

Should all patients with COPD be exercise trained?

Fernanda Ribeiro, Marie-Eve Thériault, Richard Debigaré and François Maltais

J Appl Physiol 114:1300-1308, 2013. First published 14 February 2013;

doi: 10.1152/jappphysiol.01124.2012

You might find this additional info useful...

This article cites 139 articles, 78 of which you can access for free at:

<http://jap.physiology.org/content/114/9/1300.full#ref-list-1>

Updated information and services including high resolution figures, can be found at:

<http://jap.physiology.org/content/114/9/1300.full>

Additional material and information about *Journal of Applied Physiology* can be found at:

<http://www.the-aps.org/publications/jappl>

This information is current as of May 11, 2013.

Journal of Applied Physiology publishes original papers that deal with diverse area of research in applied physiology, especially those papers emphasizing adaptive and integrative mechanisms. It is published 24 times a year (twice monthly) by the American Physiological Society, 9650 Rockville Pike, Bethesda MD 20814-3991. Copyright © 2013 the American Physiological Society. ISSN: 1522-1601. Visit our website at <http://www.the-aps.org/>.

HIGHLIGHTED TOPIC | *Muscle Dysfunction in COPD*

Should all patients with COPD be exercise trained?

Fernanda Ribeiro, Marie-Eve Thériault, Richard Debigaré, and François Maltais

Centre de Recherche, Institut Universitaire de Cardiologie et de Pneumologie de Québec, Université Laval, Québec, Canada

Submitted 14 September 2012; accepted in final form 12 February 2013

Ribeiro F, Thériault M-E, Debigaré R, Maltais F. Should all patients with COPD be exercise trained? *J Appl Physiol* 114: 1300–1308, 2013. First published February 14, 2013; doi:10.1152/jappphysiol.01124.2012.—Exercise training is one of the most powerful interventions to provide symptomatic relief in patients with chronic obstructive pulmonary disease (COPD). The purpose of this minireview is to discuss how exercise training can improve limb muscle dysfunction in this disease. Various exercise training strategies will be outlined, along with their beneficial effects and potential limitations. Strategies to optimize the gains achievable with exercise training will be presented. Whether exercise training may exert deleterious effects in some patients will also be discussed.

chronic obstructive pulmonary disease; exercise training; skeletal muscle

CHRONIC OBSTRUCTIVE PULMONARY DISEASE (COPD) is highly prevalent, and the burden of this disease is expected to increase in the coming 15–20 years. Once viewed as a disease limited to the lungs, COPD is now recognized as a multisystemic disease associated with various comorbidities, including limb muscle dysfunction (5a). This specific comorbidity of COPD is clinically relevant. Muscle weakness and atrophy are associated with poorer survival in COPD (83, 113, 121). Limb muscle dysfunction is also associated with susceptibility to muscle fatigue, increased perception of leg fatigue during exercise, and premature exercise termination (64, 104). In contrast to the respiratory system, limb muscles have a remarkable plasticity in response to exercise and are, therefore, a valuable target for therapies aimed at reducing disability and, possibly, mortality in these patients. Proof of concept for this comes from the general benefits of exercise training, an essential component of pulmonary rehabilitation (87, 88). In fact, exercise training is the most powerful intervention that is currently available to provide symptomatic relief in COPD. Despite such proven efficacy, one current challenge is to find ways of optimizing exercise training benefits and expand the ability of this intervention to improve limb muscle function, taking into account patients' characteristics and disease severity that can modulate the response to the training intervention.

This minireview will thus focus on the impact of exercise training on limb muscle function in COPD. Diverse exercise training and related training modalities will be presented, in an attempt to define in whom, when, and how each modality can be optimally used to improve skeletal muscle structure and function in COPD. Potential limitations and strategies to optimize the gains achievable with exercise training will be pre-

sented. Whether exercise training may exert deleterious effects in some patients will also be discussed.

LIMB MUSCLE DYSFUNCTION IN COPD

Limb muscle dysfunction in COPD encompasses structural and functional alterations affecting the clinical picture of the disease (5a). Historically, studies on COPD have focused predominantly on the vastus lateralis as a key representative locomotor muscle. However, the process is not exclusive to the vastus lateralis. Reduced tibialis anterior oxidative profile (51) and upper limb muscle weakness and lower endurance have been reported in patients with COPD (55). Greater susceptibility to fatigue has also been found in calf muscles of patients with COPD (57). Compared with lower limb muscles, the function and structure of the upper limb muscles are relatively spared in COPD.

STRUCTURAL ADAPTATIONS

Atrophy. Limb muscle atrophy is common in COPD, and it is estimated that 25% of patients present with a depleted whole body fat-free mass (FFM) (110). A reduced FFM index can be observed as early as in Global Initiative for Obstructive Lung Disease (GOLD) I stage, although it is more frequent in severe stages of the disease (128). The atrophying process in COPD particularly affects lower limb muscles, and biopsy studies of the vastus lateralis reveal that the cross-sectional area (CSA) of all fiber types is reduced (140), although some argue that the type IIx fibers may be more affected (60). Maintenance of *in vitro* muscle fiber contractile properties in COPD (42) implies that atrophy is mainly responsible for weakness. The mechanisms involved in the development of limb muscle atrophy are complex. Activation of the ubiquitin proteasome pathway (48, 93) and impaired satellite cell function and regenerative potential (122) are likely to be involved.

Fiber-type distribution shift. A shift in fiber-type preponderance of the quadriceps from type I to type IIx fibers is a typical

Address for reprint requests and other correspondence: F. Maltais, Institut Universitaire de Cardiologie et de Pneumologie de Québec, 2725 Chemin Ste-Foy, Québec, Québec, G1V 4G5 Canada (e-mail: francois.maltais@med.ulaval.ca).

feature of COPD (62, 66, 140). In addition, the degree of fiber-type shift correlates with disease severity (62, 134).

Metabolic alterations. Consistent with the fiber-type shift, the COPD quadriceps typically uses less effective metabolic pathways to produce ATP as the Krebs cycle and β -oxidation pathways are downregulated in favor of glycolytic metabolism (105). As a result, the energy metabolism of the quadriceps is altered during exercise as evidenced by a greater glycogen utilization and lactate accumulation for a given exercise level in COPD compared with healthy controls (105, 120). This indicates a greater reliance on glycolysis, a less efficient energetic pathway, even at low workloads. These metabolic disturbances contribute to premature muscle fatigability (106), to increased ventilatory requirements during exercise (27), and, as a consequence, to exercise intolerance (106).

Capillarization defect. The capillary network is responsible for proper blood flow distribution within the muscle tissue and allows appropriate oxygen and nutrient transport to myofibers. The total number of capillaries and number of capillaries per muscle fiber are reduced in COPD (140), although this is not a universal finding (101). Discrepancy between studies is likely related to heterogeneity in study populations; for example, differences in training status across study participants could explain divergent conclusions regarding muscle capillarization in COPD. Also, most studies on muscle capillarization are small, and their conclusions are not necessarily generalizable. Capillary density is a likely determinant of muscle fatigue in COPD as indicated by one study reporting that reduced capillary contacts of all fiber types was associated with higher susceptibility to develop quadriceps fatigue during cycling exercise (106).

Mitochondrial adaptations and oxidative stress production. In patients with moderate to severe COPD without cachexia or hypoxemia, the reduction in limb muscle oxidative capacity is due to a lower mitochondrial volume density rather than any specific mitochondrial respiratory abnormalities (61, 92, 99). Studies using isolated mitochondria have suggested the presence of specific mitochondrial impairments in COPD (95, 99). However, given the fragility of the organelles, it is possible that these abnormalities were in part due to mitochondrial damage related to the isolation procedure (92). An increase in mitochondrial generation of reactive oxygen species is found in the COPD quadriceps when compared with age-matched healthy subjects (95, 140). Oxidative stress in the limb muscles of patients with COPD is a relevant finding because it is associated with decreased oxidative capacity (92, 107), premature muscle fatigue (28, 34), muscle weakness (8, 81), and muscle wasting (43, 55).

FUNCTIONAL ADAPTATIONS

Muscle performance is mainly defined by strength (capacity of the muscle to develop force) and endurance (capacity of the muscle to maintain a force over time). A decrease in strength and/or in endurance is common in patients with COPD (11, 33, 45, 67); a 15–25% decline in upper and lower limb muscle strength is usually observed compared with age-matched controls (11, 27). This difference in muscle strength disappears when quadriceps strength is normalized to midthigh muscle CSA (11), providing additional evidence that muscle atrophy is the main mechanism of weakness in this disease. Under certain

circumstances such as chronic or repeated exposure to systemic corticosteroids, a reduction in strength that is out of proportion with the degree of atrophy may occur (11, 46).

Quadriceps fatigue, defined as a reversible postexercise reduction in muscle strength, can be documented in up to 50% of patients with COPD after cycling exercise (77, 82, 104). Muscle fatigue after exercise is not abnormal in itself; the problem in COPD is that it occurs with greater amplitude and at much lower exercise intensities than in sedentary controls of similar age (77). Although susceptibility to muscle fatigue has been mostly reported in the quadriceps after cycling exercise (82), it has also been observed after walking tasks in plantiflexors and dorsiflexors of the ankle (57).

Consequently, along with impaired lung function, patients with COPD have to deal with weaker and less fatigue-resistant muscles to perform their daily tasks. This has direct implications for exercise tolerance; premature leg fatigue (4, 58, 104), early muscle acidosis (27, 80), and heightened perception of leg fatigue (11, 64) are all mechanisms through which lower limb muscle dysfunction may lead to exercise intolerance in COPD. Moreover, lower muscle mass and muscle weakness are associated with other important consequences such as decreased quality of life (85), impaired functional status (11), more frequent hospitalization and utilization of healthcare resources (45), and even premature mortality (83, 113).

EXERCISE TRAINING IMPROVES LIMB MUSCLES IN COPD

Fortunately and contrary to lung function limitations, limb muscle dysfunction is reversible, at least partially (12, 81). Exercise training alone or combined with other strategies such as nutritional supplementation (37), noninvasive mechanical ventilation (NIV), and/or medication such as hormonal supplementation (26) is able to improve muscle mass (12), strength (12, 76, 89, 90), and endurance (78), contributing to better quality of life (69) and exercise tolerance in COPD (79). Moreover, limb muscles are also able to respond to repeated electrical stimulations, which favor muscle anabolism, force, and endurance (129).

Endurance exercise training. Endurance training is considered an essential component of pulmonary rehabilitation given its ability to enhance exercise capacity and to reduce dyspnea (102). Exercise training also exerts a number of general physiological adaptations, including reductions in ventilatory requirements and in heart rate response, a more effective breathing pattern, and a lower degree of lactic acidosis at submaximal exercise intensities (27, 28). A direct consequence of these adaptations is that patients are able to tolerate higher peak work rates and submaximal exercise loads for longer periods of time.

Endurance aerobic training improves muscle oxidative capacity (81), promotes fiber-type shift from type IIx to type I fibers (132, 136), and increases cross-sectional areas of all fiber types in normal weight (140) and even cachectic patients with COPD (131). These adaptations have been reported in the range of COPD disease severity from GOLD II to IV stages (134). Enhanced muscle bioenergetics with a more efficient substrate utilization (107), enhanced mitochondrial oxidative enzyme activity, and greater capillary density have all been reported (27, 28, 81). Upregulation of factors regulating hypertrophy (IGF-1) and regeneration (MyoD) factors have also been documented (118, 132, 138).

Resistance exercise training. The exercise training specificity should be considered when prescribing exercise training. For example, endurance exercises are not as effective as resistance exercises to yield gain in muscle strength (90, 118, 136). Conversely, although resistive training may improve aerobic capacity to some extent (56), the strategy is less effective than endurance training in doing so (29, 90). Because of this, muscle endurance and resistance exercises are commonly combined in pulmonary rehabilitation (12, 90).

Resistance exercise allows application of a localized and intense muscle training stimulus at a lower ventilatory cost, so that dyspnea is less of an issue with this training strategy, a major advantage in patients with COPD (135). As a result, training intensity as high as 80% of maximal strength can be tolerated by patients (12, 68). Resistance training is effective in counteracting the deleterious effects of inactivity by activating regenerative properties of the muscle tissue ensured by the satellite cells (6). Resistance exercise upregulates the expression of various genes in muscle tissue (66) involved in the regulation of key proteins such as myosin heavy chain isoforms and myogenic regulatory factors including myogenin, MRF4, and MyoD (141). Prolonged resistance exercise stimuli may attenuate muscle inflammation and stimulate satellite cells in patients with COPD (84). Thus it is interesting to consider that strengthening exercise may promote limb muscle regenerative properties and the appropriate regulation of inflammation in COPD. Indeed, a coordinated inflammatory cytokine expression is required to activate and promote the development of muscle precursor cells for repair (30). Conversely, anti-inflammatory medication during training attenuates the exercise-induced increase in satellite cell number and may compromise the muscle remodeling associated with training (75).

LIMITATIONS OF EXERCISE TRAINING

Suboptimal limb muscle response to training in COPD. Unfortunately, muscle function and exercise tolerance are not unfaithfully improved after a training program and, in most situations, muscle function of patients with COPD is not fully restored after exercise training. Some patients do not even show the expected benefits from exercise training (124). Muscle response to training is heterogeneous; this is not exclusive to COPD as the training response is also highly variable in healthy individuals (19, 123).

There is a genetic component to the heterogeneity of the training response (19, 131). For example, polymorphism of the angiotensin-converting enzyme (ACE) gene, with the deletion of a base-pair sequence on chromosome 17, has been associated with a better preserved muscle strength in COPD (65) and possibly with a better strength response following resistance training in healthy subjects (54). Interestingly, muscle genes associated to oxidative stress, ubiquitin proteasome, and COX pathways were only induced in patients with COPD and not in healthy subjects following aerobic training; this might indicate greater levels of tissue stress in patients with COPD than in healthy controls (100). The precise role of such molecular responses in impeding the training response has yet to be better clarified.

Variability in the tolerance to intense training exercises may also explain the heterogeneous training response in patients with COPD as highlighted by studies showing that the extent of

physiological benefits is larger in patients training at higher rather than lower intensities (27, 31, 118). Patients with COPD experiencing dynamic hyperinflation and/or severe dyspnea during exercise are frequently unable to achieve exercise intensities that are required to stress their limb muscles to the point of fatigue (25), an observation that may be relevant considering that the extent of the training response may be linked to the occurrence of quadriceps contractile fatigue during the training sessions (23).

Several personal characteristics may also influence the magnitude of the training response. Age per se should not be considered as a barrier to improvement of limb muscle function following training. To the contrary, training-induced increases in muscle mass, strength, and functional status have all been reported in elderly individuals with or without COPD (18, 68). Limb muscle adaptation to training has been reported across the range of COPD disease severity (31, 134). Gender may influence the training response in healthy individuals (38), but this has not been extensively studied in COPD. Hypoxemic and/or home-bound patients with COPD are not typically included in exercise training trials. In these individuals with poor tolerance to whole body exercise, aerobic training may not be the optimal training strategy. Localized resistance training and alternative strategies such as one-leg training (47) and neuromuscular stimulation may be better suited to provide an adequate training stimulus while minimizing the impact on the ventilatory system (115). Finally, adverse effects and safety issues deserve more attention in exercise training in patients with advanced COPD.

Body composition may potentially influence the adaptability of muscle tissue to exercise training. Obesity does not appear to impact the general response to exercise training in COPD (49, 108); however, whether it influences the muscle response to training is unknown. In contrast, cachexia is a challenging condition that may modulate the capacity of exercise training to improve limb muscle function in COPD. Encouraging reports support the use of exercise training in these individuals. Muscle remodeling capacity, for example, is at least partially preserved in response to muscle training in cachectic patients with COPD (131). However, the complexity of the mechanisms associated with muscle wasting in COPD such as energy imbalance, systemic inflammation, hypoxemia, and hormonal deficiencies (130) may limit the efficacy of exercise training in this specific COPD population (55, 97).

COPD exacerbation is associated with deterioration in skeletal muscle function (39, 119) whereas pulmonary rehabilitation has recently been suggested to counteract the deleterious effects of exacerbation on limb muscles (22, 125). Exercise training is apparently safe and beneficial in the course of an exacerbation (10, 96, 125). In one study, muscle function loss was prevented and muscle anabolism was stimulated in patients with moderate-to-severe COPD who performed resistance training during acute exacerbation (125). Because it has very little impact on cardiac and ventilatory requirements, neuromuscular electrical stimulation is also emerging as a potentially useful rehabilitation tool during COPD exacerbation (59). However, the response of muscle tissue to exercise training during an exacerbation has not been thoroughly evaluated. For example, the possible influence of systemic inflammation during the exacerbation period may modify the ability

of the muscle to respond to exercise training; this has yet to be evaluated.

An intriguing question is whether limb muscle dysfunction in COPD can be entirely explained by years of physical inactivity or whether the existence of a COPD-related myopathy could be invoked (35). This issue is currently unresolved, and valid arguments for both points of view have been put forth. On the one hand, several features of limb muscle dysfunction in COPD resemble what is seen in deconditioning (15). On the other hand, muscle strength and endurance are not necessarily proportional to the degree of physical activity, and differences in muscle function and structure may exist even when controlling for physical activity (35, 63, 126). Whether a specific COPD-related myopathy could contribute to a suboptimal training response in COPD is unknown. The obvious study design to address the role of physical inactivity in the development of limb muscle dysfunction in COPD would be to match healthy individuals and patients with COPD not only for the degree of physical inactivity but also for its duration. This has yet to be accomplished. A longitudinal study of the interactions between physical activity and limb muscle structure and function over time would also be useful to inform this debate.

OPTIMIZATION OF LIMB MUSCLE EXERCISE TRAINING IN COPD

Several adjunct modalities have been proposed to improve the tolerance to training and optimize its physiological benefits. Some of these modalities will be discussed here. Other adjuncts to exercise training such as one-legged cycling (1, 14, 47), heliox (74), and oxygen supplementation (91) have been reviewed elsewhere.

Interval training. Interval training has been introduced as an attempt to overcome the difficulty to tolerate high-intensity and long-duration training (136). Interval training that includes short periods of very intense exercise interspersed with periods of recuperation produces less dyspnea and leg fatigue and may therefore facilitate the tolerance to training (55, 135) while yielding similar improvements in exercise capacity and health-related quality of life as continuous training (9). At the muscle level, interval training is as effective as continuous training to increase type I and II fiber cross-sectional area and improve oxidative capacity (133, 135). Patients susceptible to dynamic hyperinflation and those with very poor exercise tolerance and reduced muscle mass could be targeted for this type of intervention (133). Despite those interesting features of interval training, the efficacy of interval and continuous training is very similar (9), and, as such, interval training should be viewed as an alternative training strategy that could be useful in selected patients.

Neuromuscular electrical stimulation. Neuromuscular electrical stimulation (NMES) can be used to counteract limb muscle dysfunction in patients with very severe COPD (114, 129). One appealing feature of neuromuscular electrical stimulation is that it may help improve or maintain muscle structure with little impact on the cardiorespiratory system (115). Improvements in muscle mass, strength, and endurance have been reported in patients with advanced COPD with this training modality (86, 129). An increase in type II fiber cross-sectional area with a decrease in type I fiber cross-sectional area of the

quadriceps has been reported in moderately impaired patients with COPD following 6 wk of NMES training (40). In patients with advanced COPD, NMES improved muscle cross-sectional area in association with a more favorable muscle anabolic-to-catabolic balance (129).

NMES may be particularly useful in periods of exacerbation during which whole body exercise training may be difficult to accomplish. Giavedoni and colleagues (59) recently showed that NEMS, applied at rest on one leg, was able to improve quadriceps muscle force of that leg while loss in strength was seen in the nonstimulated leg. In another study, the application of a 6-wk NMES program in patients with COPD recovering from an acute exacerbation decreased muscle oxidative stress and improved myosin heavy chain content and the proportion of type I muscle fibers in the quadriceps (2). Although the impact of these findings on clinical outcomes such as physical activity level is unknown, these studies nevertheless suggest that NEMS may act as a bridging intervention to prevent deterioration of muscle structure and function during COPD exacerbation.

Although muscle stimulation is a very attractive training strategy and a feasible option for muscle training in COPD, larger, prospective, randomized controlled trials are needed to precisely define which patients would better benefit from this therapy (114). Whether NEMS is superior to low-intensity exercise in conscious patients who are able to perform voluntary muscle contractions is also questionable. NMES training may be difficult to tolerate in some patients because of the discomfort related to the stimulations (129). One potential option to overcome this difficulty is magnetic muscle stimulation training, which may provide similar benefits on muscle function while being easier to tolerate than repeated electrical stimulations (24).

Noninvasive ventilation. Noninvasive positive pressure ventilation, applied through face or nasal masks, may unload respiratory muscles and relieve exertional dyspnea. Noninvasive ventilation (NIV) during exercise reduces the expiratory flow limitation, decreases the occurrence of dynamic hyperinflation, and lowers respiratory muscle work (4). An NIV-induced reduction in respiratory muscle perfusion along with a corresponding increase in leg blood flow and oxygenation may also contribute to increase the tolerance to high-intensity exercise (17). Considering those physiological benefits, NIV has been proposed as an adjunct to improve tolerance to high-intensity training in patients with COPD (5). Poor adherence and the difficulty of routine application of the NIV strategy may confine its use to highly selected individuals. Used as a transitional approach, this modality could allow patients to initiate training and achieve higher exercise intensities during unstable phases of the disease such as acute COPD exacerbation (50).

Nutrition. Severe dyspnea and systemic inflammation may impair dietary intake, leading to malnutrition, particularly in advanced disease (112). Energy imbalance may increase muscle protein breakdown in an attempt to provide essential amino acids for bodily functions; an inevitable consequence of this is reduced muscle mass. Malnutrition is associated with muscle weakness of the lower and upper extremities (52) and decreased muscle endurance leading to fatigability in malnourished patients (73). In undernourished patients with COPD, nutritional supplementation can improve body weight and

respiratory and limb muscle function (53). Furthermore, studies have consistently reported higher mortality rates in underweight than in overweight patients with COPD, an observation arguing in favor of nutritional support therapy (20, 94, 109). Although quality of life indexes improve after nutritional therapy in patients with COPD, it is unclear to what extent the improvement in muscle function relates to the increase in muscle mass resulting from nutritional interventions (111). Because nutritional supplementation predominantly leads to gain in body fat (20), combination therapy with an anabolic stimulus such as exercise training is warranted to optimize the benefits at the muscle level (37).

Medication. Several pharmacological strategies have been considered to promote muscle mass gain in underweight patients with COPD. Testosterone supplementation and its analogs are able to improve muscle strength and mass (26, 36, 72); however, the impact of this treatment on functional capacity has not been confirmed (26). The biochemical mechanism responsible for skeletal muscle growth and reinforcement is believed to rely on the activation of the IGF-I signaling cascade, a potent effector pathway involved in muscle tissue hyperplasia and/or hypertrophy (72). Considering the long-term detrimental effects of testosterone (13) and the potential for carcinogenesis and virilization, this approach has not made it into routine clinical care. This has led to the development of pharmacological derivatives such as selective androgen receptor modulators (SARM), molecules designed to mimic testosterone properties without the side effects (3). Combining anabolic pharmacotherapy with exercise training enhances pharmacological efficiency (127). Growth hormone and its analogs (21), megestrol acetate (139), creatine (41), L-carnitine (16), antioxidants (67, 70), and vitamin D supplementation (71), alone or in combination with exercise training, have all been tested in COPD. The efficacy of those therapies is uncertain, and additional studies are warranted. Recent advances in skeletal muscle biology are already pointing to new therapeutic targets (7). For example, myostatin inhibitors are currently investigated in clinical trials (137).

POTENTIAL ADVERSE EFFECTS OF MUSCLE TRAINING

An intriguing and important question is whether exercise training may be deleterious to some patients with COPD. For example, it has been suggested that aerobic training could result in higher muscle inflammation and oxidative stress (98, 103, 132). Systemic inflammation (116) and oxidative stress (97, 98) may be worsened by exercise training, particularly in wasted patients. On the other hand, high-intensity (>60% of peak work capacity) aerobic exercise performed under both continuous and interval training modalities has been shown to enhance fiber size, modify fiber typology, and increase hypertrophy mediators (total IGF-I, MGF, and MyoD) without triggering systemic or local inflammation (TNF- α and IL-6) (132). Another clinical trial showed that patients with COPD exhibiting higher oxidative stress levels at baseline were able to increase peak work rate and $\dot{V}O_2$ as well as 6-min walked distance after high-intensity training without increasing systemic and local oxidative stress markers (103).

Exhaustion of the muscle repair process is another potential adverse consequence of exercise training (32). After birth, muscle mass maintenance, hypertrophy, and repair are depen-

dent upon the replicative potential of the satellite cells (30). Each round of replication implies a shortening of satellite cell telomeres; eventually these structures will reach a critical length at which the cell will enter an irreversible state of arrested growth and replicative senescence (44). Considering that telomere shortening has been reported in COPD (122), it can be argued that promoting satellite cell replication with exercise training may eventually compromise the ability of the COPD muscle cells to repair.

Despite the above considerations, the bulk of evidence suggests that exercise training is safe and beneficial for the vast majority of patients with COPD. Although it is possible that rest and acute postexercise muscle tissue inflammation could be worsened in frail patients (84), or that cycles of muscle repair may eventually exhaust the ability of the satellite cell to replicate, the clinical implications of these findings remain uncertain, and further work is warranted in this area. In the meantime, patients with COPD should be strongly encouraged to enroll in exercise training programs since this intervention is currently recognized as the most potent to provide symptomatic relief and to improve limb muscle dysfunction in this disease.

CONCLUSION

Exercise training is safe and beneficial for the vast majority of patients with COPD and should be applied on a routine clinical basis to prevent and counteract the deleterious effects of a sedentary lifestyle. The positive impact of exercise training at the muscle level is indisputable, and there is no current rationale or evidence to justify a contraindication to exercise training in this disease, perhaps with the exception of the presence of severe and unstable comorbid conditions. Combining endurance and strength training appears to be the most valuable option to treat limb muscle dysfunction in stable patients with COPD. Moreover, adaptations of the training regimen using interval training and adjunct therapies such as neuromuscular electrical stimulation or noninvasive ventilation may allow selected patients to benefit from a training program that would not otherwise be possible in difficult situations such as exacerbation, or when comorbidities or disease severity compromise the ability of the patients to tolerate training. Although further work is necessary to understand the short- and long-term clinical benefits of these interventions and the specific population that is most likely to benefit from them, combination therapies consisting of classic and adjunct modalities should be considered as an answer to the challenge of personalizing exercise training and optimizing its benefits.

ACKNOWLEDGMENTS

We thank Dr. Yves Deshaies for careful editing of the manuscript.

GRANTS

F. Ribeiro is the recipient of a PhD training award from Quebec Respiratory Health Training Program in partnership with the Respiratory Health Network of the Fonds de la Recherche en Santé du Québec (FRSQ) and of the Canadian Lung Association/Canadian Respiratory Health Professionals Fellowship Award. F. Maltais holds a GSK/CIHR Research Chair on COPD at Université Laval. This work has been supported in part by CIHR Grant MOP-115136.

DISCLOSURES

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

AUTHOR CONTRIBUTIONS

Author contributions: F.R. and M.-E.T. drafted manuscript; F.R., M.-E.T., R.D., and F.M. edited and revised manuscript; R.D. and F.M. approved final version of manuscript.

REFERENCES

1. Abbiss CR, Karagounis LG, Laursen PB, Peiffer JJ, Martin DT, Hawley JA, Fatehee NN, Martin JC. Single leg cycle training is superior to double leg cycling in improving the oxidative potential and metabolic profile of trained skeletal muscle. *J Appl Physiol* 110: 1248–1255, 2011.
2. Abdellaoui A, Préfaut C, Gouzi F, Couillard A, Coisy-Quivy M, Hugon G, Molinari N, Lafontaine T, Jonquet O, Laoudj-Chenivesse D, Hayot M. Skeletal muscle effects of electrostimulation after COPD exacerbation: a pilot study. *Eur Respir J* 38: 781–788, 2011.
3. Allan G, Sbriscia T, Linton O, Lai MT, Haynes-Johnson D, Bhattacharjee S, Ng R, Sui Z, Lundeen S. A selective androgen receptor modulator with minimal prostate hypertrophic activity restores lean body mass in aged orchidectomized male rats. *J Steroid Biochem Mol Biol* 110: 207–213, 2008.
4. Amann M, Regan MS, Kobitany M, Eldridge MW, Boutellier U, Pegelow DF, Dempsey JA. Impact of pulmonary system limitations on locomotor muscle fatigue in patients with COPD. *Am J Physiol Regul Integr Comp Physiol* 299: R314–R324, 2010.
5. Ambrosino N, Strambi S. New strategies to improve exercise tolerance in chronic obstructive pulmonary disease. *Eur Respir J* 24: 313–322, 2004.
- 5a. ATS/ERS. 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* 159: S1–S40, 1999.
6. Bamman MM, Clarke MS, Feedback DL, Talmadge RJ, Stevens BR, Lieberman SA, Greenisen MC. Impact of resistance exercise during bed rest on skeletal muscle sarcopenia and myosin isoform distribution. *J Appl Physiol* 84: 157–163, 1998.
7. Barnes PJ. Emerging pharmacotherapies for COPD. *Chest* 134: 1278–1286, 2008.
8. Barreiro E, Peinado VI, Galdiz JB, Ferrer E, Marin-Corral J, Sánchez F, Gea J, Barberà JA, in COPD Project ENIGMA. Cigarette smoke-induced oxidative stress: a role in chronic obstructive pulmonary disease skeletal muscle dysfunction. *Am J Respir Crit Care Med* 182: 477–488, 2010.
9. Beauchamp MK, Nonoyama M, Goldstein RS, Hill K, Dolmage TE, Mathur S, Brooks D. Interval versus continuous training in individuals with chronic obstructive pulmonary disease—a systematic review. *Thorax* 65: 157–164, 2010.
10. Behnke M, Taube C, Kirsten D, Lehnigk B, Jörres RA, Magnussen H. Home-based exercise is capable of preserving hospital-based improvements in severe chronic obstructive pulmonary disease. *Respir Med* 94: 1184–1191, 2000.
11. 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* 158: 629–634, 1998.
12. Bernard S, Whittom F, Leblanc P, Jobin J, Belleau R, Bérubé C, Carrier G, Maltais F. Aerobic and strength training in patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 159: 896–901, 1999.
13. Bhasin S, Calof OM, Storer TW, Lee ML, Mazer NA, Jasuja R, Montori VM, Gao W, Dalton JT. Drug insight: Testosterone and selective androgen receptor modulators as anabolic therapies for chronic illness and aging. *Nat Clin Pract Endocrinol Metab* 2: 146–159, 2006.
14. Björger S, Helgerud J, Husby V, Steinshamn S, Richadson RR, Hoff J. Aerobic high intensity one-legged interval cycling improves peak oxygen uptake in chronic obstructive pulmonary disease patients; no additional effect from hyperoxia. *Int J Sports Med* 30: 872–878, 2009.
15. Booth FW, Gollnick PD. Effects of disuse on the structure and function of skeletal muscle. *Med Sci Sports Exerc* 15: 415–420, 1983.
16. Borghi-Silva A, Baldissera V, Sampaio LMM, Pires-DiLorenzo VA, Jamami M, Demonte A, Marchini JS, Costa D. L-Carnitine as an ergogenic aid for patients with chronic obstructive pulmonary disease submitted to whole-body and respiratory muscle training programs. *Braz J Med Biol Res* 39: 465–474, 2006.
17. Borghi-Silva A, Di Thommazo L, Pantoni CBF, Mendes RG, Salvini TDF, Costa D. Non-invasive ventilation improves peripheral oxygen saturation and reduces fatigability of quadriceps in patients with COPD. *Respirology* 14: 537–544, 2009.
18. Borst SE. Interventions for sarcopenia and muscle weakness in older people. *Age Ageing* 33: 548–555, 2004.
19. Bouchard C, Sarzynski MA, Rice TK, Kraus WE, Church TS, Sung YJ, Rao DC, Rankinen T. Genomic predictors of the maximal O₂ uptake response to standardized exercise training programs. *J Appl Physiol* 110: 1160–1170, 2011.
20. Broekhuizen R, Creutzberg EC, Weling-Scheepers CAPM, Wouters EFM, Schols AMWJ. Optimizing oral nutritional drink supplementation in patients with chronic obstructive pulmonary disease. *Br J Nutr* 93: 965–971, 2005.
21. Burdet L, de Muralto B, Schutz Y, Pichard C, Fitting JW. Administration of growth hormone to underweight patients with chronic obstructive pulmonary disease. A prospective, randomized, controlled study. *Am J Respir Crit Care Med* 156: 1800–1806, 1997.
22. Burtin C, Decramer M, Gosselink R, Janssens W, Troosters T. Rehabilitation and acute exacerbations. *Eur Respir J* 38: 702–712, 2011.
23. Burtin C, Saey D, Saglam M, Langer D, Gosselink R, Janssens W, Decramer M, Maltais F, Troosters T. Effectiveness of exercise training in patients with COPD: the role of muscle fatigue. *Eur Respir J* 40: 338–344, 2012.
24. Bustamante V, de Santa Maria EL, Gorostiza A, Jimenez U, Galdiz JB. Muscle training with repetitive magnetic stimulation of the quadriceps in severe COPD patients. *Respir Med* 104: 237–245, 2010.
25. Butcher SJ, Lagerquist O, Marciniuk DD, Petersen SR, Collins DF, Jones RL. Relationship between ventilatory constraint and muscle fatigue during exercise in COPD. *Eur Respir J* 33: 763–770, 2009.
26. Casaburi R, Bhasin S, Cosentino L, Pórszász J, Somfay A, Lewis MI, Fournier M, Storer TW. Effects of testosterone and resistance training in men with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 170: 870–878, 2004.
27. 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* 143: 9–18, 1991.
28. Casaburi R, Porszasz J, Burns MR, Carithers ER, Chang RS, Cooper CB. Physiologic benefits of exercise training in rehabilitation of patients with severe chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 155: 1541–1551, 1997.
29. Casaburi R. Physiologic responses to training. *Clin Chest Med* 15: 215–227, 1994.
30. Chargé SBP, Rudnicki MA. Cellular and molecular regulation of muscle regeneration. *Physiol Rev* 84: 209–238, 2004.
31. Clark CJ, Cochrane LM, Mackay E, Paton B. Skeletal muscle strength and endurance in patients with mild COPD and the effects of weight training. *Eur Respir J* 15: 92–97, 2000.
32. Collins M, Renault V, Grobler LA, St Clair Gibson A, Lambert MI, Wayne Derman E, Butler-Browne GS, Noakes TD, Mouly V. Athletes with exercise-associated fatigue have abnormally short muscle DNA telomeres. *Med Sci Sports Exerc* 35: 1524–1528, 2003.
33. Coronell C, Orozco-Levi M, Méndez R, Ramírez-Sarmiento A, Galdiz JB, Gea J. Relevance of assessing quadriceps endurance in patients with COPD. *Eur Respir J* 24: 129–136, 2004.
34. Couillard A, Maltais F, Saey D, Debigaré R, Michaud A, Koechlin C, LeBlanc P, Préfaut C. Exercise-induced quadriceps oxidative stress and peripheral muscle dysfunction in patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 167: 1664–1669, 2003.
35. Couillard A, Préfaut C. From muscle disuse to myopathy in COPD: potential contribution of oxidative stress. *Eur Respir J* 26: 703–719, 2005.
36. Creutzberg EC, Wouters EFM, Mostert R, Pluyms RJ, Schols AMWJ. A role for anabolic steroids in the rehabilitation of patients with COPD? A double-blind, placebo-controlled, randomized trial. *Chest* 124: 1733–1742, 2003.
37. Creutzberg EC, Wouters EFM, Mostert R, Weling-Scheepers CAPM, Schols AMWJ. Efficacy of nutritional supplementation therapy in depleted patients with chronic obstructive pulmonary disease. *Nutrition* 19: 120–127, 2003.
38. Croley AN. Lower capillarization, VEGF protein, and VEGF mRNA response to acute exercise in the vastus lateralis muscle of aged vs. young women. *J Appl Physiol* 99: 1872–1879, 2005.
39. Crul T, Spruit MA, Gayan-Ramirez G, Quarck R, Gosselink R, Troosters T, Pitta F, Decramer M. Markers of inflammation and disuse

- in vastus lateralis of chronic obstructive pulmonary disease patients. *Eur J Clin Invest* 37: 897–904, 2007.
40. Dal Corso S, Nápolis L, Malaguti C, Gimenes AC, Albuquerque A, Nogueira CR, De Fuccio MB, Pereira RDB, Bulle A, McFarlane N, Nery LE, Neder JA. Skeletal muscle structure and function in response to electrical stimulation in moderately impaired COPD patients. *Respir Med* 101: 1236–1243, 2007.
 41. Deacon SJ, Vincent EE, Greenhaff PL, Fox J, Steiner MC, Singh SJ, Morgan MD. Randomized controlled trial of dietary creatine as an adjunct therapy to physical training in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 178: 233–239, 2008.
 42. Debigaré R, Côté CH, Hould FS, Leblanc P, Maltais F. In vitro and in vivo contractile properties of the vastus lateralis muscle in males with COPD. *Eur Respir J* 21: 273–278, 2003.
 43. Debigaré R, Côté CH, Maltais F. Peripheral muscle wasting in chronic obstructive pulmonary disease. Clinical relevance and mechanisms. *Am J Respir Crit Care Med* 164: 1712–1717, 2001.
 44. Decary S, Hamida CB, Mouly V, Barbet JP, Hentati F, Butler-Browne GS. Shorter telomeres in dystrophic muscle consistent with extensive regeneration in young children. *Neuromusc Disorders* 10: 113–120, 2000.
 45. Decramer M, Gosselink R, Troosters T, Verschueren M, Evers G. Muscle weakness is related to utilization of health care resources in COPD patients. *Eur Respir J* 10: 417–423, 1997.
 46. Decramer M, Lacquet LM, Fagard R, Rogiers P. Corticosteroids contribute to muscle weakness in chronic airflow obstruction. *Am J Respir Crit Care Med* 150: 11–16, 1994.
 47. Dolmage TE, Goldstein RS. Effects of one-legged exercise training of patients With COPD. *Chest* 133: 370–376, 2008.
 48. Doucet M, Russell AP, Léger B, Debigare R, Joanisse DR, Caron MA, LeBlanc P, Maltais F. Muscle atrophy and hypertrophy signaling in patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 176: 261–269, 2007.
 49. Dreher M, Kabitz HJ. Impact of obesity on exercise performance and pulmonary rehabilitation. *Respirology* 17: 899–907, 2012.
 50. Dyer F, Flude L, Bazari F, Jolley C, Englebretsen C, Lai D, Polkey MI, Hopkinson NS. Non-invasive ventilation (NIV) as an aid to rehabilitation in acute respiratory disease. *BMC Pulm Med* 11: 58, 2011.
 51. Eliason G, Abdel-Halim S, Arvidsson B, Kadi F, Piehl-Aulin K. Physical performance and muscular characteristics in different stages of COPD. *Scand J Med Sci Sport* 19: 865–870, 2009.
 52. Engelen MP, Schols AM, Baken WC, Wesseling GJ, Wouters EF. Nutritional depletion in relation to respiratory and peripheral skeletal muscle function in out-patients with COPD. *Eur Respir J* 7: 1793–1797, 1994.
 53. Ferreira IM, Verreschi IT, Nery LE, Goldstein RS, Zamel N, Brooks D, Jardim JR. The influence of 6 months of oral anabolic steroids on body mass and respiratory muscles in undernourished COPD patients. *Chest* 114: 19–28, 1998.
 54. Folland J, Leach B, Little T, Hawker K, Myerson S, Montgomery H, Jones D. Angiotensin-converting enzyme genotype affects the response of human skeletal muscle to functional overload. *Exp Physiol* 85: 575–579, 2000.
 55. Franssen FME, Broekhuizen R, Janssen PP, Wouters EFM, Schols AMWJ. Limb muscle dysfunction in COPD: effects of muscle wasting and exercise training. *Med Sci Sports Exerc* 37: 2–9, 2005.
 56. Frontera WR, Meredith CN, O'Reilly KP, Evans WJ. Strength training and determinants of VO₂max in older men. *J Appl Physiol* 68: 329–333, 1990.
 57. Gagnon P, Maltais F, Bouyer L, Ribeiro F, Coats V, Brouillard C, Noël M, Rousseau-Gagnon M, Saey D. Distal leg muscle function in patients with COPD. *COPD: J Chronic Obstructive Pulm Dis*. In press.
 58. Gagnon P, Saey D, Vivodtzev I, Laviolette L, Mainguy V, Milot J, Provencher S, Maltais F. Impact of preinduced quadriceps fatigue on exercise response in chronic obstructive pulmonary disease and healthy subjects. *J Appl Physiol* 107: 832–840, 2009.
 59. Giavedoni S, Deans A, McCaughey P, Drost E, MacNee W, Rabinovich RA. Neuromuscular electrical stimulation prevents muscle function deterioration in exacerbated COPD: a pilot study. *Respir Med* 106: 1429–1434, 2012.
 60. Gosker HR, Engelen MPKJ, van Mameren H, van Dijk PJ, van der Vusse GJ, Wouters EFM, Schols AMWJ. Muscle fiber type IIX atrophy is involved in the loss of fat-free mass in chronic obstructive pulmonary disease. *Am J Clin Nutr* 76: 113–119, 2002.
 61. Gosker HR, Hesselink MKC, Duimel H, Ward KA, Schols AMWJ. Reduced mitochondrial density in the vastus lateralis muscle of patients with COPD. *Eur Respir J* 30: 73–79, 2007.
 62. Gosker HR, Zeegers MP, Wouters EFM, Schols AMWJ. Muscle fibre type shifting in the vastus lateralis of patients with COPD is associated with disease severity: a systematic review and meta-analysis. *Thorax* 62: 944–949, 2007.
 63. Gouzi F, Préfaut C, Abdellaoui A, Vuillemin A, Molinari N, Ninot G, Caris G, Hayot M. Evidence of an early physical activity reduction in chronic obstructive pulmonary disease patients. *Arch Phys Med Rehabil* 92: 1611–1617. e2, 2011.
 64. 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* 152: 2021–2031, 1995.
 65. Hopkinson NS, Nickol AH, Payne J, Hawe E, Man WDC, Moxham J, Montgomery H, Polkey MI. Angiotensin converting enzyme genotype and strength in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 170: 395–399, 2004.
 66. Hulmi JJ, Walker S, Ahtiainen JP, Nyman K, Kraemer WJ, Häkkinen K. Molecular signaling in muscle is affected by the specificity of resistance exercise protocol. *Scand J Med Sci Sport* 22: 240–248, 2012.
 67. Koechlin C, Couillard A, Simar D, Cristol JP, Bellet H, Hayot M, Préfaut C. Does oxidative stress alter quadriceps endurance in chronic obstructive pulmonary disease? *Am J Respir Crit Care Med* 169: 1022–1027, 2004.
 68. Kongsgaard M, Backer V, Jørgensen K, Kjær M, Beyer N. Heavy resistance training increases muscle size, strength and physical function in elderly male COPD-patients—a pilot study. *Respir Med* 98: 1000–1007, 2004.
 69. Laviolette L, Bourbeau J, Bernard S, Lacasse Y, Pepin V, Breton MJ, Baltzan M, Rouleau M, Maltais F. Assessing the impact of pulmonary rehabilitation on functional status in COPD. *Thorax* 63: 115–121, 2008.
 70. Laviolette L, Lands LC, Dauletbaev N, Saey D, Milot J, Provencher S, LeBlanc P, Maltais F. Combined effect of dietary supplementation with pressurized whey and exercise training in chronic obstructive pulmonary disease: a randomized, controlled, double-blind pilot study. *J Med Food* 13: 589–598, 2010.
 71. Lehouck A, Mathieu C, Carremans C, Baek F, Verhaegen J, Van Eldere J, Decallonne B, Bouillon R, Decramer M, Janssens W. High doses of vitamin D to reduce exacerbations in chronic obstructive pulmonary disease: a randomized trial. *Ann Intern Med* 156: 105–114, 2012.
 72. Lewis MI, Fournier M, Storer TW, Bhasin S, Porszasz J, Ren SG, Da X, Casaburi R. Skeletal muscle adaptations to testosterone and resistance training in men with COPD. *J Appl Physiol* 103: 1299–1310, 2007.
 73. Lopes J, Russell DM, Whitwell J, Jeejeebhoy KN. Skeletal muscle function in malnutrition. *Am J Clin Nutr* 36: 602–610, 1982.
 74. Louvaris Z, Zakynthinos SG, Aliverti A, Habazettl H, Vasilopoulou M, Andrianopoulos V, Wagner H, Wagner PD, Vogiatzis I. Heliox increases quadriceps muscle oxygen delivery during exercise in COPD patients with and without dynamic hyperinflation. *J Appl Physiol* 113: 1012–1023, 2012.
 75. Mackey AL, Kjær M, Dandanell S, Mikkelsen KH, Holm L, Døssing S, Kadi F, Koskinen SO, Jensen CH, Schröder HD, Langberg H. The influence of anti-inflammatory medication on exercise-induced myogenic precursor cell responses in humans. *J Appl Physiol* 103: 425–431, 2007.
 76. Mador MJ, Bozkanat E, Aggarwal A, Shaffer M, Kufel TJ. Endurance and strength training in patients with COPD. *Chest* 125: 2036–2045, 2004.
 77. Mador MJ, Bozkanat E, Kufel TJ. Quadriceps fatigue after cycle exercise in patients with COPD compared with healthy control subjects. *Chest* 123: 1104–1111, 2003.
 78. Mador MJ, Kufel TJ, Pineda LA, Steinwald A, Aggarwal A, Upadhyay AM, Khan MA. Effect of pulmonary rehabilitation on quadriceps fatigability during exercise. *Am J Respir Crit Care Med* 163: 930–935, 2001.
 79. Maltais F, Bourbeau J, Shapiro S, Lacasse Y, Perrault H, Baltzan M, Hernandez P, Rouleau M, Julien M, Parenteau S, Paradis B, Levy RD, Camp P, Lecours R, Audet R, Hutton B, Penrod JR, Picard D, Bernard S, Chronic Obstructive Pulmonary Disease Axis of Respiratory Health Network, Fonds de recherche en santé du Québec. Effects of home-based pulmonary rehabilitation in patients with chronic

- obstructive pulmonary disease: a randomized trial. *Ann Intern Med* 149: 869–878, 2008.
80. Maltais F, Jobin J, Sullivan MJ, Bernard S, Whittom F, Killian KJ, Desmeules M, Bélanger M, Leblanc P. Metabolic and hemodynamic responses of lower limb during exercise in patients with COPD. *J Appl Physiol* 84: 1573–1580, 1998.
 81. Maltais F, Leblanc P, Simard C, Jobin J, Bérubé C, Bruneau J, Carrier L, Belleau R. Skeletal muscle adaptation to endurance training in patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 154: 442–447, 1996.
 82. Man WDC, Soliman MGG, Gearing J, Radford SG, Rafferty GF, Gray BJ, Polkey MI, Moxham J. Symptoms and quadriceps fatigability after walking and cycling in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 168: 562–567, 2003.
 83. Marquis K, Debigaré R, Lacasse Y, LeBlanc P, Jobin J, Carrier G, Maltais F. Midthigh muscle cross-sectional area is a better predictor of mortality than body mass index in patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 166: 809–813, 2002.
 84. Menon MK, Houchen L, Singh SJ, Morgan MD, Bradding P, Steiner MC. Inflammatory and satellite cells in the quadriceps of patients with COPD and the response to resistance training. *Chest* 142: 1134–1142, 2012.
 85. Mostert R, Goris A, Welting-Scheepers C, Wouters EF, Schols AM. Tissue depletion and health related quality of life in patients with chronic obstructive pulmonary disease. *Respir Med* 94: 859–867, 2000.
 86. Neder JA, Sword D, Ward SA, Mackay E, Cochrane LM, Clark CJ. Home based neuromuscular electrical stimulation as a new rehabilitative strategy for severely disabled patients with chronic obstructive pulmonary disease (COPD). *Thorax* 57: 333–337, 2002.
 87. Nici L, Donner C, Wouters E, Zuwallack R, Ambrosino N, Bourbeau J, Carone M, Celli B, Engelen M, Fahy B, Garvey C, Goldstein R, Gosselink R, Lareau S, MacIntyre N, Maltais F, Morgan M, O'Donnell D, Prefault C, Reardon J, Rochester C, Schols A, Singh S, Troosters T, ATS/ERS Pulmonary Rehabilitation Writing Committee. American Thoracic Society/European Respiratory Society statement on pulmonary rehabilitation. *Am J Respir Crit Care Med* 173: 1390–1413, 2006.
 88. Nici L, ZuWallack R. Scope, background and definition of pulmonary rehabilitation. *Eur J Phys Rehabil Med* 47: 465–474, 2011.
 89. O'Shea SD, Taylor NF, Paratz JD. Progressive resistance exercise improves muscle strength and may improve elements of performance of daily activities for people with COPD: a systematic review. *Chest* 136: 1269–1283, 2009.
 90. Ortega F, Toral J, Cejudo P, Villagomez R, Sánchez H, Castillo J, Montemayor T. Comparison of effects of strength and endurance training in patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 166: 669–674, 2002.
 91. Palange P, Crimi E, Pellegrino R, Brusasco V. Supplemental oxygen and heliox: “new” tools for exercise training in chronic obstructive pulmonary disease. *Curr Opin Pulm Med* 11: 145–148, 2005.
 92. Picard M, Godin R, Sinnreich M, Baril J, Bourbeau J, Perrault H, Taivassalo T, Burelle Y. The mitochondrial phenotype of peripheral muscle in chronic obstructive pulmonary disease: disuse or dysfunction? *Am J Respir Crit Care Med* 178: 1040–1047, 2008.
 93. Plant PJ, Brooks D, Faughnan M, Bayley T, Bain J, Singer L, Correa J, Pearce D, Binnie M, Batt J. Cellular markers of muscle atrophy in chronic obstructive pulmonary disease. *Am J Respir Cell Mol Biol* 42: 461–471, 2010.
 94. Prescott E, Almdal T, Mikkelsen KL, Tofteng CL, Vestbo J, Lange P. Prognostic value of weight change in chronic obstructive pulmonary disease: results from the Copenhagen City Heart Study. *Eur Respir J* 20: 539–544, 2002.
 95. Puente-Maestu L, Pérez-Parra J, Godoy R, Moreno N, Tejedor A, González-Aragoneses F, Bravo JL, Alvarez FV, Camaño S, Agustí A. Abnormal mitochondrial function in locomotor and respiratory muscles of COPD patients. *Eur Respir J* 33: 1045–1052, 2009.
 96. Puhon MA, Gimeno-Santos E, Scharplatz M, Troosters T, Walters EH, Steurer J. Pulmonary rehabilitation following exacerbations of chronic obstructive pulmonary disease. *Cochrane Database Syst Rev* 10: CD005305, 2011.
 97. Rabinovich RA, Ardite E, Mayer AM, Polo MF, Vilaro J, Argilés JM, Roca J. Training depletes muscle glutathione in patients with chronic obstructive pulmonary disease and low body mass index. *Respiration* 73: 757–761, 2006.
 98. Rabinovich RA, Ardite E, Troosters T, Carbó N, Alonso J, Gonzalez De Suso JM, Vilaro J, Barberá JA, Polo MF, Argilés JM, Fernandez-Checa JC, Roca J. Reduced muscle redox capacity after endurance training in patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 164: 1114–1118, 2001.
 99. Rabinovich RA, Bastos R, Ardite E, Llinàs L, Orozco-Levi M, Gea J, Vilaro J, Barberá JA, Rodriguez-Roisin R, Fernandez-Checa JC, Roca J. Mitochondrial dysfunction in COPD patients with low body mass index. *Eur Respir J* 29: 643–650, 2007.
 100. Radom-Aizik S, Kaminski N, Hayek S, Halkin H, Cooper DM, Ben-Dov I. Effects of exercise training on quadriceps muscle gene expression in chronic obstructive pulmonary disease. *J Appl Physiol* 102: 1976–1984, 2007.
 101. Richardson RS, Leek BT, Gavin TP, Haseler LJ, Mudaliar SRD, Henry R, Mathieu-Costello O, Wagner PD. Reduced mechanical efficiency in chronic obstructive pulmonary disease but normal peak $\dot{V}O_2$ with small muscle mass exercise. *Am J Respir Crit Care Med* 169: 89–96, 2004.
 102. Ries AL, Kaplan RM, Limberg TM, Prewitt LM. Effects of pulmonary rehabilitation on physiologic and psychosocial outcomes in patients with chronic obstructive pulmonary disease. *Ann Intern Med* 122: 823–832, 1995.
 103. Rodriguez DA, Kalko S, Puig-Vilanova E, Perez-Olabarría M, Falciani F, Gea J, Cascante M, Barreiro E, Roca J. Muscle and blood redox status after exercise training in severe COPD patients. *Free Radic Biol Med* 52: 88–94, 2012.
 104. Saey D, Debigare R, LeBlanc P, Mador MJ, Cote CH, Jobin J, Maltais F. Contractile leg fatigue after cycle exercise: a factor limiting exercise in patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 168: 425–430, 2003.
 105. Saey D, Lemire BB, Gagnon P, Bombardier E, Tupling AR, Debigaré R, Côté CH, Maltais F. Quadriceps metabolism during constant workrate cycling exercise in chronic obstructive pulmonary disease. *J Appl Physiol* 110: 116–124, 2011.
 106. Saey D, Michaud A, Couillard A, Côté CH, Mador MJ, LeBlanc P, Jobin J, Maltais F. Contractile fatigue, muscle morphometry, and blood lactate in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 171: 1109–1115, 2005.
 107. Sala E, Roca J, Marrades RM, Alonso J, Gonzalez De Suso JM, Moreno A, Barberá JA, Nadal J, de Jover L, Rodriguez-Roisin R, Wagner PD. Effects of endurance training on skeletal muscle bioenergetics in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 159: 1726–1734, 1999.
 108. Sava F, Laviolette L, Bernard S, Breton MJ, Bourbeau J, Maltais F. The impact of obesity on walking and cycling performance and response to pulmonary rehabilitation in COPD. *BMC Pulm Med* 10: 55, 2010.
 109. Schols AM, Slangen J, Volovics L, Wouters EF. Weight loss is a reversible factor in the prognosis of chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 157: 1791–1797, 1998.
 110. Schols AM, Soeters PB, Dingemans AM, Mostert R, Frantzen PJ, Wouters EF. Prevalence and characteristics of nutritional depletion in patients with stable COPD eligible for pulmonary rehabilitation. *Am Rev Respir Dis* 147: 1151–1156, 1993.
 111. Schols AM, Soeters PB, Mostert R, Pluymers RJ, Wouters EF. Physiologic effects of nutritional support and anabolic steroids in patients with chronic obstructive pulmonary disease. A placebo-controlled randomized trial. *Am J Respir Crit Care Med* 152: 1268–1274, 1995.
 112. Schols AM, Wouters EF. Nutritional abnormalities and supplementation in chronic obstructive pulmonary disease. *Clin Chest Med* 21: 753–762, 2000.
 113. Schols AMWJ, Broekhuizen R, Welting-Scheepers CA, Wouters EF. Body composition and mortality in chronic obstructive pulmonary disease. *Am J Clin Nutr* 82: 53–59, 2005.
 114. Sillen MJH, Speksnijder CM, Eterman RMA, Janssen PP, Wagers SS, Wouters EFM, Uszko-Lencer NHMK, Spruit MA. Effects of neuromuscular electrical stimulation of muscles of ambulation in patients with chronic heart failure or COPD: a systematic review of the English-language literature. *Chest* 136: 44–61, 2009.
 115. Sillen MJH, Wouters EFM, Franssen FME, Meijer K, Stakenborg KHP, Spruit MA. Oxygen uptake, ventilation, and symptoms during low-frequency versus high-frequency NMES in COPD: a pilot study. *Lung* 189: 21–26, 2010.

116. Sin DD, Man SFP. Skeletal muscle weakness, reduced exercise tolerance, and COPD: is systemic inflammation the missing link? *Thorax* 61: 1–3, 2006.
118. Spruit MA, Gosselink R, Troosters T, De Paepe K, Decramer M. Resistance versus endurance training in patients with COPD and peripheral muscle weakness. *Eur Respir J* 19: 1072–1078, 2002.
119. Spruit MA, Gosselink R, Troosters T, Kasran A, Gayan-Ramirez G, Bogaerts P, Bouillon R, Decramer M. Muscle force during an acute exacerbation in hospitalised patients with COPD and its relationship with CXCL8 and IGF-I. *Thorax* 58: 752–756, 2003.
120. Steiner MC, Evans R, Deacon SJ, Singh SJ, Patel P, Fox J, Greenhaff PL, Morgan MDL. Adenine nucleotide loss in the skeletal muscles during exercise in chronic obstructive pulmonary disease. *Thorax* 60: 932–936, 2005.
121. Swallow EB, Reyes D, Hopkinson NS, Man WDC, Porcher R, Cetti EJ, Moore AJ, Moxham J, Polkey MI. Quadriceps strength predicts mortality in patients with moderate to severe chronic obstructive pulmonary disease. *Thorax* 62: 115–120, 2007.
122. Thériault ME, Paré MÈ, Maltais F, Debigare R. Satellite cells senescence in limb muscle of severe patients with COPD. *PLoS ONE* 7: e39124, 2012.
123. Timmons JA. Variability in training-induced skeletal muscle adaptation. *J Appl Physiol* 110: 846–853, 2011.
124. Troosters T, Gosselink R, Decramer M. Exercise training in COPD: how to distinguish responders from nonresponders. *J Cardiopulm Rehabil Prev* 21: 10–17, 2001.
125. Troosters T, Probst VS, Crul T, Pitta F, Gayan-Ramirez G, Decramer M, Gosselink R. Resistance training prevents deterioration in quadriceps muscle function during acute exacerbations of chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 181: 1072–1077, 2010.
126. van den Borst B, Slot IGM, Hellwig VACV, Vosse BAH, Kelders MCJM, Barreiro E, Schols AMWJ, Gosker HR. Loss of quadriceps muscle oxidative phenotype and decreased endurance in patients with mild-to-moderate COPD. *J Appl Physiol* 2012 July 19. [Epub ahead of print].
127. Velema MS, Kwa BHB, de Ronde W. Should androgenic anabolic steroids be considered in the treatment regime of selected chronic obstructive pulmonary disease patients? *Curr Opin Pulm Med* 18: 118–124, 2012.
128. Vestbo J, Prescott E, Almdal T, Dahl M, Nordestgaard BG, Andersen T, Sørensen TIA, Lange P. Body mass, fat-free body mass, and prognosis in patients with chronic obstructive pulmonary disease from a random population sample: findings from the Copenhagen City Heart Study. *Am J Respir Crit Care Med* 173: 79–83, 2006.
129. Vivodtzev I, Debigaré R, Gagnon P, Mainguy V, Saey D, Dube A, Pare ME, Belanger M, Maltais F. Functional and muscular effects of neuromuscular electrical stimulation in patients with severe COPD: a randomized clinical trial. *Chest* 141: 716–725, 2012.
130. Vogelmeier CF, Wouters EFM. Treating the systemic effects of chronic obstructive pulmonary disease. *Proc Am Thoracic Soc* 8: 376–379, 2011.
131. Vogiatzis I, Simoes DCM, Stratakos G, Kourepini E, Terzis G, Manta P, Athanasopoulos D, Roussos C, Wagner PD, Zakynthinos S. Effect of pulmonary rehabilitation on muscle remodelling in cachectic patients with COPD. *Eur Respir J* 36: 301–310, 2010.
132. Vogiatzis I, Stratakos G, Simoes DCM, Terzis G, Georgiadou O, Roussos C, Zakynthinos S. Effects of rehabilitative exercise on peripheral muscle TNF, IL-6, IGF-I and MyoD expression in patients with COPD. *Thorax* 62: 950–956, 2007.
133. Vogiatzis I, Terzis G, Nanas S, Stratakos G, Simoes DCM, Georgiadou O, Zakynthinos S, Roussos C. Skeletal muscle adaptations to interval training in patients with advanced COPD. *Chest* 128: 3838–3845, 2005.
134. Vogiatzis I, Terzis G, Stratakos G, Cherouveim E, Athanasopoulos D, Spetsioti S, Nasis I, Manta P, Roussos C, Zakynthinos S. Effect of pulmonary rehabilitation on peripheral muscle fiber remodeling in patients with COPD in GOLD stages II to IV. *Chest* 140: 744–752, 2011.
135. Vogiatzis I. Strategies of muscle training in very severe COPD patients. *Eur Respir J* 38: 971–975, 2011.
136. Vonbank K, Strasser B, Mondrzyk J, Marzluf BA, Richter B, Losch S, Nell H, Petkov V, Haber P. Strength training increases maximum working capacity in patients with COPD. Randomized clinical trial comparing three training modalities. *Respir Med* 106: 557–563, 2012.
137. Wagner KR, Fleckenstein JL, Amato AA, Barohn RJ, Bushby K, Escolar DM, Flanigan KM, Pestronk A, Tawil R, Wolfe GI, Eagle M, Florence JM, King WM, Pandya S, Straub V, Juneau P, Meyers K, Csimma C, Araujo T, Allen R, Parsons SA, Wozney JM, Lavallie ER, Mendell JR. A phase I/II trial of MYO-029 in adult subjects with muscular dystrophy. *Ann Neurol* 63: 561–571, 2008.
138. Weber MA, Hildebrandt W, Schrã Der L, Kinscherf R, Krix M, Bachert P, Delorme S, Essig M, Kauczor HU, Krakowski-Roosen H. Concentric resistance training increases muscle strength without affecting microcirculation. *Eur J Radiol* 73: 614–621, 2010.
139. Weisberg J, Wanger J, Olson J, Streit B, Fogarty C, Martin T, Casaburi R. Megestrol acetate stimulates weight gain and ventilation in underweight COPD patients. *Chest* 121: 1070–1078, 2002.
140. Whitton F, Jobin J, Simard PM, Leblanc P, Simard C, Bernard S, Belleau R, Maltais F. Histochemical and morphological characteristics of the vastus lateralis muscle in patients with chronic obstructive pulmonary disease. *Med Sci Sports Exerc* 30: 1467–1474, 1998.
141. Willoughby DS, Nelson MJ. Myosin heavy-chain mRNA expression after a single session of heavy-resistance exercise. *Med Sci Sports Exerc* 34: 1262–1269, 2002.