Disability in COPD and Chronic Heart Failure Is the Skeletal Muscle the Final Common Pathway?

Luminita DUMITRU[a]; Alina ILIESCU[a]; Horatiu DINU[a]; Ruxandra BADEA[a]; Simona SAVULESCU[a]; Simona HUIDU[b]; Mihai BERTEANU[a]

[a]Elias Emergency University Hospital, Department of Physical and Rehabilitation Medicine, Bucharest, Romania
[b]Elias Emergency University Hospital, Department of Cardiology, Bucharest, Romania

ABSTRACT

Chronic Obstructive Pulmonary Disease (COPD) and Chronic Heart Failure (CHF), two major causes of worldwide morbidity and mortality have important systemic components, affecting additional tissues, other than the lung or the heart, such as the skeletal muscle. Muscle function (or dysfunction) may not only influence the symptoms that limit exercise, but may contribute directly to the poor exercise performance, health status and increased healthcare utilization.

The present review tries to summarize the muscular abnormalities in COPD and CHF and the mechanisms underlying these alterations, which are strikingly similar, despite the obvious differences concerning the primary impairment in these two chronic diseases.

The muscles therefore represent a potential site to improve patients' functioning level and quality of life of COPD and CHF. Only one practical therapeutic intervention currently exists that can reverse some of the muscle abnormalities observed in COPD and CHF, namely exercise training, which becomes nowadays the "cornerstone" of the whole rehabilitation.

Keywords: chronic Heart Failure, chronic obstructive pulmonary disease, skeletal muscle, disability, rehabilitation

INTRODUCTION

COPD and HF, two major causes of worldwide morbidity and mortality are both chronic diseases, described not only by the primary impairment, but also by the disability and restriction of participation that derive from it (1).

One of the most prominent symptoms in HF and COPD is the decreased exercise capacity/exercise intolerance. Exercise capacity levels can be extremely varying in patients having the same degree of primary cardiac/pulmonary dysfunction (measured by LVEF- left ventricular ejection fraction and FEV1-forced expiratory volume in 1 second, respectively). It has been proven that these parameters of primary organ

failure represent poor predictors of exercise capacity in moderate to severe forms of disease. Over the past decade or more, based on clinical and laboratory studies, the concept about the systemic components in HF and COPD, affecting multiple tissues others than the heart and the lung, has been described and progressively understood. Particular interest has focused on the respiratory and peripheral skeletal muscles. The last years' research has shown that muscle dysfunction represents a strong predictor of limited exercise tolerance and of poor quality of life in CHF and COPD (2). It is independent of the primary organ's failure severity, of its slowing-down with medication and of impairment reversibility achieved through surgical interventions such: coronary by-pass surgery and cardiac transplantation or lung volume reduction surgery or lung transplantation.

Both COPD and CHF – two distinct disorders (in terms of primary impairment), with a comparably decreased exercise capacity – show striking similarities with respect to muscle dysfunction. ❑

MUSCLE ALTERATIONS IN CHF/COPD

Functional alterations

Muscle performance is defined in terms of strength and endurance. *Strength* is the ability of a muscle or muscle group to exert force to overcome the most resistance in one effort (to develop maximal force). *Endurance* is defined as the ability of a muscle or a muscle group to exert force to overcome a resistance many times, thus, to resist fatigue. Loss of one or both of these muscle performance components results in muscle weakness, which is a common feature in HF and COPD. The impact of muscle weakness on exercise capacity has already been studied. Patients which such diseases have significantly less strength in both peripheral muscles (measured by leg extension, leg flexion, seated bench press and seated row) and respiratory muscle (measured by maximal inspiratory and expiratory pressures) compared with healthy people.

The two components of muscle performance seem to be unequally affected in *respiratory* and *peripheral* muscle groups. This is highlighted by a poor correlation found between the strength of both muscle groups in HF and COPD, compared with a stronger correlation in healthy subjects.

In the **peripheral muscles** of HF/COPD patients, reduced *endurance* (i.e., fatigue) seems to be the main limiting factor of exercise capacity, because the sense of leg effort was the dominant reason to stop exercising. During exercise in COPD patients it was shown that early acidosis occurs, mainly as a consequence of lactate release from the exercising limbs (3) contributing to the peripheral muscle fatigue.

In the **respiratory muscle** group, it seems that loss of *strength* and not of endurance represents the main factor affecting the exercise capacity. It has to be told that both components (strength and endurance) are affected in COPD patients, but the fatigue of the respiratory muscle (loss of endurance) is not an independent factor that limits exercise capacity in COPD patient (4,5). Also, it is unlikely that the respiratory muscles of COPD exercising patients can contribute to the early lactate response, as in the peripheral exercising muscle. It has to be added that the respiratory muscles are adapted to a chronic mechanical load, while they have to operate against a higher airway mechanical impedance in COPD. That's why the strength component of muscle performance is of greater importance in the respiratory muscles. The same findings have been demonstrated in the respiratory muscles of patients with CHF.

Further studies are needed in order to extrapolate this finding in clinical practice, so adapting the type of training exercise on respiratory/peripheral muscle group. ❑

MUSCLE STRUCTURAL ALTERATIONS IN COPD/CHF

Fiber typing. Maybe the most studied and notable muscular changes in COPD and CHF are the relative shift of one muscle fiber type into another. This alteration appears to occur in opposite direction in peripheral and respiratory muscles.

Adult mammalian skeletal muscle contains different types of fibers, characterized by myosin heavy chain (MHC) isoforms. MHC content of muscle fibers represents the determinant factor of the functional properties of a muscle, such as speed contraction and fatigue resistance. In mammalians, embryonic and neonatal MHC isoforms are gradually replaced by adult isoforms. Four MHC isoforms are present in the adult mammalian muscle: I, IIa, IIx and IIb. Only three of these (I, IIa and IIx) have been found in human muscle. The characteris-

tics of muscle fibers types are summarized in Table 1.

Despite the variability of their results, the majority of the studies that have been performed so far, points a general tendency of an I→IIx shift in peripheral muscles and an IIx→I shift in the diaphragm of COPD and CHF patients.

The different twitch and fatigue resistance characteristics of the distinct fibers types have functional consequences in the affected muscle of COPD and CHF patients, as mentioned above: the main exercise-limiting factor is the peripheral muscle *fatigue* (conversion type I→IIb/x), whereas in the respiratory muscles (diaphragm), the major exercise-limiting contributor is the loss of *strength* (conversion IIb/x→I)

Morphologic macroscopic alterations as marked loss muscle mass or decrease in cross-sectional area have been observed in advanced stages of both COPD and CHF.

Capillary density. The results of studies investigating this abnormality are discrepant. Overall, there is a tendency toward a reduced capillary-fiber ratio. Logically, the capillary density can be unaltered, reduced, or even elevated depending on the degree of muscle atrophy (loss of number of fibers). There are also a few studies demonstrating lower mitochondrial volume densities (using electron microscopy) in skeletal muscles in CHF patients compared with controls (6), suggesting an altered oxidative capacity of skeletal muscle in CHF/COPD patients.

Metabolic muscle abnormalities. All measurements of substrate or cofactor concentrations in skeletal muscle of COPD and CHF patients demonstrate an impaired energy metabolism at rest and during exercise with reduced levels of high energy substrates. The elevated Pi/-CrP and ADP/ ATP ratios are associated with high IMP concentration, due to increased deamination of accumulating AMP, probably reflecting a reduced aerobic capacity. During exercise, a greater increase in Pi/-CrP ratio and a faster drop in pH were found in exercising COPD and CHF patients compared with healthy persons (7,8). So, lactic acidosis occurs at a much lower rate than in healthy subjects. Lactic acid accumulates when oxygen transport to the working muscles becomes inadequate, and anaerobic glycolysis is called on to supplement aerobic ATP production. This suggest that rephosphorilation of macroergic phosphates is less efficient in these patients, both during and after exercise. Also, glycogen concentrations in COPD and CHF patients tend to be lower and lactate levels higher than in healthy persons, demonstrating that anaerobic energy metabolism is enhanced in both diseases.

An overall increase in glycolytic and decrease in oxidative enzyme activities have been demonstrated in peripheral muscles of COPD and CHF patients. Enzyme activities are primarily related with the muscle fiber type, so it is plausible that the shift in the enzymatic activity is linked to the shift in muscle fibers distribution as mentioned above. Which one is the cause and which one the effect, remains unclear. ❑

POSSIBLE MECHANISMS OF MUSCLE DYSFUNCTION IN COPD AND CHF

Hypoxia

As a result of hypoxemia and/or reduced blood supply, oxygen delivery to peripheral and respiratory muscle may be insufficient in COPD and CHF (in more advanced stages).

	Type I Slow oxidative	Type II Fast oxidative	Type II$_x$ Fast glycolitic
Contraction	Slow-twitch	Fast-twitch	Fast-twitch
Fiber size	Small	Intermediate	Large
Myoglobin concentration	High	High	Low
Capillary density	High	High	Low
Color	Red	Red	White
Mitochondrial content	High	High	Low
Fatigue resistance	High	High	Low
Major storage fuel	Triglycerides	Creatinine-Phosphate and Glycogen	Creatinine-Phosphate and Glycogen
Activity used for	Aerobic	Long-term	Short-term anaerobic

TABLE 1. Characteristics of muscle fiber types.

This may result in muscle tissue hypoxia leading to the functional, structural and metabolic changes described above.

Hypoxia has been shown to change the transcriptional regulation of the expression of metabolic genes, resulting in an increased glycolytic and reduced oxidative capacity, as it is observed in COPD. Hypoxia damages the mTOR (mammalian target of rapamicin) pathway, a key regulator of cell growth and proliferation. This impairs the transcription of DNA and translation of mRNA into protein, which may contribute to muscle wasting in COPD. It has been proven that hypoxia inhibits myoblasts differentiation by degradation of the myogenic transcription factor (MyoD), via the ubiquitine proteasome pathway (9). Thereby, the regeneration potential of skeletal muscle is impaired.

Opposite to the skeletal peripheral muscle changes, in the diaphragm of COPD and CHF patients, a reduction in the oxidative capacity does not occur. In this muscle, hypoxia may cause an endurance training effect due to the increased ventilation, so resulting a shift toward a more aerobic metabolism.

Oxidative stress

Oxidative stress, which is defined as an imbalance between the formation-of and protection-against reactive oxygen species (ROS) and reactive nitrogen species (RNS) can result in structural and functional muscle abnormalities, quite similar to those observed in COPD and CHF peripheral muscles. Reactive oxygen species –ROS (free radicals) are elevated in patients with COPD both at rest and during exercise (10,11).

An abnormal oxidative stress response to submaximal and maximal exercise may be more severe in muscle-wasted than in non-muscle-wasted patients with COPD.

Susceptibility to these free radicals depends on the antioxidant status of the tissues. The main radical scavengers and enzymes are (among others): reduced glutathione, vitamin E (in the cell membrane), superoxide dismutase (SOD), glutathione peroxidase and catalase.

The elevated ROS and/or NOS production in the muscle fiber targets mitochondria and myofilaments leading to: apoptotic processes in myocytes, mitochondrial respiratory chain dysfunction and/or alterations in myofilament contractile properties. These are three molecular mechanisms explaining the peripheral muscle dysfunction by the oxidative stress.

During long-term physical training, the repeated exposure to oxidative stress stimulates the defense system against free-radicals. Thus, the concentrations of radical scavengers and

	Muscle alterations	Exercise training effects	References
Morphology/body composition	↓CSA of lower limb muscle ↓FFM	↑with resistance training ↑FFM with combined strength and endurance training	22,23,24
Fiber-type/fiber size	↑% type II$_x$ ↓% type I and MHC ↓fiber cross-sectional area (atrophy)	No significant changes in fiber-type proportion ↑cross-sectional area	25,26
Muscle capillarization	↓capillary contact to cross-sectional area of muscle fiber	↑capillary contact with increased fiber cross-sectional area(proportionally)	25,27
Muscle metabolism	↓ oxidative enzymes capacity	↑capacity with endurance training	27,28
Muscle metabolite concentrations	↓ PCr,/Pi,↓ pH, ↓ATP ↑IMP, ↑lactate	↓lactic acidemia, Normalization pH and PCr,/Pi Recovery of PCr (faster)	29,30
Inflammation	↑inflammatory markers	Insufficient studies	
Muscle performance	↓endurance, ↓ strength (quadriceps)	↑ endurance/strength skeletal muscle (↑exercise capacity)	31,32
Exercise capacity level	↓ strength respiratory muscles ↓exercise capacity	No effects on exercise capacity with IMT(COPD) Possible effects of IMT on exercise capacity(CHF) but insufficient evidence	

TABLE 2. Changes of muscle pathophysiologic abnormalities induced by exercise training in COPD.

activities of antioxidant enzymes increase. The oxygen flux to muscles increases considerably in exercising muscles, resulting in higher oxidative stress. The disuse of skeletal muscle (a frequent situation in COPD and CHF patients) and the chronic hypoxia eliminate the antioxidant-stimulating trigger, resulting in a low antioxidant status.

Hypoxia-reoxygenation studies showed that oxygen oversupply after a period of oxygen deficit may increase the risk of free-radicals formation in myocytes (12). For that reason, in COPD and CHF patients, chronic hypoxia may result in reduced antioxidant status, therefore occasional bouts of exercise may cause a burst of free radicals that exceeds the capacity of the scavenging systems. It is also possible that the low oxidative capacity of such patients itself leads to higher oxidative stress, because the abrupt oversupply of oxygen during exercise is inefficiently metabolized.

Disuse

Disuse of skeletal muscle due to a low level of physical activity in patients with COPD and CHF is a factor that contributes to the above – described muscle alterations. It is well known and demonstrated that the physical activity level of COPD patients is lower than that of the average population (13). And the situation becomes worse during and after the exacerbations of the disease. COPD and CHF patients experiencing dyspnea with activities, become more sedentary to avoid dyspnea-producing activities, so they decrease their activity level, which in turn leads to a decline in fitness and deconditioning, and an earlier occurrence of dyspnea. There is the so-called "dyspnea spiral".

In a COPD patients group compared with physical activity level -matched control group, no differences in muscle performance (strength and fatigue resistance) or contractile properties could be detected (14).

Detraining have some demonstrated muscle effects: induces muscle weakness because of reduced motor neuron activity and muscle wasting (15), may cause atrophy of each fiber type, with type I fibers being affected the most, generates a decline in the activity of enzymes involved in oxidative energy conversion.

Nevertheless, disuse alone is not capable to generate all the skeletal muscle functional and structural abnormalities. As mentioned, the di-

aphragm does not experience a disuse phenomenon. Moreover a kind of endurance training effect may occur.

Malnutrition

Cachexia that accompanies chronic diseases such COPD and CHF markedly differs from reduced nutritional intake and starvation. Nutritional depletion in these diseases is characterized by increased muscle proteolysis, preferential loss of muscle over the body compartments, systemic inflammation and poor response to nutritional intervention, which have failed to produce any clinical meaningful improvement in muscle mass and strength (16).

Inflammation

The presence of systemic and/or local inflammation is a common characteristic in many chronic diseases, including COPD and CHF. Proinflammatory cytokines such as TNF-a, interleukin-8 (IL8), interleukin-6 (IL6) released by neutrophils and macrophages has been implicated in cachexia associated with the two diseases. They stimulate proteolysis by activating the ubiquitine-proteasome pathway which is responsible for muscle wasting in several human diseases. It has been demonstrated that the ubiquitine proteasome pathway is activated in the diaphragm of patients with mild-to-moderate COPD. The result is a loss of myosin and a subsequent loss of force generation capacity (17).

Medication

Among many various drugs used in the treatment of COPD and less frequently in CHF, only corticosteroids have been linked to skeletal muscle modifications, leading to the so called "steroid-induced myophaty".

A considerable reduction in strength and atrophy of both peripheral (limbs) and ventilatory muscles has been proven in COPD patients undergoing a long-term therapy with high doses of corticosteroids. A severe quadriceps muscle weakness has been also demonstrated in COPD patients after corticosteroids short burst therapy in acute exacerbations (18). The muscle fibers vulnerability to glucocorticoids depends on muscle fiber composition (mechanism unknown); the glycolitic fibers seem to be more susceptible to steroid-induced muscle wasting than the oxidative ones. The diaph-

ragm has lower type II fibers content, whose selective atrophy by corticosteroids further leads to a reduction in diaphragm strength. It is known that strength is the main limiting factor in diaphragm performance; therefore the diaphragm seems to be more affected to CS than limb muscles. Glucocorticoids diminish the protein synthesis and increase the rate of protein degradation. Nevertheless, it is difficult to distinguish between the muscle effects of corticosteroids on COPD patients from other unfavorable frequent situations, as systemic inflammation or inactivity.

Lower limbs versus upper limbs muscle dysfunction in COPD

Although both upper and lower limbs performance (strength and endurance) is lower in COPD and CHF than in healthy subjects, the degree of this impairment seems to differ between the two groups of muscles (upper limbs/ lower limbs). This fact can be explained by the "compartment theory" by which different muscle groups, individual muscles or muscle areas may react differently to a variety of pathogenic factors or stimuli. Lower extremities alterations (functional, structural and metabolic – as described above) are responsible for limiting activities such as ambulation (walking, stairs, etc.). It has been suggest that upper-limbs muscle structure and function are relatively preserved in COPD patients. On one hand this fact is due to the involvement of the upper limbs in many of the maintained activities of daily living (ADLs) and, on the other hand, because of the use of these muscles in the ventilatory effort. Based on this, the observation that COPD patients poorly tolerate this kind of tasks (mainly those activities involving unsupported upper limb) even they are minimal, appears to be at least surprising. Two mechanisms have been discussed to explain this fact: the neuromechanical dysfunction of respiratory muscles and changes in lung volume during such activities.

The first mechanism involved is related to changes in the breathing pattern during various activities with unsupported upper limbs, even if these activities are performed at low level, as well as to the simultaneity of afferent or efferent muscle stimuli (19).

The second mechanism refers to increased ventilation during upper limb exercises that leads to dynamic hyperinflation and decreased inspiratory capacity at different workloads (20).

Only few studies have investigate the morphologic and histochemical features of upper limbs or shoulders in COPD patients, showing a nonselective atrophy of type I and type II fibers, mainly in the more severe cases of weight loss and airflow obstruction; no modifications in the proportion of the two kinds of fibers have been found.

Studies analyzing the metabolic characteristics of upper limbs in COPD patients have shown that the oxidative capacity is preserved or even higher (severe disease) in deltoid muscles, contrary to those previously observed in lower limbs muscles (21).

In conclusion, upper limb exercises result in higher ventilatory and metabolic requirements, leading to a greater fatigue and a more intense dyspnea. The morphological and functional differences between upper and lower limb in COPD patients claim specific protocols for testing and training to be developed. ❑

WHY EXERCISE TRAINING IN COPD AND CHF?

Peripheral and respiratory muscles function (or dysfunction) not only influence the symptoms that limit exercise, but may contribute directly to poor exercise performance.

The muscles therefore represent a potential site to improve patients' functioning level and quality of life. Only one practical therapeutic intervention has been shown to reverse some of the above mentioned muscle alterations, namely **exercise training**. The benefits following exercise training in COPD and CHF are well documented. Changes of muscle pathophysiologic abnormalities induced by exercise training in these two diseases, potential responsible for clinical and functional improvements are summarized in Tabel 2.

Exercise training is now widely recommended in all national and international guidelines in COPD and CHF patients (31,32).

Training protocols vary in a number of variables: *setting* (hospital, center-and home-based), *control* (supervised/ non-supervised), *intensity* (aerobic, anaerobic), *method* (continous or intermittent/ interval), *method* (continous/ intermittent-), *application* (skeletal/ respiratory muscles) *and type* (endurance, resistance-strength).

While the **endurance training** of the skeletal muscle is considered a "traditional" type of muscular training in the rehabilitation of COPD patients, an additional **strength** (or resistance) **training** also appears to be worthwhile in COPD patients (31). The combination of both is considered the best strategy to improve muscle dysfunction in COPD (32). Although it has been demonstrated that **inspiratory muscle training** (IMT) produces positive modifications in inspiratory muscle fibers size and fiber-type proportion, no additional improvement in exercise capacity has been shown in meta-analyses compared with skeletal muscle training alone (33).

In CHF, studies about the role of exercise training appeared later than in COPD (1980s). Now, regular physical activity and structured exercise training are firmly recommended. It is based on the fact that exercise training improves exercise capacity and quality of life, does not affect left ventricular remodeling and may reduce mortality and hospitalization in patients with mild-to-moderate CHF (34,32).

As in COPD, three different training modalities are suggested for CHF patients. The best described type is the **endurance** aerobic **training** (continuous and interval) of skeletal muscles because his safety and efficacy have been firmly demonstrated.

There is still a controversy on the subject of **strength training** and its detrimental effect on left ventricular function and negative remodeling. Due to the superiority of endurance training in exercise capacity, a recommendation to implement resistance training in rehabilitation programme in CHF is not very clear. This training modality has to complement (not to substitute) the endurance training.

Up-to-date systematic reviews suggests that treatment with **inspiratory muscle training** significantly improves multiple features of CHF and its muscular systemic component: functional capacity, inspiratory and peripheral muscle strength and blood flow, peripheral muscle sympathetic nervous activity, oxygen uptake efficiency, recovery oxygen kinetics (35), but new RCTs are needed on this issue. ❑

CONCLUSION

This review tries to emphasize the contribution of the skeletal muscle dysfunction in the genesis of disability in two apparently very different diseases, as COPD and HF. Despite the large differences between their primary impairment, the two diseases share not only striking similarities between the functional, structural and metabolic skeletal muscle abnormalities, but also noticeable differences between the peripheral (limbs) muscles and the respiratory ones(diaphragm), which may impose different training modalities. Based upon the contribution of the muscle dysfunction in exercise intolerance in these patients, the exercise training has nowadays become the centerpiece of the whole rehabilitation program, which represents a standard of care for patients with COPD and HF. A better understanding of the underlying mechanisms of skeletal muscle dysfunction in COPD and CHF will help to find alternative therapeutic approaches. ❑

References

1. World Health Organisation: ICF: International Classification of Functioning. Disability and Heath, Geneva 2001
2. **Wagner PD** – Chronic Cardiopulmonary Disease and the Skeletal Muscle. *Respir Care* 2006:37-40
3. **Tateishi Y, Eguchi Y, Tohyama Y** – Impaired Muscle Oxygenation During Incremental Cycle Exercise in COPD Patients Compared with Age-Matched Healthy Subjects. *Open Rehabil J* 2011; 4:32-41
4. **Romer LM, Polkey MI** – Exercise-Induced Respiratory Muscle Fatigue: Implications for Performance. *J Appl Physiol* 2008; 104:879-888
5. **Berteanu M, Iliescu A, Dumitru L** – Chapter: "Chest Physiotherapy" in Tratat de Reabilitare Pulmonara sub redactia V.Tudorache, S.Lovin, M. Friesen. Edit Mirton, Timisoara 2009, ISBN 978-973-52-0574-4, 189-208
6. **Eliason G, Abdel-Halim M, Piehl-Aulin K** – Alterations in Muscle-To-Capillary Interface in Patients with Different Degrees of COPD. *Respiratory Research* 2010;11:97
7. **Kriatselis C, Nedios S, Kelle S** – Oxygen Kinetics and Heart Rate Response During Early Recovery from Exercise in Patients with Heart Failure. *Cardiol Res Pract* 2012;2012, article ID 512857, 7 pages. doi: 10:1155/2012/512857
8. **Layec G, Haseler L, Richardson RS** – The Effect of Higher ATP Cost of

Contraction on the Metabolic Response to Graded Exercise in Patients With COPD. *J Appl Physiol* 2012; 112:1041-1048

9. **Proud CG –** The multifaceted Role of mTOR in Cellular Stress Response. *DNA Repair* (Amst) 2004; 3:927-34

10. **Givertz M –** Role of oxidative stress in heart failure 2012.http://www.update.com/contents/role-of-oxidative-stress-in heart-failure

11. **Couillard A, Maltais F, Saey D –** Exercise-Induced Quadriceps Oxidative Stress and Peripheral Muscle Dysfunction in Patients With COPD. *Am J Crit Care Med* 2003; 167:1664-9

12. **Smith DR, Stone D, Darley-Usmar VM –** Stimulation of Mitocondrial Oxygen Consumption in Isolated Cardiomyocites after Hypoxia Reoxygenation. *Free Radic Res* 1996; 24:159-66

13. **Badea R, Dumitru L, Iliescu I, et al. –** IS-ACTIVE Project in Lab Trial Phase. *Ro J Phys Rehab Med.* 2011; 21:64-65

14. **Degens H, Sanchez Horneras JM, Heijdra YF, et al. –** Skeletal Muscle Contractility is Preserved in Copd Patients with Normal Fat-Free Mass. *Acta Physiol Scand* 2005; 184:235-42

15. **Giger JM, Bodel PW, Zeng M –** Rapid Muscle Atrophy Response to Unloading: Pretranslational Processes Involving MHC and Actin. *J Appl Physiol* 2009; 107:1204-12

16. **Maltais, Debigare, Saey, et al. –** Chapter: "Integrating Non-conventional Approaches in Cardiopulmonary Rehabilitation" from Advancing Frontiers of Cardiopulmonary rehabilitation 2002, Human Kinetics USA, 180-195, ISBN 0736042164

17. **Ottenheijin CA, Heunks LM, Li YP –** Activation of Ubiquitine-Proteasome Pathway in the Diaphragm in COPD. *Am J Respir Crit Care Med* 2006; 174:997-1002

18. **Yamaguchy M, Niimi A, Minakuchi M –** Corticosteroids-Induced Myopathy Mimicking Theraphy-Resistant Asthma. *Ann Allergy Asthma Immunol* 2007; 99:371-4

19. **Foschini Miranda E, Malaguti C, Dal Corso S –** Peripheral Muscle Dysfunction in COPD: Lower Limb versus Upper Limbs. *J Bras Pneumol* 2011; 37:380-388

20. **Colucci M, Cortopassi F, Porto E, et al. –** Upper Limb Exercise using Varied Workloads and Their Association with Dynamic Hyperinflation in Patients with COPD. *Chest* 2010; 138:39-46

21. **Gea JG, Pasto M, Carmona MA, et al. –** Metabolic Characteristics of the Deltoid Muscle in Patients with COPD. *Eur Respir J* 2001; 17:939-45

22. **Bernard S, Whittom F, Le Blanc P –** Aerobic and Strength Training in Patients with Chronic Obstructive Pulmonary Disease. *Am J Crit Care Med* 1999; 159:896-901

23. **Senden PJ, Sabelis LW, Zonderland M –** The Effect of Physical Training on Workload, Upper Leg Muscle Function and Muscle Area in Patient with Chronic Heart Failure. *Int J Cardiol* 2005; 100:293-300

24. **Meredith CN, Frontera WR, O'Reilly KP –** Body Composition in Elderly Man; Effect on Dietary Modification During Strength Training Jam Geriatr Soc 1992;155-162

25. **Whittom F, Jobin J, Simard PM –** Histochemical and Morphological Characteristics of the Vastus Lateralis Muscle in Patients with COPD. *Med SCi Sport Exerc* 1998; 30:1467-1474

26. **Maurer Mm, Schulze C –** Exercise Intolerance in Heart Failure with Preserved Ejection Fraction. Shifting Focus from the Heart to Peripheral Skeletal Muscle. *J Am Coll Cardiol* 2012; 60:129-131

27. **Williams A, Carey M, Selig S –** Circuit Resistance Training in Chronic Heart Failure Improves Skeletal Muscle Mitochondrial ATP Production Rate – a Randomised Controlled Trial. *J Card Fail* 2007; 13:79-85

28. **Maltais F, Le Blanc P, Simard C –** Skeletal Muscle Adaptations to Exercise Training in Patients with COPD. *Am J Crit Care Med* 1996; 154:442-447

29. **Casaburi R, Patessio A, Joli F –** Reduction in Exercise Lactic Acidosis and Ventilation as a Result of Exercise Training in Patients with Obstructive Lung Disease. *Am Rev Respir Dis* 1991; 143:9-18

30. **Larsen A, Aarsland T, Kristansen M –** Assessing the Effects of Exercise Training in Men with Heart Failure. *Eur Heart J* 2001; 22:684-692

31. **Piepoli M, Conraads V, Corra U –** Exercise Training in Heart Failure: From Theory to Practice. A Consensus Document of the Heart Failure Association and the European Association for Cardiovascular Prevention and Rehabilitation. *Eur J Heart Fail* 2011; 13:347-357

32. **Ries A, Gerene SB, Carlin B –** Pulmonary Rehabilitation: Joint ACCP/AACVPR Evidence-Based Clinical Practice Guidelines. *Chest* 2007; 131:4-42

33. **Lotters F, Van Toll B, Kwakkel G –** Effects of Controlled Inspiratory Muscle Training in Patients with COPD: a Meta-analysis. *Eur Respir J* 2002; 20:570-576

34. **Keteyian SJ, Pina IL, Hibner BA –** Clinical Role of Exercise Training in the Management of Patients with Chronic Heart Failure. *J Cardiopulm Rehabil Prev* 2010; 30:67-76

35. **Plentz RDM, Sbruzzi G, Ribeiro RD –** Inspiratory Muscle Training in Patients with Heart Failure: Meta-analysis of Randomized Trials. *Arq Bras Cardiol* 2012; 99:762-771.