Muscle Dysfunction Associated With Chronic Obstructive Pulmonary Disease

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Summary

Skeletal-muscle (both respiratory and limb) abnormalities are common and can have profound effects in patients with chronic inflammatory states such as chronic obstructive pulmonary disease (COPD). Causes include direct inflammatory-mediator effects on muscle function, malnutrition, blood-gas abnormalities, compromised oxygen delivery from right-heart dysfunction, electrolyte imbalances, drugs, and comorbid states. In COPD patients, respiratory muscles are overloaded, which leads to increased fatigue potential, especially during exercise, when hyperinflation worsens. Interestingly, overloaded respiratory muscles develop structural changes that help them adapt to these conditions. In contrast, limb (especially lower extremity) muscles in COPD patients are underloaded as a consequence of disuse, and this leads to muscle atrophy. Treatment is aimed at optimizing lung function, nutritional repletion, aerobic exercise training, and (in certain patients) oxygen therapy. Resistive breathing training is more controversial. Lung-volume-reduction surgery may help with the hyperinflation effects and improve gas exchange and respiratory-muscle function in selected patients. *Key words: chronic obstructive pulmonary disease, COPD, respiratory muscles.* [Respir Care 2006;51(8):840–848. © 2006 Daedalus Enterprises]

Introduction: Systemic Effects of Chronic Obstructive Pulmonary Disease on Skeletal Muscle

Skeletal muscle composes approximately 73% of total body mass. It is critical not only for locomotion and task performance, but also for providing the vital pumping function of the diaphragm and the heart. The primary structures of skeletal muscle are sarcomeres.[1–5] Sarcomeres contain actin and myosin components that contract under nerve stimulation, which causes calcium-ion changes across the membrane. Skeletal muscle is composed of several different fiber types, which perform different functions and have different metabolic properties (Table 1).[1–5] The distribution of fiber types in a given muscle depends on the functions the muscle performs. Type I fibers have considerable oxidative capacity and have high mitochondrial density. These fibers provide tonic or repetitive function such as maintaining antigravity conditions and pumping actions of the heart or the diaphragm. Type I fibers are noticeably resistant to fatigue. Type II fibers have relatively more sarcomeric structures and have less mitochondrial density.

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Table 1. Properties of Muscle-Fiber Types

Muscle-Fiber Type	Description	Metabolism	Myoglobin/mitochondria	Function
I	Slow, fatigue-resistant	Oxidative	Rich, "red"	Standing Quiet breathing
IIa*	Fast, fatigue-resistant	Oxidative/glycolytic	Mixed	Walking Hyperventilating
IIb*	Fast, fatigable	Glycolytic	Low, "white"	Jumping Coughing

* An intermediate Type IIx fiber with fast twitch features and intermediate fatigability has also been described.

Table 2. Systemic Effects of COPD on Skeletal Muscle

Direct Effects
   Myotoxic cytokines are produced as part of the chronic pro-inflammatory state
   Hypoxia is produced by impaired oxygen delivery
   Acidosis is produced by hypercapnia and glycolytic metabolism
Complicating Factors
   Malnutrition
   Comorbid conditions
   Age
Pathologic Consequences
   Direct muscle protein structural and biochemical changes
   Ischemia reperfusion injury
   Reduced glutathione and defense against oxidative stress

COPD = chronic obstructive pulmonary disease

They are capable of performing more sudden, intense tension-generation, but, depending on their mitochondrial density, become less and less resistant to fatigue. These muscles perform activities such as jumping and coughing.

Chronic inflammatory states such as chronic obstructive pulmonary disease (COPD) can profoundly affect skeletal muscle function.[6–9] This is related to systemic inflammatory mediators that are persistently elevated in these chronic disease states and to various other physiologic and comorbid effects (Table 2).

Systemic inflammatory mediators accelerate muscle-protein turnover through ubiquitins.[10–16] This leads to loss of muscle mass and the clinical appearance of "muscle wasting."[6–9,17,18] Chronic inflammation also increases muscle oxidative stress and increases reactive oxygen species, which directly damage muscle proteins and impair their function.[19–21] Additionally, during muscle-fatigue recovery, an ischemia reperfusion injury mediated through additional reactive oxygen species may also develop in the muscles, which further impairs muscle function.[19–21]

Patients with COPD are also malnourished, and weight loss occurs in approximately 30% of COPD out-patients[22–27] because of decreased caloric 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 used for fuel (catabolism). This is particularly true of the sarcomere 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.[28–32]

In COPD, hypoxemia is common. Hypoxemia leads to lower O_2 content in the blood and can elevate pulmonary vascular resistance, creating pulmonary arterial hypertension and consequent right-heart failure.[33–37] The resulting reduced cardiac output, coupled with the low oxygen content, reduces oxygen delivery to all the organs of the body, including skeletal muscle. Interestingly, because the work of breathing (load) on the diaphragm is substantially increased in COPD (see below), the respiratory-muscles "steal" blood away from skeletal muscles, which further compromises systemic muscle function.[38,39]

Systemic inflammation may also impair the oxygen transport through the cytoplasm and into the mitochondria and directly impair mitochondrial oxygen utilization,[33–36,40–42] which produces muscle-cell hypoxia and thus a conversion to anaerobic metabolism at low levels of exercise. This leads to lactate accumulation and earlier fatigability of the muscles.[28,43–46]

Hypercarbia is also a common occurrence in COPD, as the central respiratory controllers in the brainstem reduce ventilation to "protect" overloaded ventilatory muscles.[47] Some data suggest that a mild respiratory acidosis might attenuate some forms of cellular injury,[48] but this has not been well studied in skeletal muscle. In contrast, an acute severe respiratory acidosis, as might occur during a COPD exacerbation, can impair muscle enzyme activity and function.[49–51]

COPD patients often use corticosteroids. As much as 10% of the COPD population may be on long-term oral steroids, and the majority of patients with moderately severe COPD take inhaled corticosteroids.[52] COPD patients also take corticosteroids during COPD 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.[53–55]

Finally, COPD often coexists with other chronic diseases that can, by 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 can also impair muscle function. Diabetes and altered glucose metabolism can also contribute to muscle dysfunction. The aging process also impacts muscle function, as there is a normal age-related decline in muscle mass.[56,57]

Respiratory Versus Other Skeletal Muscle Function in COPD

Respiratory muscles in COPD have considerably different loading patterns than other skeletal muscles. In limb muscles, especially lower-extremity limb muscles, muscle weakness and respiratory insufficiency lead to inactivity and chronic underloading of the muscles. In contrast, respiratory muscles have to deal with an increased work to breathe and are thus chronically overloaded. These different loading patterns produce profoundly different biochemical and structural effects over time, as well as affecting the pattern of regional blood flow.

In limb muscles, underloading leads to less muscle mass, especially decreases in the type I fibers.[58–63] This reduces the oxidative capacity of the muscles and makes them more prone to fatigue. There is also less capillary density with underloading, which leads to reduced regional blood flow delivery, nutrient delivery, and waste removal. Unloading also leads to less glutathione and other defenses against oxidative stress.

In COPD the high inspiratory (and expiratory) airway resistance can dramatically increase the pressure requirements for airflow and thus dramatically increase the work of breathing.[64,65] To put numbers on this, consider that the normal work of breathing 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-fold or even 10-fold.[65]

Compounding the effects of excessive loading is the fact that the work pattern is of an inefficient type, in that high pressure is required for a given movement or displacement of the sarcomeres.[65] This "isometric" type work is far less oxygen-efficient than the low-pressure work pattern of normal breathing, and it predisposes to early fatigue. Respiratory muscles are also compromised by hyperinflation produced by airway collapse and low elastic recoil.[66,67] As the hyperinflation increases, the diaphragm is pushed downward and flattens, which shortens the resting length of the diaphragm, producing a substantial mechanical disadvantage and loss of tension-generation capabilities.

It is important to note that respiratory muscles have adaptive capabilities to deal with the chronically elevated work load and distorted diaphragm geometry.[68,69] Structurally, diaphragmatic sarcomeres become shorter 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 these increase endurance capabilities. Capillary density is also increased, which leads to the respiratory muscles "stealing" blood flow.[38,70,71] However, along with this is a small decrease in type II fibers, which can lead to less force-generation capability by the diaphragm.[70] Also observed in diaphragm biopsies of hyperinflated COPD patients are structural changes in titins and nebulins, which are large muscle proteins that stabilize the actin and myosin contractile proteins.[72]

An important question is whether respiratory muscles in fact fatigue. Fatigue, by definition, is the loss of muscle contractile capabilities induced by heavy loading and recoverable by rest.[73] Fatigue must be distinguished from reduced muscle capability and from muscle injury that reduces function.[74] Fatigue is of 2 types: peripheral (direct muscle failure) and central (either a reduction in neural stimulation or an increase in inhibitor neuron activity). Central fatigue is sometimes thought of as a "protective" mechanism that prevents muscles from being injured under overload conditions.[75] Interestingly, endorphins may play an important role in reducing 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.[76] 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:

$$\text{PTI} = P_{di}/P_{di\text{-max}} \times T_I/T_{tot}$$

in which PTI is the pressure-time index, P_{di} is the diaphragm pressure during the breath, $P_{di\text{-max}}$ is the maximum diaphragm pressure possible, and T_I/T_{tot} is the ratio of the inspiratory time to the total-breathing-cycle time (ie, duty cycle).[77] When the PTI of the respiratory muscles is ≥ 0.15, fatigue will occur (Fig. 1).

What Effect Do These Muscle Abnormalities Have on Function (Exercise Tolerance) in COPD?

Muscle dysfunction affects exercise tolerance in several ways in COPD patients. Respiratory muscle impairment
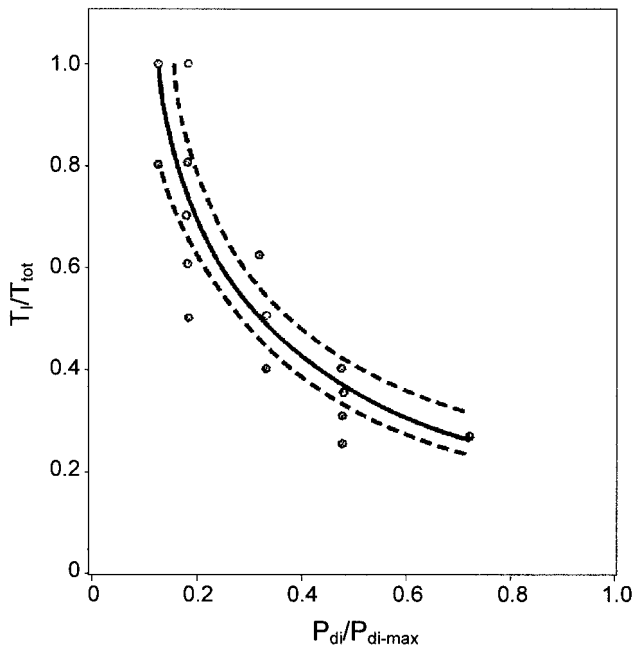
Fig. 1. Relationship between duty cycle (ratio of inspiratory time to total-breathing-cycle time [T_I/T_{tot}]) and critical transdiaphragmatic pressure (ratio of the diaphragm pressure to the maximum diaphragm pressure [P_{di}/P_{di-max}]) and development of respiratory muscle fatigue. The dashed lines indicate the 95% confidence intervals for the critical P_{di}/P_{di-max}. Fatigue develops with breathing patterns that fall to the right of the curve, but not for those that fall 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 above 0.15 fall to the right of the curve and predict fatigue. (From Reference 77, with permission.)
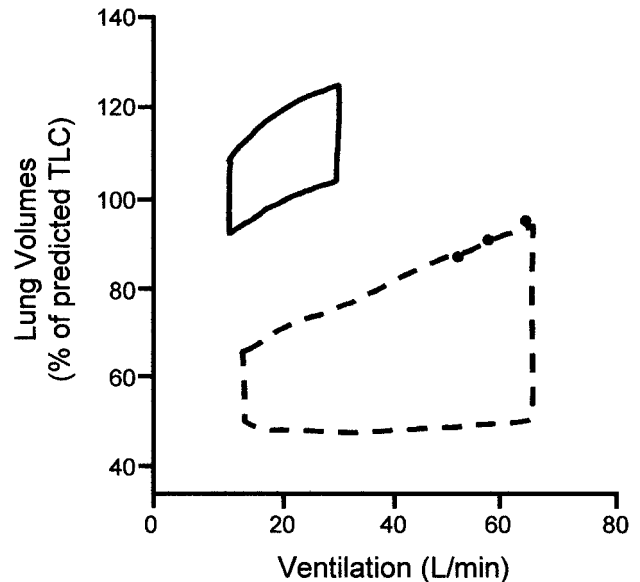

Fig. 2. Lung volume (percent of predicted total lung capacity [TLC]) in normal lungs (broken line) versus the lungs of a patient with chronic obstructive pulmonary disease (solid line). As ventilation increases in the normal lungs (as with exercise), the tidal volume (lung-volume change) increases, but the end-expiratory volume remains unchanged. In contrast, the lungs of the patient with chronic obstructive pulmonary disease have 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. (From Reference 67, with permission.)

directly limits exercise ventilation capability.[6,64,78] In addition, exercise-induced wasted ventilation and early lactic acidosis in these patients further increases the exercise ventilation requirement and thus further worsens the load/capability relationship in the respiratory muscles.[45] Importantly, the lung hyperinflation in COPD patients increases with exercise, which further shortens the diaphragm and further compromises its force-generation capability during exercise (Fig. 2).[67] In the limb muscles, the structural and metabolic abnormalities noted above lead to early lactic acidosis and task failure with exercise.[58–61,79]

In a large sample of COPD patients undergoing pulmonary rehabilitation, we found that 25% of this population had primary ventilatory load/capability limitations to exercise (ie, the ratio of required exercise ventilation to maximum voluntary ventilation exceeded 0.8).[80] Another 18% of this population was limited by gas exchange (oxygen saturation [measured via blood-gas analysis or pulse oximetry] fell below 88%), whereas 25% were primarily limited by the cardiovascular system (maximum heart rate was achieved). This cardiovascular group probably represents both patients with true cardiac dysfunction (espe-

cially right-ventricular dysfunction) and those with simple skeletal-muscle deconditioning. Interestingly, 20% of our total COPD population did not appear limited by any of these factors yet still complained of dyspnea and/or fatigue that prevented further exercise. One might speculate that peripheral muscle factors might be playing a role in limiting many of these patients. Taken together, these data suggest that skeletal-muscle (both respiratory and limb) dysfunction contribute to substantial exercise limitation in the majority of COPD patients.

Approaches to Treatment

There are a number of ways to address both the respiratory and the systemic muscle dysfunction associated with COPD. Appropriate bronchodilator therapy reduces inspiratory (and expiratory) loading and air trapping, which increases ventilatory capability, improves oxygenation, and reduces load on the respiratory muscles.

Exercise therapy is clearly beneficial in patients with COPD.[45,81–85] Lower-limb muscle exercise in particular has been shown in numerous studies and several meta-analyses to increase muscle mass and increase functional performance (Fig. 3). Both strength and endurance train-
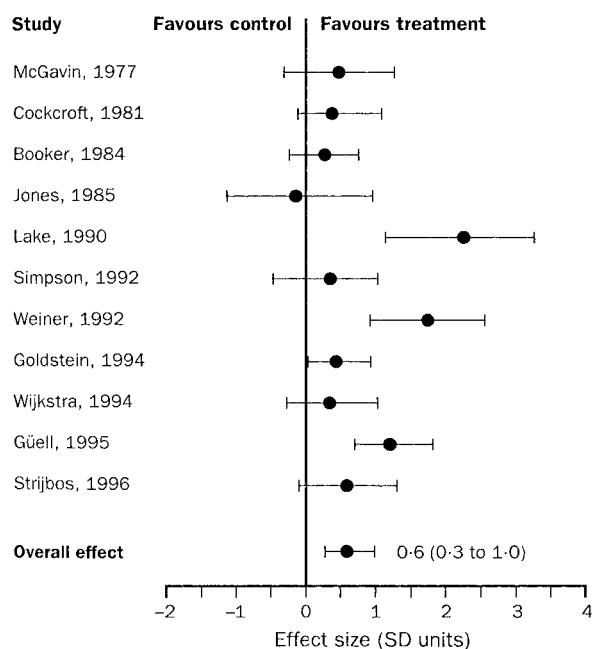
Fig. 3. A summary and meta-analysis of trials that examined functional changes after a formal exercise-training program for patients with chronic obstructive pulmonary disease. The study results are represented by the black dots (mean values) and the horizontal bars (95% confidence intervals). Studies with results to the right of zero represent significant benefits from the exercise-training program. This meta-analysis indicates significant functional benefit from the exercise intervention. (From Reference 82, with permission.)

ing are effective, but have different effects.[86–89] Strength training involves high-pressure loading of the muscles, using such techniques as weight lifting or other "isometric" procedures. These tend to build more sarcomeres, especially type II fibers. In contrast, endurance training involves motion loading of the muscles, using such techniques as cycling or walking. These tend to build oxidative and endurance capabilities in muscles, especially in type I fibers. In general, the higher the exercise training load, the better is the effect (Fig. 4).[45] This is the rationale for the recommendation that patients exercise as close to their maximum heart rate as possible during rehabilitation sessions.[81]

Exercising (and thereby possibly conditioning or training) respiratory muscles specifically is less well understood. Leith and Bradley[87] found that isocapnic hyperventilation (motion work) can improve the maximum voluntary ventilation but not the maximum strength. In contrast, resistive breathing (pressure work) could improve maximum strength but not maximum voluntary ventilation. It would therefore stand to reason that increasing ventilation with increasing limb exercise should improve diaphragmatic endurance capabilities, although few data exist to support this concept. Indeed, significant maximum voluntary ven-

tilation increases rarely occur after pulmonary rehabilitation, even though ventilatory efficiency is improved.[83] Perhaps the exercise ventilation these patients can generate during limb exercise is simply insufficient to endurance condition or train the respiratory muscles.

The data supporting strength training of respiratory muscles using periods of high-resistive breathing are mixed.[81,83] On one hand, respiratory muscles are chronically exposed to high-resistive loads imposed by airway obstruction, so further pressure loading might not be expected to provide benefit. There are, however, clinical reports that the resistive breathing reduces dyspnea and improves respiratory muscle strength in some (but not all) patients.[83] Current recommendations suggest limiting respiratory muscle strength training to only those patients with documented respiratory muscle weakness.[81]

The role of oxygen in hypoxemic COPD patients seems well established, as oxygen improves outcomes and reduces mortality[90] and improves exercise performance in hypoxemic patients.[91–93] On the other hand, few data indicate that oxygen improves long-term training effects in these patients, and there are no data on whether oxygen in between the exercise periods benefits nonresting hypoxemic patients. One interesting note about oxygen is that there are several reports that supplemental oxygen during exercise, even in only borderline-hypoxemic patients, seems to reduce exercise ventilation (presumably through reduced carotid-body output), which may allow a longer or a higher training period in patients who are otherwise limited by ventilation.[94]

There are 2 other approaches to building muscle mass: nutrition and hormonal therapy. The American Thoracic Society has recommended that caloric supplementation intervention should be considered for the following conditions: a body-mass index < 21 kg/m^2, involuntary weight loss of $> 10\%$ during the last 6 months or $> 5\%$ in the past month, or depletion of lean body mass.[81] Caloric support should be based on activity level and the goal of restoring body weight.[95–98] High-energy supplements may also be helpful. Adequate protein is essential to stimulate muscle protein synthesis. Various hormonal approaches have also been used to build muscle mass,[99–103] including anabolic steroids and growth hormones, and these are often used in conjunction with exercise. In the short-term, both drug classes increase muscle mass and exercise capability, but there are important adverse effects (eg, fluid retention and altered glucose metabolism) and long-term outcomes are not known. The progestational agent megestterol acetate stimulates appetite and weight gain in COPD patients, but much of this weight gain is fat, and long-term functional outcome is unclear.

There are 2 surgical approaches to COPD: lung-volume-reduction surgery (LVRS), and lung transplantation. LVRS reduces air trapping and improves ventilatory ca-
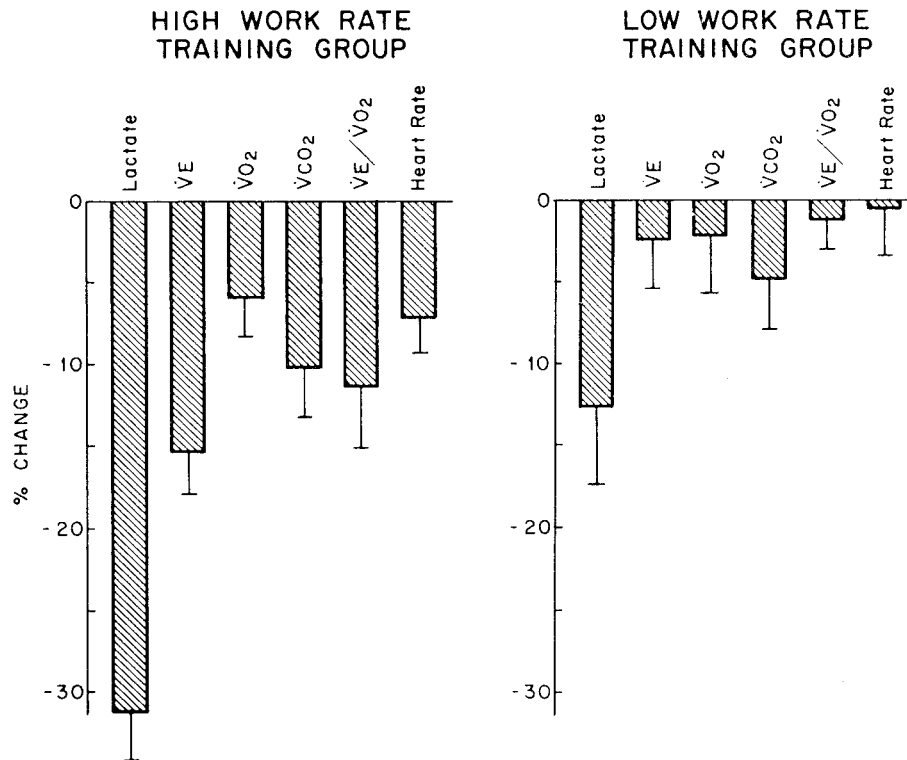
Fig. 4. Changes in exercise-test results after exercise rehabilitation in patients with chronic obstructive pulmonary disease. The exercise tests were performed before and after the exercise rehabilitation, using the same exercise work load, so decreases represent improved function (less lactate development), lower ventilation requirement, lower oxygen need, lower carbon-dioxide production, and lower heart-rate requirement. Patients in the left panel underwent a high-intensity exercise program; patients in the right panel underwent a less intense exercise program. Though both the exercise programs improved function, the high-intensity program produced a greater effect. (From Reference 45, with permission.)

pability and exercise performance in selected patients with heterogeneous emphysema and who have large, over-inflated lung regions that are amenable to resection.[104] Interestingly, all the studies of LVRS have been done in conjunction with rehabilitation programs that emphasize aerobic training. Lung transplantation for COPD removes the chronic inflammatory state, reduces air trapping, and improves gas exchange. All of these should enhance skeletal muscle recovery and conditioning if aerobic training is part of the postoperative management. However, lung-transplant patients must stay on long-term immunosuppression therapy and are at risk for repeated infections. What role these may have in skeletal muscle function is largely unknown.

Summary

Skeletal muscle abnormalities are profound in patients with chronic inflammatory states, including COPD. These are caused by direct inflammatory-mediator effects on muscle function, as well as malnutrition, drugs, and other co-morbid states. In the patient with COPD, skeletal muscle dysfunction is further worsened by blood-gas abnormali-

ties and compromised oxygen delivery from right-heart dysfunction. In these patients, the chronic overloading of respiratory muscles leads to a risk of fatigue at low levels of exercise, and this is made worse by hyperinflation. Importantly, the overloaded respiratory muscles can structurally and metabolically adapt to a certain extent to restore some functional capabilities. In the limb muscles of COPD patients, chronic underloading leads to muscle atrophy. Treatment is aimed at optimizing lung function, nutritional repletion, oxygen therapy in the hypoxemic patient, and aerobic exercise training. LVRS may help with the hyperinflation effects and improve gas exchange. Lung transplantation likewise should improve respiratory function and allow more aerobic training, although the effects of long-term immunosuppression and recurrent infection are unknown.

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Discussion

Mehta: I am interested in patients with COPD who present with acute respiratory failure. You said that controlled ventilation is probably not the right approach, because it could lead to further atrophy of the respiratory muscles. You want to challenge the respiratory muscles a bit, without overloading them, so how do you titrate ventilator support in the absence of esophageal-pressure measurements?

MacIntyre: It's a fascinating question. I struggle back and forth as to what to do with an acutely overloaded respiratory muscle system, and I'm not yet sure what the best way is. We tend to put them on a high level of support initially—sometimes controlled mechanical ventilation—the idea being that these muscles have really been beaten and battered and we need to unload them. So I start with a fairly high level of support—though I wouldn't use intermittent mandatory ventilation on them—a high level of either volume- or pressure-assist con-

trol. And I'd let them try to trigger as much as possible, if for no other reason than to keep the muscles stimulated and performing at least *some* contraction.

After the first 24 to 48 hours, and with stabilization of the lung injury, I think providing some additional loading makes some sense—ideally a near-normal kind of workload is probably the right way to go. Now the obvious question is, how in the heck do you figure out what a near-normal workload is? You can insert an esophageal balloon and measure the patient work,

as you and probably others here have done. But I think that you can do it without such a monitor, by simply looking at the patient. The patient's own sensors, which Josh Benditt described,[1] are actually pretty good load indicators.

If you get the patient on a level of ventilatory support where they're comfortable, they're triggering and in synchrony with the ventilator, the respiratory rate is not particularly high, they're not diaphoretic, and they're not fighting the ventilator, then that's probably where you want to be. I'm sorry I have to leave this conference early and will miss the discussion about trying to gradually reduce support and increase loading versus simply leaving the patient alone on a comfortable interactive ventilatory support mode (weaning versus not-weaning).

I admit that I used to be a real "weaner" (some say I still am); I was turning the knobs daily—hourly even!—trying to get this or that level down. As I get older and more crotchety, I've come to believe that maybe all this knob-twirling really isn't worth the trouble. The available evidence does not support knob-twirling over simple stable ventilator settings and daily spontaneous breathing trials, in terms of improving outcomes. Yes, I want to put them on an assisted mode. Yes, I want them to be doing *something*. But rather than trying to adjust that load on an hourly or some other regular basis, maybe you should just leave them alone and do a daily spontaneous breathing trial to see where they are.

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Hill: Sounds like you're describing noninvasive ventilation.

Mehta: Can we talk more about that first day when the patient comes in with acute respiratory failure? The diaphragm has a very high oxygen consumption, and often in respiratory failure there is an ATP [adenosine triphosphate] or oxygen deficit. I've read that, not so much in COPD but in other conditions, it can take 24 to 48 hours to restore the ATP reserves, so we're doing them a disservice if we push them very hard at the beginning. How do you decide clinically how to ventilate them?

MacIntyre: Geeta, you're exactly right. I think a high level of support, particularly over the first 24 to 48 hours, is important. But I don't think controlled ventilation is where we want to be. Perhaps that's more opinion than evidence-based, but I like the idea that the patient is still at least getting a neural stimulus on the diaphragm, and having some contractions, even though it's a very unloaded contraction. Amal, please chirp in here, because I don't want to be blindsided by your paper tomorrow.

Jubran: I agree with Neil that patients should not receive controlled ventilation.

MacIntyre: Yeah!

Jubran: Tomorrow I will present data from animal studies that show that ventilator-induced diaphragmatic dysfunction occurs during controlled mechanical ventilation. So I agree with Neil that we should use an assisted ventilation mode, even during the first 24 hours of initiating ventilation. You want the patient to trigger the ventilator; you want them to do a little bit of work.

To follow up on what Neil said, that he's not a "weaner," I disagree with that statement. Neil is still "weaning" patients from the ventilator. Daily spontaneous breathing trials are a form of weaning. The purpose of a weaning trial is to reload the respiratory muscles for a brief period, as a way of reconditioning the respiratory muscles. Breathing through a T-piece for an hour or two is still an attempt to recondition the muscles.

MacIntyre: You're right, although I look at the spontaneous breathing trial more as an assessment than as a weaning technique. Maybe I'm just arguing semantics here. What I was trying to get across is that when I used to make rounds and I saw a patient on pressure-support of, say, 16 cm H_2O, I would say, "Let's go to 14 cm H_2O." Today I'm not sure that's worth the trouble. I think you need to assess the patient every day, but in between the assessments I think it makes more sense to leave them where they are, with some comfortable, near-normal kind of load pattern.

Jubran: The problem is that we don't know what is the ideal load for a patient on the ventilator in the intensive care unit. What Neil is suggesting is probably all we can do at this stage; that is, "eyeball" the patient and see how much work they appear to be doing. Alternatively, we can insert an esophageal catheter and measure patient effort.

The problem is that when we get a number for pressure-time product, our index of patient effort, we don't know how to interpret it. We can compare it to that of a normal person. For example, we know that a pressure-time product of 100 cm $H_2O \cdot$ s/L is a value reported for normals. But is that the target we should aim for in patients? Or should we aim for a lower or higher value? Is the target different for patients with COPD than for those with acute respiratory distress syndrome? We simply don't know.

On another subject, regarding lung-volume-reduction surgery [LVRS]? Were you surprised by the negative results of the NETT [National Emphysema Treatment Trial], that mortality did not decrease with LVRS?[1]

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MacIntyre: I should ask Josh Benditt for help on this, since he was also one of the investigators, along with my institution. Now that it's all said and done, I'm not surprised. There was a subgroup of patients who did extremely well with LVRS. These were patients with very obvious heterogeneous emphysema, primarily if it was upper-lobe predominant, and who were very disabled. And that would make some sense. These are horribly hyperinflated patients, and LVRS relieves the over-inflation, which puts the diaphragm in a better position. And, sure enough, those patients' mortality, exercise tolerance, and quality of life were improved by LVRS.

Now, having said that, those patients were a small minority of the patients who were studied, and you're quite right that most of the patients did not see those kinds of results. Indeed, in some patient groups, LVRS actually gave worse results, which, in the middle of the trial, prompted taking out those patients from being further randomized. These were the patients with homogenous emphysema and really bad lung function.

LVRS is not for everybody. But I think now that if we go back and think about this, we probably saw what should have been expected. The patients who should get LVRS are those with grossly regional over-inflation that's easy to get at surgically, and the potential to reduce the over-inflation. Josh, do you have anything to add to that?

Benditt: A recent paper by Naunheim et al[1] found that at 5 years the mortality for the overall group was actually lower in the LVRS group. That is, as time went on, more people

in the medical arm died, so at 5 years the study is now apparently positive. But, as Neil said, there is a subgroup of patients who does much better. I think the reason for that is that there are a lot of effects from LVRS. It would be great if we could just reduce the volume, and have the effect on the breathing muscles, which I think there is, without affecting the pulmonary vasculature or other parts of lung function, because I think that it has a lot of effects, some of which are not necessarily good. For instance, there are people who develop hypertension after LVRS.

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Jubran: For whom would you recommend surgery?

Benditt: We have a little group of surgeons and pulmonologists who review each case that comes up for that. We suggest surgery for those individuals with upper lobe emphysema and low exercise capacity. This was the subgroup that showed clear benefit. We certainly have not been recommending it for people with homogeneous disease or very severe disease. And with those other people, who are kind of in the middle, we have not been pushing them in any way, and actually try to avoid it.

Deem: Neil, I was interested in your comment on how systemic inflammation may affect skeletal muscle in COPD, because corticosteroids have similar effects on muscle proteolysis. Is it possible to separate out the effects of inflammation from corticosteroids in those patients?

MacIntyre: I'm not sure it is possible, because these patients are almost universally "contaminated" with steroid therapy, so sorting those out could be quite problematic.

Deem: Are there any animal-model studies that help?

MacIntyre: Animal models of emphysema are always kind of short-term things. They throw elastase down the trachea, create an injury, and then study them over a matter of weeks and months. Yes, you can see muscle effects of the systemic inflammation independent of the corticosteroids, but it's hard to sort those out.[1]

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Mehta: What's the drive for this chronic inflammatory state? Is it hypoxemia, hypercapnia? Can you distinguish between those 2 populations? Is one more inflammatory than the other? Is it intercellular acidosis?

MacIntyre: Well, you're getting into the pathogenesis of COPD. It's a chronic inflammatory state of the airways, potentiated by external stimuli (ie, tobacco smoke), repeated infections, perhaps environmental factors involving multiple cells, the CD-8 family of lymphocytes, macrophages, neutrophils. I'm not sure I can separate all those things out. Rajiv, you've done a lot of work in this area.

Rajiv Dhand: We do studies on elastase-induced emphysema, and one of the things that we are really intrigued by is that we give a single instillation of elastase, and then we sacrifice the animals after 7 days, 14 days, or 21 days. We've found that there's a progressive increase in the amount of emphysema that's produced, so a single instillation leads to a sort of repetitive injury, and it's very intriguing what is

the source of that injury. One of the possibilities is that this is the release of elastin fragments that causes immune-mediated injury to the lung.

Brown: Neil, with regard to weaning, I think you made one error. You're not getting older and more crotchety, you're getting older and wiser!

MacIntyre: I can only hope!

Brown: With regard to diaphragm dysfunction in these various disorders, another approach to take would be to ask the question, how much stimulation does the diaphragm require to avoid atrophy? We have published one sort of anecdotal paper in that regard.[1]

We had a patient years ago who had bilateral diaphragm dysfunction from C1–C2 neurologically complete tetraplegia, and he had bilateral phrenic pacemakers, one of which got infected and had to be removed. The red tape at the hospital led to 3 months before a new pacemaker could be obtained for him, and during that 3 months we stimulated the intact hemidiaphragm for 30 minutes a day, with a phrenic-nerve pacemaker. Then after 3 months, when the new pacemakers were put in, we monitored the tidal volume and diaphragm thickness on the side that had been stimulated for 30 minutes a day, and on the side that had not been stimulated at all for 3 months.

What we found was the typical outcome—that with retraining the diaphragm that had not been stimulated developed larger and larger and larger tidal volumes at a given stimulus intensity, and then reached a plateau. That diaphragm hypertrophied. The evidence for that was that it got thicker and thicker; we were able to estimate its thickness with ultrasonographic techniques. On the other hand, the diaphragm that had been stimulated for only 30 minutes a day, albeit via electrophrenic stimulation, probably engaging all of the fibers, did not increase in thickness during the period

of retraining of the other diaphragm, and the tidal volumes remained flat, no matter what stimulus we used.

So it appeared that a mere 30 minutes a day of stimulation preserved the function of that hemidiaphragm. It makes you wonder whether diaphragm atrophy occurs in our intensive-care-unit patients. We know that even when they're ventilated they contract their diaphragms, and it appears that it doesn't take much to preserve diaphragmatic function.

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MacIntyre: I would agree that it may not be very much, but it's gotta be something. If you put them down completely, so that they're not doing anything, that could lead to diaphragm dysfunction. I think Amal Jubran's going to discuss that issue more tomorrow.

Brown: I agree completely. I just suspect that it doesn't take much.

MacIntyre: Doesn't take much; that may be true.

Panitch: In infant and toddler pediatrics, the analogy to COPD is bronchopulmonary dysplasia. We frequently take care of infants who require prolonged mechanical ventilatory support, and our practice, typically, is to give them at least a low rate of mandatory breaths and allow them to breathe spontaneously with pressure-support. And then in the process of liberating them from support, we use longer and longer periods of time off mechanical ventilation. In addition to worrying about gas exchange, we also have to worry about growth and development in these children, and that often dictates the speed with which we can withdraw support.

It's always been my concept, and my argument to the house staff, that we need not necessarily wean levels of pressure support—that, in fact, we're using those periods that we euphemistically refer to as "sprints" as exercise periods for those children, and then allow them to rest once they're back on ventilatory support. Am I totally off the wall?

MacIntyre: How long are your sprints?

Panitch: They can go hours.

MacIntyre: I said I'm no longer a "weaner" in the intensive care unit, but I want to differentiate the intensive-care-unit population from the patients who require prolonged mechanical ventilation and patients who require more than 21 days of support. The patients might be quite different in the world of long-term assisted care and long-term acute care facilities, where patients are on ventilators for weeks or months. In that population—though it hasn't been studied in a randomized controlled trial—the results from multiple observational trials argue strongly that the kind of weaning strategy you just mentioned makes sense. Almost universally, those clinicians use progressive reduction of support, at least initially. However, almost every one of them, when they get to a *certain* level of support—be it 30% or 50% of total support—they'll start doing spontaneous breathing trials for ventilator-discontinuation assessment. So maybe there is a role for that kind of weaning with more long-term patients.[1]

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Lechtzin: I have a question about peripheral muscle involvement. I've seen literature[1–3] on relatively young patients with cystic fibrosis who have reasonably good lung function, who are still active (compared to age-matched controls); they have fairly pronounced arm and leg weakness, but still have preserved abdominal-muscle strength, presumably because they've had a daily cough all their lives and therefore use their abdominal muscles so much. I don't know if there's similar literature on COPD patients, but I wonder what implications this has for strength training in those patients, and should we be starting rehabilitation much earlier than we typically do with these patients?

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MacIntyre: If you're asking me whether rehabilitation should be done sooner rather than later, I would support "sooner" 100%. I think it's silly to wait for somebody to be horribly disabled before they finally go into a rehabilitation program. The time to start is at the earliest stages of functional impairment. What you said about cough is intriguing. I wasn't aware of that. That's quite interesting, and it makes sense.

Panitch: Hayot et al[1] looked at the tension-time index of children with cystic fibrosis who had mild-to-moderate obstructive disease but were clearly abnormal, compared with healthy controls. It seemed that the diaphragm may not be working as well, even in children with mild-to-moderate obstructive disease.

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Hill: Regarding rehabilitation and what limits exercise capacity, you showed some data that suggested there are probably several mechanisms that contribute to functional-exercise-capacity limitation in these patients, and it probably varies from patient to patient, and maybe over time within individual patients. Investigators have taken different approaches to how to deal with the respiratory-muscle contribution, and one, of course, is muscle training, and you showed some of that data. It doesn't look terribly helpful in improving function.

But another tack that you didn't mention was noninvasive ventilation, and there are a couple of studies, representing 2 different approaches; one was by Garrod et al[1] They used noninvasive ventilation just for 2 hours at night and found a significant improvement in exercise capacity, measured with the shuttle walk test. And the other approach is to use noninvasive ventilation during exercise.[2] The idea was that by permitting patients to exercise at a greater rate, noninvasive ventilation would enhance the training effect on peripheral muscles. What are your thoughts on these approaches?

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MacIntyre: Both of those concepts make some sense. The nocturnal strategy, however, is a little confusing to me. It is unclear whether unloading the muscles at night translates into an outcome benefit during the day, as you know better than any of us. Some studies suggest that can happen,[1] but what's sort of depressing is that in those studies the patients generally chose not to continue using the device at night. So whatever benefit they got wasn't enough for them to think that it was a good idea to continue.

Regarding exercising with the ventilator, I find that a very interesting idea. I showed data on using oxygen to reduce the ventilatory load. It would be logical to extrapolate that to a mechanical device that could somehow be rigged up to help you during your exercise. You could hardly do it walking, but perhaps during cycling or on a treadmill. It makes some sense.

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