

Mechanisms of Functional Loss in Patients With Chronic Lung Disease

Neil R MacIntyre MD FAARC

Introduction
Assessing Function
Ventilatory Factors
Gas-Exchange Limitations
Cardiovascular Factors
Skeletal Muscle Factors
Other Factors
Summary

Functional loss (often quantified as exercise limitation) is common in patients with chronic lung disease. The factors involved are multiple and many may be present together in a given patient. Ventilatory factors involve an imbalance in load/capacity relationships. Specifically, breathing loads from abnormal respiratory-system mechanics and/or excessive ventilatory demand cannot be handled by respiratory muscles that are dysfunctional or malpositioned. Gas-exchange factors involve impaired ventilation-perfusion relationships that lead to hypoxemia, impaired oxygen delivery, and pulmonary hypertension. Cardiovascular factors involve coexisting intrinsic heart disease, right-ventricular overload from pulmonary vascular abnormalities, and simple deconditioning. Skeletal muscle (both respiratory and limb) factors involve direct inflammatory mediator effects on muscle function, malnutrition, blood-gas abnormalities, compromised oxygen delivery from right-heart dysfunction, electrolyte imbalances, drugs, and comorbid states. Other less well understood factors include excessive dyspnea, impaired motivation, orthopedic issues, and psychiatric issues. Key words: functional loss, exercise limitation, chronic lung disease, ventilation, respiratory mechanics, ventilation-perfusion, hypoxemia, pulmonary hypertension, oxygenation. [Respir Care 2008;53(9):1177–1184. © 2008 Daedalus Enterprises]

Introduction

Patients with chronic lung disease often complain of exercise intolerance. Up until the late 20th century, ven-

Neil R MacIntyre MD FAARC is affiliated with Respiratory Care Services, Duke University Medical Center, Durham, North Carolina.

The author reports no conflicts of interest related to the content of this paper.

Dr MacIntyre presented a version of this paper at the 23rd Annual New Horizons Symposium at the 53rd International Respiratory Congress of the American Association for Respiratory Care, held December 1-4, 2007, in Orlando, Florida.

tilatory impairment was thought to be the major limiter of exercise capacity in these patients because exercise impairment usually correlated with the loss of ventilatory capacity (ie, the forced expiratory volume in the first second [FEV₁] and the maximum voluntary ventilation). Over the last 2 decades, however, it has become increasingly apparent that exercise intolerance in patients with chronic lung disease is often multifactorial and can involve various combinations of ventilatory impairment, gas-exchange ab-

Correspondence: Neil R MacIntyre MD FAARC, Respiratory Care Services, PO Box 3911, Duke University Medical Center, Durham NC 27710. E-mail: neil.macintyre@duke.edu.

Table 1. Factors That Impair Function in Patients With Chronic Lung Disease

Ventilatory factors (load/capacity imbalance)
High work load
High airway resistance
Wasted ventilation
Increased minute-ventilation demand
Impaired respiratory-muscle capabilities
High-pressure/low-volume work pattern
Hyperinflation
Respiratory-muscle dysfunction
Gas-exchange limitations
Cardiovascular factors
Right-heart overload
Hypoxic pulmonary vasoconstriction
Pulmonary vascular injury
Coexisting left-ventricular abnormalities
Deconditioning
Skeletal-muscle factors
Systemic inflammatory response
Malnutrition
Muscle hypoxemia/acidemia
Corticosteroid therapy effects
Deconditioning
Miscellaneous factors
Exaggerated dyspnea sensation
Orthopedic issues
Motivation/psychiatric issues

normalities, cardiovascular issues (eg, right- and/or left-ventricular dysfunction, dysrhythmia, and even deconditioning), skeletal muscle dysfunction, and psychological factors (Table 1).¹ This paper will address these factors in some detail.

Assessing Function

Functional impairment can be assessed in a number of ways. For example, questionnaires can elicit what patients perceive they can do. Similarly, careful patient histories can elicit the patient's ability to perform activities of daily living and other tasks. However, formal assessment of exercise or work capability is generally considered a more objective way to quantitate functional status.²

Formal assessments of exercise or work capabilities can take many forms.^{2,3} Perhaps the easiest are tests such as a simple stair-climb or the 6-min-walk test, in which patients walk as far as they can in 6 min without regard to walking pace or rest requirements. Although heart rate, pulse oximetry, subjective dyspnea, et cetera, can be measured during a 6-min-walk test, the primary measurement is the distance walked.

At the other extreme is a detailed, symptom-limited maximal exercise test,^{2,3} in which the patient is pushed to

maximal exertion, using graded exercise loads on a treadmill or a bicycle. Measurements of ventilation, oxygen consumption, carbon-dioxide production, dead-space behavior, gas exchange (P_{aO_2} and P_{aCO_2}), and cardiac function (heart rate, electrocardiogram) can be used to determine what factor(s) are important in limiting exercise performance. These can be used in conjunction with other assessments to characterize the mechanism(s) of impairment, to better guide treatment. The major factors involved in exercise limitation during such tests in patients with chronic lung disease are reviewed below:

Ventilatory Factors

Ventilatory factors involve the "bellows" or "pumping" capabilities of the respiratory system. Under normal conditions, healthy individuals can increase their breathing frequency and their tidal volume (V_T) to provide up to a 20-fold increase in minute ventilation to meet the increased oxygen demand and clear the carbon dioxide production associated with exercise. Importantly, under normal circumstances, ventilatory function is not the limiting factor for exercise: the cardiovascular system is.^{2,3} Thus, at maximal exercise, ventilation should be well below the maximal breathing capacity, as reflected in the maximum voluntary ventilation.

The main drives for ventilation during exercise are CO_2 production and pH changes. The respiratory-drive center attempts to keep pH near normal during exercise. At a low level of exercise, pH is determined primarily by CO_2 production and P_{CO_2} . However, as cardiac output becomes limited at a high level of exercise, muscle lactate production becomes another important determinant of pH and a further stimulus to ventilation. Thus P_{CO_2} remains relatively unchanged at a low exercise level but then decreases at a higher level, which produces the classic 2-phase response of ventilation to increasing exercise.

Hypoxemia also contributes to the ventilatory drive. As described below, hypoxemia does not develop under normal exercise conditions, but if it does develop with lung disease, it is a potent ventilatory stimulus. Interestingly, even modest a level of hypoxemia (ie, not enough to severely impact oxygen delivery) can increase carotid-body output and thus stimulate ventilation.^{4,5} A corollary to this is that under these circumstances, supplemental O_2 can blunt this component of ventilatory drive and thus allow a patient to tolerate a slightly lower pH and higher P_{CO_2} , which may extend the ventilatory limit and allow more exercise.^{4,5}

On a maximal exercise test, ventilatory limitation is defined as the inability to clear enough CO_2 to maintain an appropriate pH at maximal exercise. Clinically this is defined by one of 2 criteria:

1. Because under normal circumstances ventilation at maximal exercise is well below the measured maximum voluntary ventilation (ie, ventilation is never exercise-limiting under normal circumstances), an exercise ventilation that approaches or exceeds the maximum voluntary ventilation means that a ventilatory limit has been reached.

2. Because P_{CO_2} should fall to maintain pH with increasing exercise, a rising P_{CO_2} or excessively falling pH indicates the ventilatory limit has been reached.

In a study of patients with COPD, 28% had predominantly ventilatory limiting factors.⁶

There are multiple reasons why patients with chronic lung disease develop ventilatory limitations: chief among these is the development of a “load/capacity imbalance” (ie, the mechanical load to breathe exceeds the muscle strength and endurance capacity). In patients with chronic lung disease the high inspiratory (and expiratory) airway resistance and/or reduced compliance can dramatically increase the pressure requirement for air flow and thus dramatically increase the work to breathe.^{7,8} To put numbers on this, consider that the normal work to breathe at rest is roughly 5 J/min and the respiratory muscles require roughly 5 mL/min of oxygen delivery to do this. In COPD, however, these loads and energy requirements can be increased 5–10 fold.⁸

Compounding the effects of excessive loading is the fact that the ventilatory work pattern is of an inefficient type, in that high pressure is required for a given movement or displacement of the sarcomeres.⁸ This “isometric” type work is far less oxygen-efficient than the low-pressure work pattern of normal breathing, and it predisposes to muscle dysfunction. Finally, exercise-induced wasted ventilation and early lactic acidosis in these patients (see below) further increases the exercise ventilation requirement and thus further worsens the load/capability relationship in the respiratory muscles.⁹

The increased ventilatory loading of chronic lung disease is often accompanied by respiratory muscle dysfunction. As described in more detail below in the broader discussion on skeletal muscles, a chronic inflammatory state in the lungs can reduce respiratory muscle strength and endurance through systemic inflammatory mediators, reduced oxygen delivery, chronic respiratory acidosis, malnutrition, corticosteroid use, and the effects of various comorbidities. In the patient with COPD, respiratory muscles are also compromised by hyperinflation produced by airway collapse and low elastic recoil.^{10,11} As the hyperinflation increases, the diaphragm is pushed downward and flattened, so the resting length of the diaphragm becomes shorter, which creates substantial mechanical disadvantage and loss of tension-generation capability. Importantly, the increased minute ventilation with exercise can increase the hyperinflation during the exercise, which further impairs muscle function (Fig. 1).

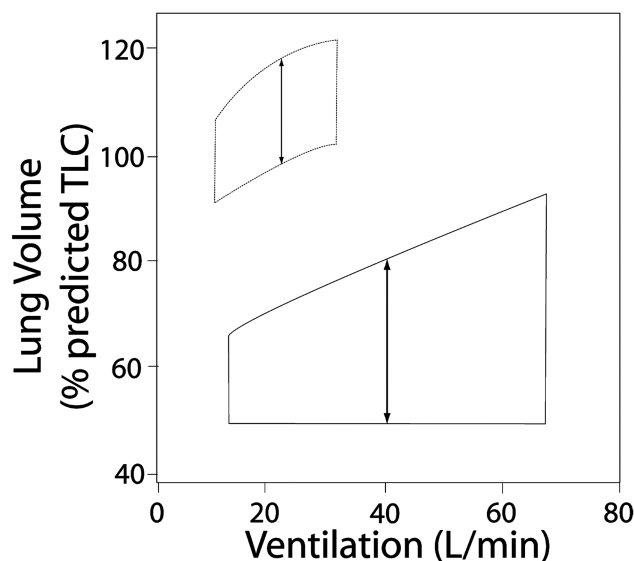


Fig. 1. Lung volume versus ventilation in a normal lung (bottom) and a lung of patient with chronic obstructive pulmonary disease (COPD) (top). As ventilation increases with exercise in the normal lung, the tidal volume (lung-volume change) increases but the end-expiratory volume remains unchanged. In contrast, the COPD lung has an elevated end-expiratory lung volume even at rest, and it increases further with increasing ventilation. An increase in tidal volume is thus made more difficult and the ventilatory impairment worsens with exercise. TLC = total lung capacity; arrows = tidal volume. (Adapted from Reference 11.)

It is important to note that respiratory muscles have adaptive capabilities to deal with the chronically elevated work load and distorted diaphragm geometry.^{12,13} In the hyperinflated patient with COPD, diaphragmatic sarcomeres become shorter in order to adapt to the new shorter resting length. This returns some of the efficiency lost in the earlier phases of COPD. More oxidative or type-I sarcomeres also develop and increase endurance. Capillary density also increases, which leads to a respiratory muscle blood flow “steal” syndrome.^{14–16} However, along with this is a small decrease in type-II fibers, which can decrease the diaphragm-force-generation capability.¹⁵ Also observed in diaphragm biopsies of hyperinflated patients with COPD are structural changes in large-muscle proteins that serve to stabilize the actin and myosin contractile proteins.¹⁷

An important question is whether respiratory muscles do in fact fatigue. Fatigue, by definition, is the loss of muscle contractile capabilities induced by heavy loading and recoverable by rest.¹⁸ Fatigue must be distinguished from either reduced muscle capability or from a muscle injury that reduces function.¹⁹ Fatigue is of 2 types: peripheral (direct muscle failure) and central (either reduced neural stimulation or increased inhibitor neuron activity). Central fatigue is sometimes thought of as a “protective” mechanism to prevent muscles from injury under overload

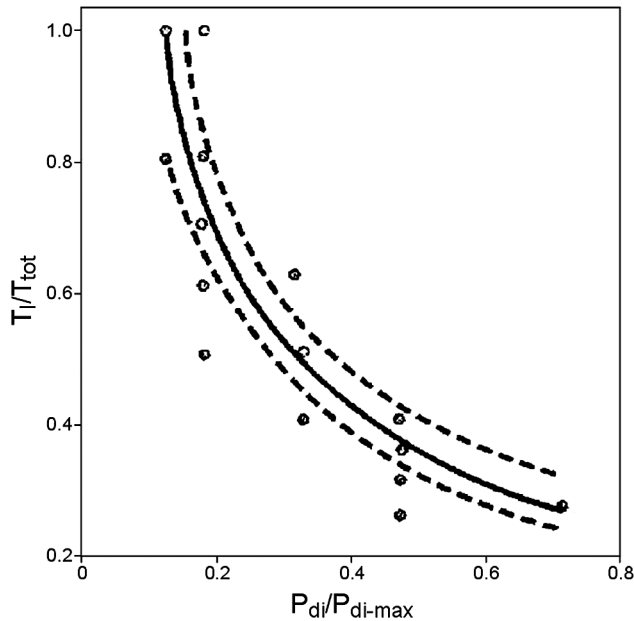


Fig. 2. Relationship between duty cycle (ratio of inspiratory time T_I to total respiratory-cycle time T_{tot}) and critical transdiaphragmatic pressure (ratio of transdiaphragmatic pressure P_{di} to maximum P_{di} [P_{di-max}]) for development of respiratory muscle fatigue. The dashed lines indicate the 95% critical P_{di}/P_{di-max} confidence interval. Fatigue develops with breathing patterns that fall to the right of the curve but not for those to the left. This relationship can be mathematically represented by the product of the T_I/T_{tot} and the critical P_{di}/P_{di-max} , which is termed the pressure/time index. Pressure/time index values ≥ 0.15 fall to the right of the curve and predict fatigue. (Adapted from Reference 22, with permission.)

conditions.²⁰ Interestingly, endorphins may play an important role in creating a reduction in neural stimulation of the muscles.

Under normal conditions, respiratory muscles appear capable of maintaining approximately 40% of their maximum pressure-generation capability on a repetitive basis almost indefinitely.²¹ But when the pressure requirement to breathe is high, especially if the inspiratory time required to deliver an adequate tidal breath becomes sufficiently long, it does appear that respiratory muscle can fatigue. This is most easily represented by the pressure/inspiratory-time relationship or pressure/time index, which is:

$$\text{Pressure/time index} = P_{di}/P_{di-max} \times T_I/T_{tot}$$

in which P_{di} is the transdiaphragmatic pressure, P_{di-max} is the maximal P_{di} , T_I is the inspiratory time, and T_{tot} is the total breathing-cycle time.²² When the pressure/time index of the respiratory muscles is ≥ 0.15 , fatigue will occur (Fig. 2).

Gas-Exchange Limitations

Under normal circumstances, regional ventilation and regional perfusion remain well matched with increasing exercise.^{2,3,11,23} Thus, the ventilation-perfusion (\dot{V}/\dot{Q}) relationship in the alveolar regions remains near unity, as both ventilation and perfusion increase several-fold with exercise. Moreover, alveolar-capillary diffusion also remains intact, except with the most extreme exercise, when the transit time of blood through alveolar capillaries is very short.²⁴ As a consequence P_{aO_2} remains normal, even at a high exercise level, under most circumstances.^{2,3,11}

Chronic lung diseases can involve the airways, the pulmonary vasculature, and the alveolar-capillary interface to varying degrees and produce varying degrees of abnormal \dot{V}/\dot{Q} relationship and diffusion impairment, resulting in resting hypoxemia. Although in some chronic lung diseases (eg, primary airway disease such as chronic bronchitis) increasing ventilation may transiently improve \dot{V}/\dot{Q} and thus improve P_{aO_2} with exercise, more commonly, impaired regional ventilation and perfusion regulation worsen \dot{V}/\dot{Q} and thus worsen hypoxemia with exercise. Impaired diffusion can make this worse.²⁴

To be considered exercise-limiting the P_{O_2} should fall below 55 mm Hg (arterial oxygen saturation $< 85\%$), because that level corresponds to impaired oxygen delivery and to the development of pulmonary vasoconstriction and resulting right-ventricular overload.¹ Severe hypoxemia can also stimulate the ventilatory response and further tax ventilatory muscles. This response was seen in 18% of patients with COPD.⁶

In normal subjects, exercise-induced V_T increase occurs in the setting of relatively fixed anatomic dead space (V_D), so the V_D/V_T ratio decreases such that effective alveolar ventilation increases as a proportion of the increased minute ventilation. In chronic lung diseases that affect the pulmonary vasculature, however, increasing V_D can develop, which increases (rather than decreases) V_D/V_T , which increases ventilatory load to provide adequate CO_2 clearance.

Cardiovascular Factors

The cardiac output in normal subjects can increase several-fold in response to exercise.^{2,3,11} This is accomplished by both an increase in stroke volume and an increase in heart rate. Indeed, in normal subjects cardiac output is the “rate-limiting step” to exercise, and normal maximal exercise is usually accompanied by a maximal heart rate $(220 - \text{age})$.² Importantly, even at maximal cardiac output, exercise can continue to increase, because muscle cells can switch to anaerobic metabolism. This switch (often referred to as the “anaerobic threshold”) is accompanied by

rising lactate and thus an increased ventilatory demand to clear the acidosis,^{2,3,11} as noted above.

Impaired cardiac output capability usually results in reaching the maximum heart rate at a low level of exercise. This is often reflected in a low “oxygen pulse” (the oxygen consumption with each heart beat). In normal subjects this should rise several-fold as maximal heart rate is approached.

Cardiovascular factors fall into several discrete categories and are seen in 34% of patients with COPD.⁶

First, coexisting right- or left-ventricular dysfunction can impair exercise function simply because of poor cardiac-output capability,^{2,3,11} which leads to impaired oxygen delivery and early development of lactic acidosis. Similarly, functionally important dysrhythmias can also impair cardiac output. Importantly, the systemic effects of chronic lung disease on skeletal muscle, described below, may also impact cardiac muscle function.

Second, in chronic lung disease, especially in the presence of pulmonary vascular abnormalities, pulmonary hypertension and right-ventricular dysfunction may develop.²⁵ The impaired right ventricle thus contributes to a reduced cardiac output. These phenomena may worsen in the presence of hypoxemia, as noted above.

Finally, deconditioning of both cardiac and skeletal muscle contributes to functional loss in patients with chronic lung disease. This is often represented as a downward spiral initiated by dyspnea and depression, which leads to inactivity, which leads to deconditioning, further dyspnea/depression, and further loss of function. On a simple exercise test that measures only heart rate and cardiac rhythm, deconditioning will be manifest as a low oxygen pulse at maximal heart rate, and thus may be difficult to distinguish from other cardiovascular factors. Ruling out cardiac disease, therefore, requires more focused cardiac assessments (eg, echocardiography, multi-lead electrocardiogram, or invasive procedures). Interestingly, deconditioning appears to be an important phenomena in patients with chronic lung disease, and the improved exercise tolerance following an exercise training program in patients with chronic lung disease is often due to reconditioning of heart and skeletal muscle.²⁶

Skeletal Muscle Factors

Chronic inflammatory states can profoundly affect skeletal muscle function.²⁷⁻³⁰ These are related not only to systemic inflammatory mediators that are persistently elevated in these chronic disease states, but also to various other physiologic and comorbid effects, discussed below.

Systemic inflammatory mediators accelerate muscle protein turnover through ubiquitins.³¹⁻³⁷ This leads to loss of muscle mass and the clinical appearance of “muscle wasting.”^{27-30,38,39} Chronic inflammation also increases muscle oxidative stress and increases reactive oxygen species,

which directly damage muscle proteins and impair their function.⁴⁰⁻⁴² Additionally, during muscle fatigue recovery, an ischemia reperfusion injury mediated through additional reactive oxygen species may also develop in the muscles that further impairs muscle function.⁴⁰⁻⁴²

Patients with chronic lung disease are often malnourished, and weight loss occurs in approximately 30% of out-patients with COPD,⁴³⁻⁴⁸ because of decreased calorie intake and the effects of chronic inflammation on energy metabolism in general. Reduced protein intake leads to muscle breakdown as muscle proteins and amino acids are utilized for fuel (catabolism). This is particularly true of the sarcomeric structures in type-II muscle fibers. Malnutrition also contributes to reduced muscle enzyme capacity and reduced availability of energy substrates such as adenosine triphosphate, magnesium, and potassium.⁴⁹⁻⁵³

In chronic lung disease, hypoxia is common. Hypoxia not only leads to lower oxygen content in the blood but can elevate pulmonary vascular resistance and create pulmonary arterial hypertension and consequent right-heart failure.^{25,54-57} The resulting reduced cardiac output, coupled with the low oxygen content, reduces oxygen delivery to all organs of the body, including skeletal muscle. Interestingly, because the work of breathing (load) on the diaphragm is often substantially increased in chronic lung disease, there is also a respiratory muscles “steal” of blood away from skeletal muscles, which further compromises systemic muscle function.^{14,58}

Systemic inflammation may also impair the oxygen transport through the cytoplasm and into the mitochondria, as well as impair mitochondrial oxygen utilization directly.^{25,54-56,59-61} These produce muscle-cell hypoxia and thus a conversion to anaerobic metabolism at a low level of exercise. This leads to lactate accumulation and earlier muscle fatigability.^{9,49,62-64}

Hypercarbia is also a common occurrence in chronic lung disease, as the central respiratory controllers in the brainstem reduce ventilation to “protect” overloaded ventilatory muscles.⁶⁵ An acute severe respiratory acidosis, as might occur during an exacerbation, can impair muscle enzyme activity and function.⁶⁶⁻⁶⁸

Patients with chronic lung disease often use corticosteroids. As much as 10% of patients with COPD may be on long-term oral steroids, and the majority of patients with moderately severe COPD take inhaled corticosteroids.⁶⁹ Patients with chronic lung disease also take corticosteroids during exacerbations. Corticosteroids can profoundly affect skeletal muscle. Specifically, corticosteroids reduce contractile proteins, increase protein breakdown and turnover, down-regulate growth factors, reduce glycolytic activity, and lead to sarcomere and type-II cell atrophy.⁷⁰⁻⁷²

Finally, chronic lung disease often coexists with other chronic diseases that can in themselves affect skeletal muscle. Congestive heart failure and reduced cardiac output

can impair oxygen delivery, as described above. Electrolyte and metabolic disturbances from chronic renal or liver disease may also impair muscle function. Diabetes and altered glucose metabolism may also contribute to muscle dysfunction. The aging process also impacts muscle function, as there is a normal age-related decline in muscle mass.^{73,74}

In limb muscles, especially lower-extremity limb muscles, muscle weakness and respiratory insufficiency lead to inactivity and chronic under-loading of the muscles, which leads to less muscle mass, especially type-I fibers.⁷⁵⁻⁸⁰ This reduces the oxidative capacity of the muscles and makes them more prone to fatigue. There is also less capillary density with under-loading, which reduces regional blood flow delivery, nutrient delivery, and waste removal. Unloading also leads to less glutathione and other defenses against oxidative stress.

In the limb muscles the structural and metabolic abnormalities noted above lead to early lactic acidosis and task-failure with exercise.⁷⁵⁻⁷⁹

Other Factors

In up to 20% of patients with COPD undergoing maximal exercise testing, ventilatory, gas-exchange, and cardiovascular limitations are not reached.⁶ Thus, other factors must come into play. The skeletal-muscle issues described above could explain exercise limitations in some of these patients. However, factors such as profound subjective dyspnea, reduced motivation, orthopedic issues, and even psychiatric issues may all play roles.¹ Sorting out these factors can be challenging, but it is important to explore them in order to manage the functional limitations of chronic lung disease.

Summary

Functional loss (often quantified as exercise limitation) is common in patients with chronic lung disease. The factors involved are multiple and many may be present together in a given patient. A careful exercise assessment can help delineate which mechanisms are most important and help to focus therapy. Importantly, exercise therapy in addition to maximizing cardiorespiratory function in patients with chronic lung disease can improve functional performance.

REFERENCES

- Gallagher CG. Exercise limitation and clinical exercise testing in chronic obstructive pulmonary disease. *Clin Chest Med* 1994;15(2):305-326.
- Wasserman K, Hansen JE, Sue DY, Stringer WW, Whipp BJ. Principles of exercise testing and interpretation. Baltimore: Lippincott, Williams & Wilkins; 1999.
- American Thoracic Society; American College of Chest Physicians. Statement on cardiopulmonary exercise testing. *Am J Respir Crit Care Med* 2003;167(2):211-277. Erratum in: *Am J Respir Crit Care Med* 2003;May 15:1451-1452.
- Emtner M, Pórszász J, Burns M, Somfay A, Casaburi R. Benefits of supplemental oxygen in exercise training in non hypoxemic COPD patients. *Am J Respir Crit Care Med* 2003;168(9):1034-1042.
- Somfay A, Pórszász J, Lee SM, Casaburi R. Effect of hyperoxia on gas exchange and lactate kinetics following exercise onset in non hypoxemic COPD patients. *Chest* 2002;121(2):393-400.
- Plankeel JF, McMullen B, MacIntyre NR. Exercise outcomes after pulmonary rehabilitation depend on the initial mechanism of exercise limitation among non-oxygen-dependent COPD patients. *Chest* 2005;127(1):110-116.
- Levison H, Cherniack RM. Ventilatory cost of exercise in chronic obstructive pulmonary disease. *J Appl Physiol* 1968;25:21-27.
- MacIntyre NR, Leatherman NE. Mechanical loads on the ventilatory muscles: a theoretical analysis. *Am Rev Res Dis* 1989;139(4):968-973.
- Casaburi R, Patessio A, Ioli F, Zanaboni S, Donner CF, Wasserman K. Reductions in exercise lactic acidosis and ventilation as a result of exercise training in patients with obstructive lung disease. *Am Rev Respir Dis* 1991;143(1):9-18.
- Similowski T, Yan S, Gauthier AP, Macklem PT, Bellemare F. Contractile properties of the human diaphragm during chronic hyperinflation. *N Engl J Med* 1991;325(13):917-923.
- O'Donnell DE. Exercise limitation and clinical exercise testing in chronic obstructive pulmonary disease. In: Weisman IM, Zeballos RJ, editors. *Progress in respiratory research, volume 32: clinical exercise testing*. Basel: Karger; 2002:138-158.
- Levine S, Gregory C, Nguyen T, Shrager J, Kaiser L, Rubinstein N, Dudley G. Bioenergetic adaptation of individual human diaphragmatic myofibers to severe COPD. *J Appl Physiol* 2002;92(3):1205-1213.
- Levine S, Kaiser L, Leferovich J, Tikunov B. Cellular adaptations in the diaphragm in chronic obstructive pulmonary disease. *N Engl J Med* 1997;337(25):1799-1806.
- Dempsey JA, Harms CA, Ainsworth DM. Respiratory muscle perfusion and energetics during exercise. *Med Sci Sports Exerc* 1996;28(9):1123-1128.
- Levine S, Nguyen T, Kaiser LR, et al. Human diaphragm remodeling associated with chronic obstructive pulmonary disease: clinical implications. *Am J Respir Crit Care Med* 2003;168(6):706-713.
- Sheel AW, Derchak PA, Pegelow DF, Dempsey JA. Threshold effects of respiratory muscle work on limb vascular resistance. *Am J Physiol Heart Circ Physiol*. 2002;282(5):H1732-H1738.
- Ottenheim CA, Heunks LM, Hafmans T, van der Ven PF, Benoist C, Zhou H, et al. Titin and diaphragm dysfunction in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2006;173(5):527-534.
- Vøllestad NK. Measurement of human muscle fatigue. *J Neurosci Methods* 1997;74(2):219-227.
- Merton PA. Voluntary strength and fatigue. *J Physiol* 1954;123(3):553-564.
- Gandevia SC, Allen GM, McKenzie DK. Central fatigue: critical issues, quantification, and practical applications. *Adv Exp Med Biol* 1996;384:281-294.
- Roussos C, Macklem PT. Diaphragmatic fatigue in man. *J Appl Physiol* 1977;43(2):189-197.
- Bellemare F, Grassino A. Evaluation of human diaphragm fatigue. *J Appl Physiol* 1982;53(5):1196-1206.
- West JB. State of the art. Ventilation perfusion relationships. *Am Rev Respir Dis* 1977;116(5):919-943.

24. Rice AJ, Thornton AT, Gore CJ, Scroop GC, Greville HW, Wagner H, et al. Pulmonary gas exchange during exercise in highly trained cyclists with arterial hypoxemia. *J Appl Physiol* 1999;87(5):1802-1812.
25. Naeije R. Pulmonary hypertension and right heart failure in chronic obstructive pulmonary disease. *Proc Am Thorac Soc* 2005;2(1):20-22.
26. Lacasse Y, Wong E, Guyatt GH, King D, Cook DJ, Goldstein RS. Meta-analysis of respiratory rehabilitation in chronic obstructive pulmonary disease. *Lancet* 1996;348:1115-9.
27. Begin P, Grassino A. Inspiratory muscle dysfunction and chronic hypercapnia in chronic obstructive pulmonary disease. *Am Rev Respir Dis* 1991;143(9035):905-912.
28. Ottenheijm CA, Heunks LM, Sieck GC, Zhan WZ, Jansen SM, Degens H, et al. Diaphragm dysfunction in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2005;172(2):200-205.
29. DeTroyer A, Pride NB. The chest wall and respiratory muscles in chronic obstructive pulmonary disease. In: Ch Roussos, editor. *The Thorax, Part C: disease*, 2nd ed. New York: Marcel Dekker; 1995: 1975-2006.
30. Skeletal muscle dysfunction in chronic obstructive pulmonary disease. A statement of the American Thoracic Society and European Respiratory Society. *Am J Respir Crit Care Med* 1999;159(4 Pt 2):S1-S40.
31. Tiao G, Fagan JM, Samuels N, James JH, Hudson K, Lieberman M, et al. Sepsis stimulates nonlysosomal, energy-dependent proteolysis and increases ubiquitin mRNA levels in rat skeletal muscle. *J Clin Invest* 1994;94(6):2255-2264.
32. Llovera M, García-Martínez C, Agell N, López-Soriano FJ, Argilés JM. TNF can directly induce the expression of ubiquitin-dependent proteolytic system in rat soleus muscles. *Biochem Biophys Res Commun* 1997;230(2):238-241.
33. Biolo G, Toigo G, Ciochi B, Situlin R, Iscra F, Gullo A, Guarnieri G. Metabolic response to injury and sepsis: changes in protein metabolism. *Nutrition* 1997;13(9 Suppl):52S-57S.
34. Di Francia M, Barbier D, Mege JL, Orehek J. Tumor necrosis factor- α levels and weight loss in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 1994;150(5 Pt 1):1453-1455.
35. de Godoy I, Donahoe M, Calhoun WJ, Mancino J, Rogers RM. Elevated TNF- α production by peripheral blood monocytes of weight-losing COPD patients. *Am J Respir Crit Care Med* 1996;153(2):633-637.
36. Schols AM, Buurman WA, Staal-van den Brekel AJ, Dentener MA, Wouters EF. Evidence for a relation between metabolic derangements and increased levels of inflammatory mediators in a subgroup of patients with chronic obstructive pulmonary disease. *Thorax* 1996;51(8):819-824.
37. Mitch WE, Goldberg AL. Mechanisms of muscle wasting. The role of the ubiquitin-proteasome pathway. *N Engl J Med* 1996;335(25):1897-1905.
38. Gosker HR, Kubat B, Schaart G, van der Vusse GJ, Wouters EF, Schols AM. Myopathological features in skeletal muscle of patients with chronic obstructive pulmonary disease. *Eur Respir J* 2003;22(2):280-285.
39. Agustí AG, Sauleda J, Miralles C, Gomez C, Togores B, Sala E, et al. Skeletal muscle apoptosis and weight loss in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2002;166(4):485-489.
40. Jackson MJ, O'Farrel S. Free radicals and muscle damage. *Br Med Bull* 1993;49(3):630-641.
41. Buck M, Chojkier M. Muscle wasting and dedifferentiation induced by oxidative stress in a murine model of cachexia is prevented by inhibitors of nitric oxide synthesis and antioxidants. *EMBO J* 1996;15(8):1753-1765.
42. Llesuy S, Evelson P, González-Flech B, Peralta J, Carreras MC, Poderoso JJ, Boveris A. Oxidative stress in muscle and liver of rats with septic syndrome. *Free Radic Biol Med* 1994;16(4):445-451.
43. Engelen MP, Schols AM, Baken WC, Wesseling GJ, Wouters EF. Nutritional depletion in relation to respiratory and peripheral skeletal muscle function in an outpatient population with chronic obstructive pulmonary disease. *Eur Respir J* 1994;7(10):1793-1797.
44. Schols AM, Soeters PB, Dingemans AM, Mostert R, Rantzen PJ, Wouters EF. Prevalence and characteristics of nutritional depletion in patients with stable COPD eligible for pulmonary rehabilitation. *Am Rev Respir Dis* 1993;147(5):1151-1156.
45. Kelsen SG, Ferenc M, Kapoor S. Effects of prolonged undernutrition on structure and function of the diaphragm. *J Appl Physiol* 1985;58(4):1354-1359.
46. Vaz M, Thangam S, Prabhu A, Shetty PS. Maximal voluntary contraction as a functional indicator of adult chronic undernutrition. *Br J Nutr* 1996;76(1):9-15.
47. Fiaccadori E, Zambrelli P, Tortorella G. [Physiopathology of respiratory muscles in malnutrition]. *Minerva Anestesiol* 1995;61(3):93-99. *Article in Italian.*
48. Openbrier DR, Irwin MM, Rogers RM, Gottlieb GP, Dauber JH, Van Thiel DH, Pennock BE. Nutritional status and lung function in patients with emphysema and chronic bronchitis. *Chest* 1983;83(1):17-22.
49. Mitch WE, Medina ER, Greger S, May RC, England BK, Price SR, et al. Metabolic acidosis stimulates muscle protein degradation by activating the adenosine triphosphate-dependent pathway involving ubiquitin and proteasomes. *J Clin Invest* 1994;93(5):2127-2133.
50. Fiaccadori E, Coffrini E, Ronda N, Vezzani A, Cacciani G, Fracchia C, et al. Hypophosphatemia in course of chronic obstructive pulmonary disease: prevalence, mechanisms, and relationships with skeletal muscle phosphorus content. *Chest* 1990;97(4):856-868.
51. Knochel JP. Neuromuscular manifestations of electrolyte disorders. *Am J Med* 1982;72(3):521-535.
52. Fiaccadori E, Coffrini E, Fracchia C, Rampulla C, Montagna T, Borghetti A. Hypophosphatemia and phosphorus depletion in respiratory and peripheral muscles of patients with respiratory failure due to COPD. *Chest* 1994;105(5):1392-1398.
53. Stendig-Lingberg G, Bergström J, Hultman E. Hypomagnesium and muscle electrolytes and metabolites. *Acta Med Scand* 1977;201(4):273-280.
54. Sieck GC, Johnson BD. Metabolic and structural alterations in skeletal muscle with hypoxia. In: Haddad GG, Lister, G, editors. *Tissue oxygen deprivation: from molecular to integrated function*. New York: Marcel Dekker; 1996:779-827.
55. Howald H, Pette D, Somoneau JA, Uber A, Hoppeler H, Cerretalli P. Effect of chronic hypoxia on muscle enzyme activities. *Int J Sports Med* 1990;11(Suppl 1):S10-S14.
56. Hultman E, Carale S, Sjöholm H. Effect of induced metabolic acidosis on intracellular pH, buffer capacity and contraction force of human skeletal muscle. *Clin Sci* 1985;69(5):505-510.
57. Wuyam B, Payen JF, Levy P, Bensaidane H, Reutenauer H, Le Bas JF, Benabid AL. Metabolism and aerobic capacity of skeletal muscle in chronic respiratory failure related to chronic obstructive pulmonary disease. *Eur Respir J* 1992;5(2):157-162.
58. Harms CA, Babcock MA, McClaran SR, Pegelow DF, Nickle GA, Nelson WB, Dempsey JA. Respiratory muscle work compromises leg blood flow during maximal exercise. *J Appl Physiol* 1997;82(5):1573-1583.
59. Wittenberg B, Wittenberg J, Caldwell P. Role of myoglobin in the oxygen supply to red skeletal muscle. *J Biol Chem* 1975;250(23):9038-9043.

60. Möller P, Hellstrom K, Hermansson IL. Myoglobin content in leg muscle in patients with chronic obstructive lung disease. *Respiration* 1984;45(1):35-38.
61. Enad JG, Fournier M, Sieck GC. Oxidative capacity and capillary density of diaphragm motor units. *J Appl Physiol* 1989;67(2):620-627.
62. Westerblad H, Lee JA, Lännergren J, Allen DG. Cellular mechanisms of fatigue in skeletal muscle. *Am J Physiol* 1991;261(2 Pt 1):C195-C209.
63. Reid MB. Muscle fatigue: mechanisms and regulation. In: Sen CK, Packer L, Hanninen O, editors. *Exercise and oxygen toxicity*, 2nd ed. Amsterdam: Elsevier Science; 1998.
64. Kwast KE, Hand SC. Acute depression of mitochondrial protein synthesis during anoxia: contributions of oxygen sensing, matrix acidification, and redox state. *J Biol Chem* 1996;271(13):7313-7319.
65. Eldridge FL. Central integration of mechanisms in exercise hyperpnea. *Med Sci Sports Exerc* 1994;26(3):319-327.
66. Bangsbo J, Madsen K, Kiens B, Richter EA. Effect on muscle acidity on muscle metabolism and fatigue during intense exercise in man. *J Physiol* 1996;495(Pt 2):587-596.
67. Karlsson J, Diamant B, Folkers K. Exercise-limiting factors in respiratory disease. *Respiration* 1992;59(Suppl 2):18-23.
68. Gertz I, Hedenstierna G, Hellers G, Wahren J. Muscle metabolism in patients with chronic obstructive lung disease and acute respiratory failure. *Clin Sci Mol Med* 1977;52(4):395-403.
69. MacIntyre NR. Corticosteroids and chronic obstructive lung disease. *Respir Care* 2006;51(3):289-296.
70. Decramer M, Lacquet LM, Fagard R, Rogiers P. Corticosteroids contribute to muscle weakness in chronic airflow obstruction. *Am Rev Respir Dis* 1994;150(1):11-16.
71. Decramer M, deBock V, Dom R. Functional and histologic picture of steroid-induced myopathy in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 1996;153(6 Pt 1):1958-1964.
72. Hall-Angerås M, Angerås U, Zamir O, Hasselgren PO, Fischer JE. Interaction between corticosterone and tumor necrosis factor stimulated protein breakdown in rat skeletal muscle similar to sepsis. *Surgery* 1990;108(2):460-466.
73. Larsson L, Ansved T, Edström L, Gorza L, Schiaffino S. Effects of age on physiological, immunohistochemical and biochemical properties of fast-twitch single motor units in the rat. *J Physiol* 1991;443:257-275.
74. Grimby G, Saltin B. The aging muscle. *Clin Physiol* 1983;3(3):209-218.
75. Gosselink R, Troosters T, Decramer M. Peripheral muscle weakness contributes to exercise limitation in COPD. *Am J Respir Crit Care Med* 1996;153(3):976-980.
76. Hamilton AL, Killian KJ, Summers E, Jones NL. Muscle strength, symptom intensity and exercise capacity in patients with cardiorespiratory disorders. *Am J Respir Crit Care Med* 1995;152(6 Pt 1):2021-2031.
77. Bernard S, Leblanc P, Whittom F, Carrier G, Jobin J, Belleau R, Maltais F. Peripheral muscle weakness in patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 1998;158(2):629-634.
78. Serres I, Gautier V, Varray AL, Préfaut C. Impaired skeletal muscle endurance related to physical inactivity and altered lung function in COPD patients. *Chest* 1998;113(4):900-905.
79. Booth FW, Gollnick PD. Effects of disease on the structure and function of skeletal muscle. *Med Sci Sports Exerc* 1983;15(5):415-420.
80. Coyle EF, Martin WH III, Bloomfield SA, Lowry OH, Holloszy JO. Effects of detraining on responses to submaximal exercise. *J Appl Physiol* 1985;59(3):853-869.