87%) and specificity (74%) than standard ECG (46% and 66%, respectively).[6] When flattening and ECG abnormalities concur during the test, the ECG shows evidence of myocardial ischemia at work rates soon after the $\dot{V}O_2$/WR flattening.

Along with $\dot{V}O_2$, a series of ventilatory variables provide relevant insights in the data interpretation of cardiac patients, primarily, HF patients.[7] $\dot{V}E$ inefficiency is a typical manifestation that is conventionally defined by looking at the rate of increase in $\dot{V}E$ vs $\dot{V}CO_2$ (*Figure 1*, plot 6). This relationship is assessed as $\dot{V}E$ vs $\dot{V}CO_2$ or, less commonly, by the ratio at anaerobic threshold or at the nadir point of the ratio. The information obtained by these variables is not only diagnostic, but also especially useful in the clinical and prognostic assessment of patient follow-up. A 4 class $\dot{V}E$ severity classification has been identified and proposed[4] and is now suggested by statements from Balady et al and Guazzi et al as basic parts of the report in cardiac patients.[1,2]

The origin of an increased and inefficient ventilatory response to exercise is multifactorial and primarily reflects how left ventricular dysfunction may impair lung physiology and both central and peripheral ventilatory control.[7] For these latter peripheral mechanisms, main putative factors are an impaired chemoreflex sensitivity and regulation along with early developing acidosis.

High $\dot{V}E/\dot{V}CO_2$ slopes are observed in patients with moderate to severe forms of pulmonary hypertension, and end-tidal CO_2 is a determinant that becomes clinically and prognostically relevant.[8]

Another ventilatory abnormality peculiar to some HF patients is the pattern of oscillatory gas kinetics classified as exertional oscillatory ventilation (EOV), a pattern that resembles, in some instances, the occurrence of Cheyne-Stokes respiration during sleep.[9] This is an ominous sign of disease severity that is now recognized in up to 30% of symptomatic HF patients with a similar rate in heart failure with reduced ejection fraction and heart failure with preserved ejection fraction.[9]

What is useful in pulmonary lung diseases and arterial pulmonary hypertension?

Exercise limitation in patients with respiratory disease is complex, multifactorial, and may be difficult to establish and clearly quantitate. Ventilatory limiting factors include decreased ventilatory capacity (mostly due to mechanical factors; *Figure 1, plot 7*), abnormal gas exchange (ie, hypoxemia and increased VD/VT), and respiratory muscle dysfunction.

As for cardiac patients, the literature pertaining to patients with obstructive lung disease emphasizes the relevance of $\dot{V}O_2$ *(Figure 1, plot 3)* as a primary variable to be addressed[10] as a peak $\dot{V}O_2$<10 mL/min/kg portends a particularly poor prognosis (*Figure 1*, plot 3).[11]

The role of deconditioning in patients with chronic cardiopulmonary disease and in patients after heart, heart/lung, or lung transplantation has increased awareness of the role of peripheral limitation in

exercise performance and the importance of considering this as a contributing factor in their exercise limitation.

The prognostic ability of peak $\dot{V}O_2$ in patients with pulmonary disease has led the American College of Chest Physicians to recommend that CPX be used presurgically in lung resection candidates to assess postsurgical risk.[12] Initial evidence also indicates the $\dot{V}_E/\dot{V}CO_2$ slope is a significant postsurgical prognostic marker in patients with chronic obstructive pulmonary disease (COPD) undergoing lung resection *(Figure 1, plot 6)*.[13]

A key value of CPX in detecting potential pulmonary vascular limitation and the role of vasculopathy, or gauging disease severity once a diagnosis has been made, is the ability of this exercise approach to noninvasively quantify $\dot{V}/\dot{Q}$ abnormalities. Specifically, abnormalities in the $\dot{V}_E/\dot{V}CO_2$ slope and $P_{ET}CO_2$ *(Figure 1, plot 9)* are strongly suggestive of pulmonary vasculopathy whose etiology is either idiopathic or secondary pulmonary hypertension as a consequence of other primary conditions such as heart failure, hypertrophic cardiomyopathy, COPD, interstitial lung disease, or systemic connective tissue diseases.[14,15]

Universal cardiopulmonary exercise test report

In the recent joint European Association for Cardiovascular Prevention & Rehabilitation/American Heart Association statement on CPX application, a major goal has been to provide a universal report that may allow collecting all relevant CPX data in a concise and organized manner, which seems essential for meaningful data interpretation and clinical utilization. Specifically, the universal CPX reporting form *(Figure 2)* provides clinicians with the ability to collect relevant data that may subsequently be used for interpretation according to a patient's specific condition/test indication.

<table>
<tr><td colspan="3">Exercise modality: [ ] Treadmill [ ] Lower extremity ergometer</td></tr>
<tr><td colspan="3">Protocol:</td></tr>
<tr><td>Peak VO_2 (mL O_2•kg^{-1} min^{-1}) VO_2 at V_T (mL O_2•kg^{-1} min^{-1})</td><td>Per cent-predicted peak VO_2 (%)[a]
Peak RER</td><td>V_E/VCO_2 slope EOV [ ] Yes [ ] No</td></tr>
<tr><td>$P_{ET}CO_2$ (mmHg) Resting:
Increase during ET:</td><td>V_E/VO_2 at peak ET</td><td>$\Delta VQ/\Delta VO_2$[b]</td></tr>
<tr><td>V_E/MVV[c]</td><td>PEF (L/min): Pre-ET Post-ET</td><td></td></tr>
<tr><td colspan="3">O_2 pulse trajectory[d]
[ ] Continual rise throughout ET [ ] Early and sustained plateau [ ] Decline</td></tr>
<tr><td colspan="3">$\Delta VO_2/\Delta WR$ trajectory[d]
[ ] Continual rise throughout ET [ ] Early and sustained plateau [ ] Decline</td></tr>
<tr><td>Resting HR (b.p.m.)
Peak HR (b.p.m.)</td><td>Resting BP (mmHg)
Peak BP (mmHg)</td><td rowspan="2">Resting pulse oximetry (%)
Peak pulse oximetry (%)</td></tr>
<tr><td>Percent of age-predicted maximal HR[e] HRR at 1 min (beats)</td><td>Maximal workload
[ ] Treadmill speed/grade:
[ ] Cycler ergometer Watts:</td></tr>
<tr><td colspan="2">ECG criteria
[ ] No arrhythmias/ectopy/ST-segment changes
[ ] Arrhythmias/Ectopy/ST-segment changes: not exercise limiting
[ ] Arrhythmias/Ectopy/ST-segment changes: exercise limiting</td><td>ECG description</td></tr>
<tr><td colspan="3">Subjective symptoms (check box for primary termination criteria)
RPE [ ] Angina [ ] Dyspnoea [ ]</td></tr>
<tr><td colspan="3">Additional notes</td></tr>
</table>

Fig. 2 *Universal CPX report.*
Abbreviations: *$\Delta VQ/\Delta VO_2$, change in cardiac output/change in oxygen consumption; BP, blood pressure; CPX, cardiopulmonary exercise testing; $\Delta VO_2/\Delta W$, change in oxygen consumption/changes in Watts; ECG, electrocardiogram; EOV, exercise oscillatory ventilation; ET, exercise testing; HR, heart rate; HRR, heart rate recovery; MVV, maximal voluntary ventilation; O_2, oxygen; PEF, peak expiratory flow; $P_{ET}CO_2$, partial pressure of end-tidal carbon dioxide production; RER, respiratory exchange ratio; RPE, rating of perceived exertion; V_E/MVV, peak minute ventilation/maximal voluntary ventilation; V_E/VCO_2, minute ventilation/carbon dioxide production; V_E/VO_2, minute ventilation/oxygen consumption; VO_2, oxygen consumption; V_T, ventilator threshold.*
[a]Use equations proposed by Wasserman. [b]Requires additional equipment to assess Q response to exercise through noninvasive rebreathing technique. [c]Directly measures MVV at baseline. [d]Requires O_2 pulse and $\Delta VO_2/\Delta WR$ plot from initiation of ET. If these variables required for assessment, electronically braked cycle ergometer should be used for testing. [e]Use equation: (peak HR/220-age) x 100.
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It should be noted that the CPX reporting form is primarily focused on the most common cardiovascular and pulmonary diseases. However, other reported variables may be relevant in conditions that are less frequent, but may still be a matter of useful investigation in the presence of exercise limitation (eg, mitochondrial myopathy and peripheral vascular disease).

Conclusions

Applications and use of CPX in the cardiology arena is increasing and is now included in the routine clinical diagnostic workup of patients with cardiopulmonary disorders. Data interpretation for diagnostic and prognostic purposes is based on physiological principles sustaining the matching between the external and internal ventilation and O_2 transport. The most recent statements and official documents have provided simplified easy-to-apply reports that may consistently help the practicing clinicians in their daily clinical practice. ■

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The "skeletal muscle–fat" interplay in heart failure

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Independent from specific areas of commitment, the "obesity paradox" and the U-shaped mortality risk at the extremes of obesity in heart failure (HF) are well known principles in cardiovascular medicine.[1]

Indeed, this topic has typically generated intense controversy. First, body mass index (BMI), the most frequently used parameter for the definition of obesity, has been criticized for the inability to distinguish between fat and nonfat body composition. Nonetheless, targeted research has shown that both fat and nonfat body components independently affect cardiovascular outcome.[2]

Adipose tissue and heart failure

Adipose tissue is an effective endocrine organ,[3] capable of secreting adipokines that have been implicated in HF and related cardiometabolic complications.[4] The underlying mechanisms have not been fully elucidated, but are likely to involve a complex interplay between inflammation, oxidative stress, impaired mitochondrial biogenesis, multiple paracrine and endocrine factors, insulin resistance with impaired glucose utilization, and functional and structural modifications of the vessel that precede the early stages of cardiac dysfunction.[5] In line with these considerations, markers of HF such as osteopontin[6] and osteoprotegerin are elevated in obesity.[7]

Heart failure and skeletal muscle

A number of alterations in skeletal muscles have been described in HF including impaired O_2 utilization with reduced mitochondrial oxidative enzyme activity and volume density.[8] In addition, increased levels of circulating catecholamines, angiotensin II, arginine, vasopressin, and endothelin-1 induce enhanced vasoconstriction and reduced nitric oxide mediated vasodilation.[9,10]

Adipose tissue, heart failure, and skeletal muscle

As previously mentioned, obesity is associated with a series of metabolic, inflammatory,[11] and hormonal changes,[12] which ultimately favors the incidence of HF. Conversely, data concerning skeletal muscles derive from models of already established HF.

Such observations have led us to perceive the link between HF and body composition in the following chronologic sequence: obesity increases the incidence of HF; the latter, perpetuated by obesity itself, induces skeletal muscle dysfunction with reduced mobility and increased morbidity, which further contributes to the maintenance of the vicious circle. In line with these considerations, nonintentional weight loss has been shown to be an independent predictor of mortality in HF patients.[13] Therefore, obese patients are collocated at the beginning of the observation period, which results in a relatively better prognosis when compared with lean patients.

On the other hand, these data appear in contrast with preventive medicine, historically attributing obesity with a negative impact on cardiovascular health. However, the "obesity paradox" has been mainly identified in individuals with low cardiorespiratory fitness.[14] Indeed, sedentary lifestyle negatively affects cardiocirculatory physiology, pulmonary gas exchange, and exercise tolerance.[15] Moreover,

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Abbreviations

BMI: body mass index; **HF:** heart failure

aerobic exercise training with purposeful weight loss improves outcome in HF patients.[16] Therefore, these observations acknowledge that obese patients have a relatively worse prognosis.

Conclusion

In conclusion, the feeling is that, when we adopt a "watchful attitude," obesity represents the "starting point" toward a negative cardiac outcome; conversely, when an "interventional attitude" with purposeful weight loss is adopted, the tendency can be inverted, with obesity being allocated relatively nearest to the negative outcome *(Figure 1)*. ■

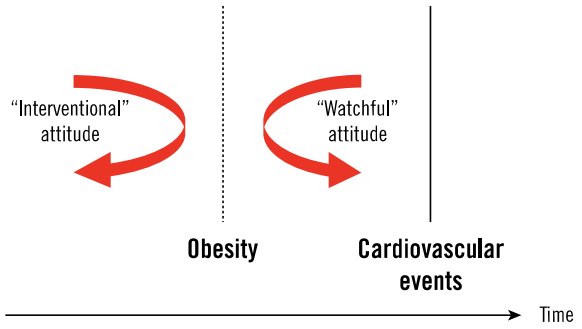

Fig. 1 *Illustration of the effects of an interventional attitude or a watchful attitude on cardiovascular events over time.*

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Body Mass Index (BMI)

BMI is a formula for measuring an individual's relative weight based on their mass and height and is calculated by the formula BMI=((mass (kg)/ (height(m))^2). A healthy BMI is generally considered to be in the range of 18.5 to 24.9, whereas those with BMIs in the 25 to 29.9 range are classified as being overweight, and those with BMIs >30 are classified as obese. Although BMI is frequently used to assess general body mass in patient populations, the BMI does not take into account age, gender, or muscle mass, and it can result in large BMI scores for people that actually have very low body fat percentages, such as body builders.

Ghrelin

Ghrelin is a peptide hormone secreted in the gastrointestinal tract via ghrelin cells and is commonly referred to as the "hunger hormone" since its plasma levels increase in the preprandial state and decrease in the postprandial state, suggesting that ghrelin has a physiological role in meal initiation.

Inorganic phosphate

Inorganic phosphate (HPO_4^{2-}) functions as a substrate, along with ADP to form ATP via the process of mitochondrial oxidative phosphorylation. It is a product when ATP is hydrolyzed to ADP to provide cellular energy for various processes including active transport, anabolic metabolism, and muscle contraction.

Osteopontin

Osteopontin is an abundantly expressed adipose tissue cytokine (adipokine) that plays a major role in inflammation, though it is also expressed in other cell types/tissues such as macrophages, smooth muscle cells, and skeletal muscle. Osteopontin regulates inflammation/immune function via modulating monocyte adhesion, migration, differentiation, and phagocytosis, whereas reducing osteopontin action has been shown to attenuate inflammation.

Osteoprotegerin

Osteoprotegerin is a cytokine receptor that is a member of the tumor necrosis factor receptor superfamily and acts as a receptor for the ligands receptor activator of nuclear factor κB ligand and tumor necrosis factor-related apoptosis-inducing ligand. Osteoprotegerin levels are elevated in patients with cardiovascular disease and thus osteoprotegerin may serve as a potential biomarker in the risk stratification of patients with cardiovascular disease.

Oxygen

Oxygen is a chemical element characterized by the atomic number 8 (ie, its nucleus contains eight protons). With respect to aerobic energy substrate metabolism, diatomic oxygen (ie, O_2) serves as the terminal electron acceptor in the mitochondrial electron transport chain, and is reduced to water in the process of oxidative phosphorylation, where the oxidation of reducing equivalents (NADH and $FADH_2$) is coupled to the synthesis of ATP from ADP and inorganic phosphate.

Oxygen consumption

Oxygen consumption refers to the amount of oxygen that is utilized by the body per minute. Following inspiration, and alveolar exchange oxygen is transported by the cardiovascular system to systemic tissues and is utilized via oxidative phosphorylation to generate ATP. Oxygen consumption is typically reported in absolute units (ie, L/min) or it is normalized to body mass (mL/kg/min)

Peak oxygen consumption ($\dot{V}0_2$)

Peak oxygen consumption ($\dot{V}O_2$) refers to the highest value of oxygen consumption that is obtained in response to an increase in energy demand (ie, increased work/effort or exercise). Maximal oxygen consumption ($\dot{V}O_2$max) occurs when progressive increases in energy demand do not elicit further increases in oxygen consumption (ie, oxygen consumption has plateaued), and is a measure of mitochondrial function/aerobic capacity. $\dot{V}O_2$max is compromised in a number of clinical conditions including heart failure.

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Phosphocreatine

Phosphocreatine (PCr) is a high-energy phosphate compound that functions to buffer intracellular ATP concentrations. When increases in energy demand deplete ATP, intracellular PCr is utilized to phosphorylate ADP, yielding ATP and creatine, a reversible reaction catalyzed by the enzyme creatine kinase (ie, $ADP + H^+ + PCr \leftrightarrow ATP + Cr$). This reaction replenishes intracellular ATP at a rate that is greater than that of ATP generation from catabolic pathways.