The physiological basis of rehabilitation in chronic heart and lung disease

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Although the primary impairments in chronic obstructive pulmonary disease (COPD) and congestive heart failure (CHF) clearly differ, there is considerable resemblance in the systemic consequences of these disease entities and their effects on exercise capacity and health-related quality of life (23). In fact, it is well documented that although indexes of primary organ failure (left ventricular ejection fraction for CHF and forced expiratory volume in 1 s for COPD) are poor determinants of exercise capacity, impaired peripheral muscle function is indeed an important predictor of exercise limitation in both disease entities (8, 24). Furthermore, reversion of the primary impairments in optimally treated COPD and CHF patients can be achieved only through surgical interventions, such as lung volume reduction surgery and lung transplantation for COPD (40) or coronary bypass surgery and heart transplantation for CHF (4). In the absence of these surgical interventions, regular skeletal muscle reconditioning as part of a comprehensive cardiopulmonary rehabilitation program constitutes a noninvasive therapeutic approach that can ameliorate skeletal muscle dysfunction, thereby improving functional capacity, daily symptoms, and quality of life.

The present article focuses on the physiological rationale for prescribing cardiopulmonary rehabilitation to patients with COPD or CHF to improve patients’ functional capacity independently of the degree of the primary cardiopulmonary impairment. Furthermore, the present article focuses on COPD and CHF because these disease entities are frequent and a great deal of research findings has been published in the area of rehabilitation in COPD and CHF. To better understand the physiological adaptations taking place during cardiopulmonary rehabilitation, this article initially presents the pathophysiological basis of rehabilitation in chronic heart and lung disease.
ical factors that limit exercise capacity in patients with CHF or COPD and subsequently outlines the benefits of cardiopulmonary rehabilitation on the various physiological systems giving particular emphasis on the improvements in peripheral muscle structure and function that importantly contribute to enhanced functional capacity. Although cardiopulmonary rehabilitation constitutes an interdisciplinary therapeutic approach involving exercise training, physiotherapy, breathing retraining, nutritional and psychological support, optimization of pharmacological therapy, and education (Table 1), this article focuses on exercise training targeting the improvement of locomotor muscle structure and function. However, the benefits of cardiopulmonary rehabilitation are numerous and expand beyond the improvement in patient’s functional capacity (Table 2) (16, 36). Accordingly, there are important nonphysiological benefits that account for much of the improved exercise tolerance in patients with lung and heart disease, namely desensitization to dyspnea, psychological changes associated with reduced anxiety and depression, and improvements in mechanical efficiency of the body to perform work (36).

Table 1. Components of cardiopulmonary rehabilitation

- Exercise training (aerobic and resistance conditioning)
- Patient assessment and optimization of medical therapy
- Education and psychosocial/behavioral management
- Chest physical therapy and breathing techniques
- Diet/nutritional counseling
- Weight control management
- Smoking cessation

Table 2. Benefits of cardiopulmonary rehabilitation

- Improves functional capacity
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- Improves health-related quality of life
- Reduces the frequency of hospital admissions and length of hospital stay
- Reduces the use of health care resources

amplification of respiratory drive and intensification of dyspnea sensations (34).

FACTORS LIMITING EXERCISE CAPACITY IN PATIENTS WITH CHF

Patients with CHF experience significant limitation upon physical exertion owing to intense sensations of dyspnea and particularly to locomotor muscle discomfort (44). Although central hemodynamic abnormalities are the hallmark of this disorder, studies have not shown a significant and clinically relevant relationship between left ventricular ejection fraction, or exercise pulmonary capillary wedge pressure, and exercise intolerance (5, 20).

Ventilatory abnormalities and alterations in peripheral vaso-motor control and skeletal muscle structure and function, as well as alterations in several neurohumoral systems, importantly contribute to exercise intolerance in patients with CHF (27, 53). Sympathetic hyperactivity plays a profound role in CHF, being associated with cardiac dysfunction and remodeling as well as skeletal muscle dysfunction (18, 26).

In addition, early lactate appearance (34) occurs in these patients during moderate exercise workloads and is reputed to be caused by a combination of reduced locomotor muscle blood flow and decreased aerobic enzyme content in peripheral skeletal muscles (29, 42, 43). Furthermore, peripheral muscle fiber atrophy across all fiber types (17) and alterations in skeletal muscle fiber typing are accompanied by alterations in contractile function of locomotor muscles. More specifically, locomotor muscle histological alterations include a shift from slow-twitch type I oxidative fibers to fast-twitch type II glycolytic fibers (17, 29). The fast, more fatigable type II fibers reach anaerobic metabolism earlier, thereby leading to the occurrence of peripheral muscle fatigue and muscle discomfort but to concurrently increase respiratory drive and thus dyspnea sensations (9, 32, 51, 52). This is the reason why in both CHF and COPD patients, exercise performance is usually limited by

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FACTORS LIMITING EXERCISE CAPACITY IN PATIENTS WITH COPD

Exercise intolerance in patients COPD is also multifactorial, involving ventilatory, gas exchange, cardiovascular, and peripheral muscle abnormalities. The mechanisms of limitation relate to 1) the imbalance between ventilatory capacity and demand, 2) the imbalance between energy demand and supply to working respiratory and locomotor muscles, and 3) the intrinsic factors that induce peripheral muscle dysfunction (49). In practice, intolerable exertional symptoms, (i.e., dyspnea and/or leg discomfort) constitute the main symptoms that limit physical capacity in patients with COPD.

More specifically, during exercise a disparity is developed between the decreased ventilatory capacity and the increased ventilatory requirement and work of breathing (21) that exacerbates the intensity of dyspnea (30). With respect to the cardiovascular factors, these are often associated with coexisting right- and/or left-ventricular dysfunction, functional arrhythmias, and various negative cardiopulmonary interactions that are often caused by dynamic lung hyperinflation and the large swings in intrathoracic pressures; these can in turn impair central hemodynamic function and thus exercise capacity (49).

Patients with COPD, similarly to those with CHF, also present with muscle weakness and altered muscle fiber distribution (50) in particular with reference to the proportion of type I slow-twitch fibers that are high oxidative, low tension, and fatigue resistant (1). Reduction in the proportion of oxidative type I fibers decreases the oxidative potential of the muscles and makes them more vulnerable to fatigue during exercise. There is also reduced capillary density that compromises regional blood flow and oxygen/nutrient delivery and thus exercise tolerance (33).

COMMON UNDERLYING MECHANISMS OF EXERCISE LIMITATION

It has been well documented that in both disease entities, muscular impairment is multifactorially determined by hypoxia, oxidative stress, disuse, medication, nutritional depletion, and local muscle inflammation (Fig. 1) (1, 27).

Histologic and metabolic data (23) show that in both disease entities peripheral muscles undergo a shift from oxidative to glycolytic energy metabolism. This in turn leads to early lactic acid production and the accumulation of inorganic phosphates and hydrogen ions that are known not only to accelerate the occurrence of peripheral muscle fatigue and muscle discomfort but to concurrently increase respiratory drive and thus dyspnea sensations (9, 32, 51, 52). This is the reason why in both CHF and COPD patients, exercise performance is usually limited by
the combination of intense symptoms of dyspnea and leg discomfort. Hence improving the oxidative potential of the peripheral muscle fibers is an important goal of rehabilitative exercise training programs in both disease entities, because postrehabilitation these muscles will not heavily rely on anaerobic metabolism, thereby allowing a greater amount of work to be achieved with lower sensations of dyspnea and leg discomfort (22, 36). These improvements take place without any change in cardiac or respiratory function.

### COMPONENTS OF REHABILITATION THAT IMPROVE MUSCLE FUNCTIONAL CAPACITY

There is strong evidence that in patients with CHF or COPD cardiopulmonary rehabilitation induces significant improvements in work and aerobic capacities (13, 22, 28, 36). In patients with CHF rehabilitation improves autonomic and neurohumoral activation and endothelial function and catecholamines serum levels. In patients with COPD rehabilitation lessens ventilatory requirement and the degree of exercise-induced dynamic hyperinflation (36). The unaltered cardiac and lung function with physical training and the absence of a correlation between the magnitude of improvement in physical capacity postrehabilitation and the baseline degree of left ventricular dysfunction in CHF or the baseline degree of expiratory flow limitation and lung hyperinflation in COPD has increasingly lead the scientific community to believe that the main effects of physical training in patients with CHF or COPD are of peripheral rather than central nature (16, 36). Accordingly in CHF patients, the beneficial effects of exercise training are associated with better neural control of the cardiovascular system and specifically with reduced sympathetic nerve activity. One of the potential candidates for a reduction in sympathetic activity following exercise training is the afferent autonomic control of sympathetic nerve activity, coordinated by arterial baroreceptors, cardiopulmonary receptors, ergoreceptors, and chemoreceptors. Such adaptations are paralleled by a significantly increased local muscle blood flow/oxygen availability and increased oxidative capacity secondary to the increased capillary and mitochondrial volume density and oxidative enzyme concentration (7, 39). In patients with COPD, improved exercise tolerance postrehabilitation is attributable to reductions in intrapulmonary and intrathoracic pressure swings at a given level of physical work, leading to improved arterial oxygen content and central hemodynamic responses reflected by increased systemic and peripheral muscle blood flow and oxygen availability (49). In both disease entities, therefore, the peripheral muscles undergo important adaptations with exercise training (Tables 3 and 4) that allow them to more efficiently utilize the increased local muscle blood flow/oxygen supply associated with improvement in both capillary and mitochondrial volume densities (22, 36).

Because muscle disuse has been suggested to be an important factor that importantly contributes to the alterations in muscle fiber structure and function in both COPD and CHF patients, it is possible that reversing muscle disuse by the implementation of regular muscle conditioning could partially reverse the abnormalities within the peripheral muscles in the absence of changes in cardiac or lung function (22, 36).

**Endurance training.** Increased cross-sectional areas of oxidative fibers and elevated oxidative enzyme activities as well as increased capillary-to-fiber ratios in quadriceps muscles collectively lead to reduction in exercise-induced lactic acid production in trained patients with COPD (25, 31). Endurance training-induced increases in oxidative capacity of the quadriceps muscles (documented by the increase in the activity of oxidative enzymes and the capillary to fiber ratio) are also associated with lower lactate accumulation during exercise in patients with CHF after completion of an endurance rehabili-

### Table 3. Effects of exercise training on locomotor muscles in CHF

- Improved oxidative and metabolic muscle capacity
- Increased citrate synthase activity
- Increased mitochondrial volume density
- Atrophy and/or reversal of skeletal muscle atrophy
- Decreased oxidative stress
- Improved vasodilatory capacity and endothelial function
- Reduced systemic vascular resistance
- Increased musculoskeletal blood flow
- Inhibition of elevation of proinflammatory cytokines
- Reduced skeletal myocyte apoptosis
- Increased expression of local muscle growth factors in skeletal muscles

CHF, congestive heart failure.

### Table 4. Effects of exercise training on locomotor muscles in COPD

- Improved muscle performance
- Increased cross sectional area of thigh muscle
- Improved oxidative and metabolic muscle capacity
- Increased mitochondrial volume density
- Increase in muscle cross sectional muscle fiber size
- Reduced distribution of fast-twitch type II glycolytic fibers
- Increase in capillary contact for each muscle fiber
- Increased expression of muscle growth and myogenic factors

COPD, chronic obstructive pulmonary disease.
tative training protocol (Tables 3 and 4) (25, 31). Accordingly, prolonged endurance training in patients with COPD or CHF leads to delayed reliance on anaerobic metabolism, thereby resulting in higher muscle fatigue resistance, while it simultaneously lessens the ventilatory requirement and thus the degree of breathing discomfort. Reduced ventilatory requirement is associated with reduced mechanical restriction to tidal volume expansion and thus with a lower intensity of perceived dyspnea at a given level of physical work (36, 45).

Interestingly, it has been shown that endurance training can improve skeletal muscle oxidative capacity in patients with moderate to severe COPD by reducing exercise-induced lactic acidosis. In fact a significant inverse relationship has been found between the percent changes in skeletal muscle oxidative enzymatic activities of citrate synthase and 3-hydroxyacyl-CoA dehydrogenase and the percent changes in arterial lactic acid during exercise. This in turn suggests that peripheral muscle changes with exercise training particularly apply to those COPD patients who are able to train at relatively high intensities that induce lactic acid metabolism during exercise (1, 9, 32, 33).

In recent years, there has been considerable interest in interval training (i.e., alternating periods of high-intensity exercise by resting periods or periods of lower-intensity exercise) for patients with advanced COPD or CHF, because it is well documented that it is possible to achieve a greater total work using interval training than constant-load exercise and therefore achieve even larger training adaptations (47, 54). More specifically in patients with COPD, high-intensity interval training leads to improved aerobic fitness by enhancing muscle oxidative capacity (e.g., the activity of citrate synthase and the capillary-to-fiber ratio) and the cross-sectional areas of both type I oxidative muscle fibers, while it reduces the proportion of type II glycolytic fibers (47). However, superiority of interval training leads to improved aerobic fitness by enhancing muscle oxidative capacity (e.g., the activity of citrate synthase and the capillary-to-fiber ratio) and the cross-sectional areas of both type I oxidative muscle fibers, while it reduces the proportion of type II glycolytic fibers (47). However, superiority of interval training compared with constant work rate training has not been demonstrated. In patients with CHF, interval training has shown superior effects to continuous training in terms of improving aerobic capacity, endothelial function, and quality of life (54).

Resistance training. Resistance training also appears to be worthwhile in patients with COPD or CHF who have reduced muscle mass and strength of their peripheral muscles. Because falling appears to be common in elderly people and muscle weakness is an important risk factor for falls in this population (35), optimizing muscle strength is likely an important goal of rehabilitation. Furthermore, resistance training has greater potential to improve muscle mass and strength than endurance training (10, 11), two aspects of muscle function that are only modestly improved by endurance exercise. A point in favor of resistance-muscle training is that it stresses the cardiorespiratory system less than the traditional endurance exercise, allowing the application of intense loads on peripheral muscles with lower perception of dyspnea (19). In the clinical setting, this makes resistance exercise an attractive and feasible option for patients with advanced COPD or CHF who may not be able to complete high-intensity endurance or interval training because of intolerable dyspnea sensations.

Combinations of resistance and endurance training result in a higher physiological response to training compared with endurance training alone in patients with COPD (6) or CHF (19).

NUTRITIONAL INTERVENTIONS ALONG WITH REHABILITATIVE EXERCISE TRAINING

Methods to promote anabolic pathways in view of the high prevalence of fat-free mass loss observed in COPD and CHF patients are particularly relevant during cardiopulmonary rehabilitation where exercise training is associated with increased energy expenditure (41). In COPD, combining nutritional supplementation (in the form of high-protein oral nutritional supplements) with in-patient pulmonary rehabilitation of depleted patients has shown improvements in weight, fat-free mass, exercise capacity, respiratory and peripheral muscle strength, and health-related quality of life (12, 14). In addition, the efficacy of a multimodal intervention approach, including nutrition, anabolic steroids, and exercise training, was proven successful in improving body weight, fat free mass, and exercise tolerance in patients with COPD (37). However, the later study (37) did not identify which of the components of the intervention were responsible for these benefits. In patients with CHF, energy-protein intake when combined with amino acid supplementation has been shown to have a positive impact on nutritional and metabolic status and to improve exercise tolerance, peak oxygen consumption, and functional capacity (3).

WHICH TYPE OF PATIENT BENEFITS MOST FROM CARDIOPULMONARY REHABILITATION?

Exercise training has beneficial effects on functional classification because this is defined either by the Medical Research Council (MRC) scale in COPD or according to the NYHA in patients with CHF (38). More explicitly, cardiopulmonary rehabilitation has important clinical impact by reducing the severity of MRC or NYHA functional classification (36, 45). Furthermore, a recent study demonstrated lack of significant differences among patients with COPD across GOLD stages II, III, and IV in terms of improving exercise tolerance, quality of life, and muscle fiber morphology and typology in response to a comprehensive pulmonary rehabilitation program. These findings highlight the importance and potential benefits of implementation of such pulmonary rehabilitation programs in all patients with COPD irrespective of disease severity (48).

Another study examining skeletal muscle hypertrophy and regeneration in high and low muscle mass COPD patients revealed that high-intensity endurance training induced a significant and highly comparable increase in the vastus lateralis muscle mean fiber cross-sectional area and capillarization in both high and low muscle mass patients. These findings indicate that endurance training induces peripheral muscle adaptations and modifications in factors regulating skeletal muscle hypertrophy and regeneration, independently of body composition and degree of muscle wasting (46).

Table 5. Contraindications to exercise training in CHF and COPD patients

- Complex ventricular arrhythmias at rest or during mild exercise
- Significant ischemia at low exercise levels, uncontrolled diabetes
- Active pericarditis or myocarditis
- Moderate to severe aortic stenosis
- Valvular heart disease requiring surgical treatment
- Myocardial infarction within the past month
- Musculoskeletal problems impairing the ability to exercise
In patients with CHF, exercise training has been shown to improve neurovascular control and functional capacity regardless of age or disease severity (2). In addition, there is evidence that exercise training improves exercise capacity and muscle structure and function (25) to a highly comparable magnitude in patients spanning from mild to moderate and advanced heart failure across NYHA functional classes I to III (15). There are, however, numerous contraindications for exercise training in patients with CHF or COPD shown in (Table 5).

CONCLUSIONS

In patients with COPD or CHF, endurance exercise training induces significant peripheral muscular adaptations, such as increased capillary density, mitochondrial volume density, fiber size, proportion of slow twitch fibers, and decreased metabolic acidosis, that collectively allow a given work task to be undertaken with lower sensations of dyspnea and leg discomfort, thereby enhancing exercise tolerance. These improvements take place without any change in cardiac or respiratory function. Combination of strength and endurance training results in more significant improvements of muscle strength and endurance, with equivalent improvements in whole body functional capacity, compared with endurance training alone. These effects are largely independent of COPD or CHF severity.

DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the author(s).

AUTHOR CONTRIBUTIONS

Author contributions: I.V. and S.Z. prepared figures; I.V. and S.Z. drafted manuscript; I.V. and S.Z. edited and revised manuscript; I.V. and S.Z. approved final version of manuscript.

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