

# COPD and muscle loss: is blood flow restriction a potential treatment?

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Chronic obstructive pulmonary disease (COPD) is one of the leading causes of death in the United States and results in a significant reduction in lung function and exercise tolerance. In addition, there is a significant decline in muscle mass and strength in these individuals. Unfortunately, other comorbidities associated with this disease such as osteoporosis, osteoarthritis and obesity may prevent them from exercising at sufficiently high loads to promote muscle hypertrophy. Also, acute exacerbations may prevent them from performing exercise at all.

**Objectives:** This brief review will discuss the potential benefits of using blood flow restriction (BFR) when combined with walking, resistance training and electrical stimulation in COPD patients and possible safety concerns.

**Design and Methods:** Non-systematic review.

**Results:** BFR improves muscle size and function when combined with low-intensity walking or low-load resistance training. This treatment appears to be safe and has been used by many different populations including individuals with ischaemic heart disease. For COPD patients who are contraindicated to perform exercise, a potential treatment may be to combine neuromuscular electrical stimulation with BFR.

**Conclusions:** BFR appears to be a potential treatment for increasing strength and muscle mass for COPD patients when high-intensity exercise may not be tolerated. In addition, BFR may provide benefits for COPD patients who are unable to exercise by combining it with neuromuscular electrical stimulation.

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**Key words:** electrical stimulation ■ muscle hypertrophy ■ lung disease ■ pulmonary rehabilitation

## Introduction

Chronic obstructive pulmonary disease (COPD) is currently the fourth leading cause of death in the United States and its prevalence around the world ranges from 4% in Hanover, Germany to 22% in Cape Town, South Africa.<sup>1</sup> COPD is characterized by persistent decreased expiratory flow and dyspnea due to a remodeling of the small airways.<sup>2</sup> The exact cause of COPD is complex and involves both genetic susceptibility and environmental factors but risk factors include cigarette smoke, maternal smoking, secondhand smoke exposure, childhood asthma, childhood respiratory infections, tuberculosis, outdoor air pollution, and occupational exposure to workplace irritants.<sup>3</sup> Not only is this disease associated with impaired lung function, but also comorbidities such as cardiovascular disease, obesity, osteoporosis and osteoarthritis have been associated with it.<sup>4</sup>

One consequence of COPD is a significant decline in muscular strength and muscle mass.<sup>5</sup> COPD patients have lower levels of upper leg strength and muscle cross-sectional area (CSA) compared to age-matched individuals.<sup>6,7</sup> The decline in strength is particularly concerning as muscular weakness is correlated with decreased exercise performance and mortality in COPD patients.<sup>8,9</sup> Furthermore, a decreased

proportion of type I fibers and a decrease in CSA of both Type I, IIA, and IIB fibers are found in COPD patients compared to age-matched healthy individuals.<sup>10</sup> Several factors may explain the decline in muscle mass in this population such as increased oxidative stress, systemic inflammation, corticosteroid treatment, hypoxia and physical inactivity levels.<sup>5</sup> However, COPD may take many years to develop before symptoms appear. Because of this, the age-related loss of muscle mass and function, also known as sarcopenia, may contribute to the loss of muscle mass/function in addition to the effects that COPD has on muscle mass. Therefore, the purpose of this short review will be to briefly discuss how traditional forms of exercise improve muscle size and function in COPD patients, and the potential use of combining BFR with exercise or electrical stimulation to enhance muscle hypertrophy in this population.

## Exercise or non-exercise treatment for patients with COPD

### Exercise Treatments

In order to overcome the loss of muscle mass and strength, several strategies have been used. One strategy has been continuous aerobic exercise. For example, continuous aerobic exercise at 50-70% of maximal power output increased peak

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oxygen uptake by 11% and type I and IIa fiber CSA by 21-31% after 12 weeks of training.<sup>10</sup> Another study found that after training for 10 weeks at 75% peak work rate, type I, type IIa and type IIb fibers CSA significantly increased by 10%, 10%, and 13%.<sup>11</sup> Finally, Bernard et al.<sup>12</sup> found a significant increase in quadriceps strength (8%) but not thigh muscle CSA (3%) after performing 12 weeks of aerobic training; however, combining aerobic training with strength training increased quadriceps strength significantly (20%) and thigh CSA (8%) more than aerobic only training. Not surprisingly, another study found that strength significantly increased more after strength training than endurance training in COPD patients.<sup>13</sup> Therefore, high-intensity aerobic training may improve strength and possibly muscle fiber size but to a lesser degree than resistance training. Unfortunately, some COPD patients cannot sustain continuous endurance exercise at high enough intensities to achieve these benefits due to several reasons. For example, earlier onset lactic acidosis, dynamic hyperinflation of the lungs, increased pulmonary vascular resistance and decreased right ventricular stroke volume can lead to earlier onset of muscle fatigue or exercise intolerance.<sup>14</sup>

Several studies have investigated the benefits of resistance training alone on muscular adaptations in COPD patients. Kongsgaard et al.<sup>15</sup> had COPD patients perform high-intensity (80% 1RM) lower body exercises for 12 weeks and found that both strength and mid-thigh quadriceps CSA increased while in the control group both actually declined. Another study examined the effects of only seven resistance training sessions (70% 1RM) and observed an increase in quadriceps strength and a decrease in myostatin mRNA expression.<sup>16</sup> The ability to increase muscle mass and strength in COPD patients may be similar to healthy adults. To illustrate, Constantin et al.<sup>17</sup> found that thigh lean mass and strength increased similarly to healthy subjects after performing 8 weeks of maximal isokinetic knee extensions. Furthermore, resistance training has been shown to not only increase strength but also exercise capacity.<sup>18</sup> The current evidence suggests that high-intensity resistance training can be an important training mechanism for COPD patients to enhance muscle hypertrophy and strength when it is well tolerated by the individual. However, it is less clear whether resistance training also improves functional and maximal exercise capacity in COPD patients.<sup>19</sup> Several concerns with resistance training may be that some COPD patients may not be able to perform such high-intensity resistance exercise due to an increased risk of muscle tears from chronic steroid treatment.<sup>14</sup> Furthermore, those COPD patients who have osteoporosis may be contraindicated to perform high-intensity resistance exercise due to the high amount of stress placed on the joints.

### **Non-exercise treatment**

A major advantage of a non-exercise treatment for COPD patients is that it does not produce any ventilatory stress during passive exercise. Neuromuscular electrical stimulation is a non-exercise treatment that has potential to increase strength and potentially muscle mass in COPD patients. When using electrical stimulation in rats, intracellular signaling pathways

associated with muscle hypertrophy were activated, and significant increases in muscle mass and myofibrillar protein were found.<sup>20</sup> In humans, Chaplin et al.<sup>21</sup> found that electrically stimulating the quadriceps of hospitalized COPD patients for 30 minutes a day improved isometric quadriceps strength. In another study, hospitalized COPD patients had one leg randomly assigned to neuromuscular electrical stimulation and the other leg assigned as the control. After 14 days, the control leg had a decrease in strength by 3 N but the electrically stimulated leg increased strength by 19 N.<sup>22</sup> One study also found that quadriceps strength, mid-thigh CSA and calf muscle CSA significantly increased after 6 weeks of neuromuscular electrical stimulation.<sup>23</sup> These increases in muscle CSA, although significant, were only 6%. Neuromuscular electrical stimulation could be a potential non-exercise treatment for COPD patients to improve strength and potentially muscle size without substantially increasing the stress on the respiratory system. However, the increases in muscle size and strength may not be very large. Therefore, because of a limited number of studies and the small changes, more evidence is needed before a definitive conclusion is drawn.

Due to acute exacerbations, limited physical ability or contraindications to performing high-intensity exercise, some patients with COPD may not be able to perform high-load exercise to induce muscle hypertrophy. In addition, some of the most common comorbidities associated with COPD are osteoarthritis and osteoporosis which may contraindicate some individuals from using high-intensity resistance training. One potential alternative to traditional forms of exercise may be blood flow restriction (BFR). BFR can be used without exercise to attenuate muscle atrophy and can be used with low-intensity or low-load exercise to significantly increase muscle size and strength. Therefore, it could be a major advantage for COPD patients who cannot handle the high-intensity or high-load exercise.

### **Blood flow restriction and COPD**

The novelty of BFR comes from the fact that significant muscle hypertrophy and strength gains are found when using it with low intensities or low loads.<sup>24</sup> In addition, in the absence of exercise it can attenuate muscle loss.<sup>25</sup> Both younger and older individuals have benefited from this technique as well as those recovering from injury<sup>25-27</sup>. Although few clinical populations have used this technique, it appears that it could be an alternative treatment for these individuals.<sup>28</sup> The exact mechanism by which BFR enhances the increased muscle size and strength response to low-loads is not currently known. However, activation of the mechanistic target of rapamycin (mTORC1) and mitogen activated protein kinase (MAPK) signaling pathways occurs with BFR and these appear to be key players involved with muscle hypertrophy<sup>29</sup>. In addition, decreased myostatin mRNA expression<sup>30</sup>, downregulation of proteolytic transcripts<sup>31</sup>, and proliferation of satellite cells<sup>32</sup> occur with BFR. These events may be potentially activated through muscle cell swelling<sup>33</sup> or metabolite buildup in the restricted exercising limb<sup>34</sup>.

### Walking exercise with BFR

Increases in muscle size and strength are found when BFR is combined with low-intensity exercises such as walking. For instance, Abe et al.<sup>35</sup> found that muscle CSA and volume significantly increased by 4-7% and strength increased by 8-10% when walking (50 m/min) was combined with BFR. In addition, Ozaki et al.<sup>36</sup> found that older women who walked (45% heart rate reserve) with BFR for 10 weeks increased muscle CSA and volume by 3-4% and strength by 6-22%. Therefore, despite the low-intensities associated with walking, combining it with BFR improves muscle size and strength. This type of exercise may thus be advantageous for COPD patients who cannot perform intense aerobic exercise. However, the adaptations are considerably less for BFR combined with walking compared to BFR combined with resistance exercise.

### Resistance exercise with BFR

With regards to combining BFR with resistance exercise, there is substantial evidence showing its beneficial effects on muscle size and strength.<sup>37</sup> When physically active males performed low-load resistance exercise (20%) with BFR, knee extension strength increased by 40% compared to 36% in the high-intensity group and 21% in the low-intensity only group.<sup>30</sup> In addition, quadriceps CSA increased by 6% in both the low-intensity BFR group and high-intensity group.<sup>30</sup> In older men and women, low-intensity resistance exercise combined with BFR has also been shown to significantly increase strength and muscle size.<sup>38-40</sup> In addition, it has proved beneficial during rehabilitation from ACL surgery. After 16 weeks of combining BFR with traditional rehabilitation, knee extensor strength, knee flexor strength and knee extensor muscle CSA significantly recovered more compared to exercise without BFR.<sup>41</sup> Interestingly, BFR exercise has also been noted to increase size and strength in muscle not directly under BFR (e.g. pectoralis major).<sup>42</sup> It is thus a possibility that some respiratory muscles may be affected by BFR training but this is currently unknown. Therefore, when combining BFR exercise with low loads, muscle size and strength significantly increase and could be a useful strategy for COPD patients.

### Non-exercise with BFR

Interestingly, improvements are found when BFR is applied in the absence of exercise. For instance, when low and high BFR pressures (50 and 200 mmHg) were used on unloaded limbs, a significantly smaller decline in muscular force was found than non-BFR limbs.<sup>43,44</sup> Beneficial effects on attenuating muscle atrophy were also found in ACL reconstructive surgery patients.<sup>25</sup> In that study, an experimental group had BFR applied to the surgically repaired limb while the other group did not. The BFR pressure started at 180 mmHg and gradually increased during the next two weeks to levels varying from 200-260 mmHg. The stimulus was applied for five minutes and then removed for three minutes and repeated for five sets two times a day. After two weeks, a significant attenuation in the loss of muscle CSA was found for the BFR group versus the control group for men (9% vs.

18%) and women (11% vs. 23%).<sup>25</sup> Therefore, in COPD patients this may be a particularly useful treatment to attenuate loss of muscle and strength at times when exercise cannot be performed.

Taken as a whole, when BFR is combined with low-intensity walking or low-load resistance training, improvements in both muscular function and size happen and would be expected to also occur in COPD patients. What may be beneficial to treating the muscular declines found in COPD patients, especially those experiencing acute exacerbations, may be the application of BFR without exercise. In COPD patients, some studies have tried to electrically stimulate the muscle to produce muscular changes. A potentially new and exciting treatment for these individuals could be to combine BFR with electrical stimulation. BFR by itself in the absence of exercise attenuates the loss of muscle strength and size. One study noted that when combining BFR with neuromuscular electrical stimulation, a significant increase in metabolites was produced which lead to a greater release of serum immunoreactive growth hormone compared to the non-stimulated BFR limb.<sup>45</sup> Thus, by electrically stimulating the muscle in combination with BFR, both muscle cell swelling and increased metabolites could occur potentially triggering a greater muscle hypertrophy response than neuromuscular electrical stimulation by itself. This is a future area of research that should be investigated.

### Methodology

When using BFR it is important to recognize several methodological issues. Blood flow restriction involves placing a narrow cuff around the most proximal part of the exercising limb. The cuff is then inflated to a predetermined pressure with the intention to produce venous occlusion while restricting arterial inflow. Various methods have been used to produce this restrictive pressure but this produces problems when trying to compare studies<sup>46</sup>. Evidence shows that cuff pressures should be individualized based on the circumference of the limb and the size of the cuff being used.<sup>47</sup> Several types of cuffs have been used such as elastic cuffs, nylon cuffs, and knee wraps. Larger cuff sizes produce significantly greater cardiovascular and perceptual responses compared to more narrow cuffs when a similar pressure is used<sup>48</sup>, and they produce arterial occlusion at lower pressures than narrow cuffs at rest<sup>47</sup>. However, when similar cuff sizes of different materials are used at the same target pressure, similar repetitions and exertion levels are found (unpublished data). In addition, similar arterial occlusion pressures are found at rest.<sup>49</sup> These findings have been observed in young, healthy adults and future studies should investigate if a similar response would be found in an older and diseased population. Due to the individual differences in limb size and different physiological responses that can occur with different sized cuffs, it is very important that these things be considered when using BFR.

### Safety Concerns

Currently, no studies have examined the safety of using BFR

with COPD patients. Some potential concerns for COPD patients when exercising with BFR may be underlying cardiovascular disease and impaired respiratory capacity. When exercise is performed with BFR, a significant increase in oxygen consumption, heart rate, and blood pressure occur relative to the same exercise without BFR.<sup>50,51</sup> It has been documented that different size cuffs can produce significant differences in cardiovascular responses so this should be considered when prescribing BFR exercise.<sup>52</sup> Despite this, in healthy adults very few side effects have been reported.<sup>53</sup> Also, studies have shown that it may not affect markers of coagulation<sup>54-56</sup> but may acutely increase fibrinolytic potential<sup>54,56</sup>. More recently, patients with stable ischaemic heart disease who performed low-intensity exercise with BFR did not have significantly different changes in D-dimer and fibrinogen/fibrin degradation products and high-sensitive C-reactive protein compared to exercise at low-intensity exercise without BFR.<sup>28</sup> Other concerns have been proposed such as increased oxidative stress potentially initiating greater muscle damage but a substantially greater increase in oxidative stress with BFR compared to high-intensity exercise has not been found.<sup>28,57</sup> Although it is unlikely, more research is needed to verify if using BFR in severe COPD patients would damage skeletal muscle.

### Conclusion

In conclusion, BFR may be a potential treatment for COPD patients for improving muscular size and function. COPD patients have significantly impaired respiratory capacity and some may be incapable of performing a substantial volume of exercise to improve muscle size and strength. However, combining BFR with electrical stimulation may be a potentially novel treatment to improve muscle size and function in these individuals.

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