Smoking-induced Skeletal Muscle Dysfunction
From Evidence to Mechanisms
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Abstract

Smoking is the most important risk factor for the development of chronic obstructive pulmonary disease (COPD). Patients with COPD commonly suffer from skeletal muscle dysfunction, and it has been suggested that cigarette smoke exposure contributes to the development of skeletal muscle dysfunction even before overt pulmonary pathology. This review summarizes the evidence that muscles of nonsymptomatic smokers are weaker and less fatigue resistant than those of nonsmokers. Although physical inactivity of many smokers contributes to some alterations observed in skeletal muscle, exposure to cigarette smoke per se can also induce skeletal muscle dysfunction. Cigarette smoke constituents and systemic inflammatory mediators enhance proteolysis and inhibit protein synthesis, leading to loss of muscle mass. Reduced skeletal muscle contractile endurance in smokers may result from impaired oxygen delivery to the mitochondria and ability of the mitochondria to generate ATP due to interaction of carbon monoxide with hemoglobin, myoglobin, and components of the respiratory chain. Besides hampering contractile function, smoking may have immediate beneficial effects on motor skills, which are attributable to nicotine. In contrast to pulmonary pathology, many of the effects of smoking on skeletal muscle are most likely reversible by smoking cessation.

Keywords: smoking; muscle; fatigue; force

Muscle Force-Generating Capacity and Muscle Mass in Smokers

In Vivo Evidence

Table 1 gives an overview of the studies on the impact of smoking on muscle mass and function. Several studies reported a lower maximal force-generating capacity of the quadriceps muscle of smokers than nonsmokers (6, 7), but this is equivocal (8). A study that matched smokers and nonsmokers for levels of physical activity did not observe a lower muscle force in smokers (9), suggesting that disuse may play a role in the loss of muscle strength in smokers. A small effect of smoking per se on muscle force cannot be excluded, however, and large study populations may be required to address this issue. A recent longitudinal study in a large cohort of...
young healthy subjects showed that smoking 100 g tobacco per week was associated with a 2.9 and 5% reduction of muscle force in 15 years, independent of physical activity, in men and women, respectively (10).

Part of the muscle weakness may be attributable to loss of muscle mass. Several studies in humans and animal models provide evidence that smoking does indeed result in muscle wasting. For example, a 25% smaller fiber cross-sectional area was observed in the vastus lateralis muscle of smokers (11), even when matched for physical activity (12). In addition, lean body mass is lower in smoking men compared with similarly physically active nonsmoking control subjects (8). This, however, could also be the result of a lower food intake secondary to smoking, which has hitherto not been evaluated. Whatever the cause, smoking has also been identified as a risk factor for a low lean body mass in community-dwelling elderly men even without differences in physical activity (13).

Also, in rodents cigarette smoke exposure results in fiber atrophy (14), reduced muscle mass (15, 16), and progressive myosin breakdown (17). Yet, the lower lean body mass in human smokers was not accompanied by lower maximal voluntary muscle force (8). This intriguing finding could be explained by the enhanced ability of smokers to voluntarily activate their muscles (9). Such improved ability to activate the muscle may be the result of increased sympathetic nerve activity caused by nicotine (18). Thus, a fair amount evidence exists that smoking per se can induce skeletal muscle wasting, but with only modest effects on maximal force-generating capacity.

### Mechanisms of Smoking-induced Muscle Wasting

Muscle wasting is the net result of an increased protein degradation and/or reduced protein synthesis. In smokers, the quadriceps muscle displayed an increased expression of muscle atrophy F-box (MAFBx) (19), a muscle-specific regulating factor of ubiquitin-mediated proteolysis. Similarly, 8 weeks of cigarette smoke exposure in mice led in their limb muscles to increased mRNA levels of MAFBx and Muscle Ring Finger-1 (MuRF1), another regulator of muscle proteolysis (16, 19). In vitro studies on smoke-exposed muscle cells (i.e., myotubes) show atrophy and loss of myosin concomitant with an increased expression of MAFBx, MuRF1, and ubiquitin-specific proteases (17, 20). Phosphorylation of p38 mitogen-activated protein kinase (MAPK) and extracellular signal–regulated kinase (ERK) appears to play a central role, as inhibition of p38 and ERK abolishes muscle atrophy, myosin degradation, and the activation of the ubiquitin–proteasome pathway in smoke-exposed myotubes (17, 20). The smoke-induced increase in MuRF1 expression in myotubes can also

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**Table 1. The Impact of Smoking on Skeletal Muscle Mass and Function**

<table>
<thead>
<tr>
<th>Species</th>
<th>Mass</th>
<th>Force</th>
<th>Fatigue Resistance</th>
<th>Comments on Design</th>
<th>Comments on Results</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mouse</td>
<td>Gastrocnemius &amp; soleus ↓</td>
<td></td>
<td></td>
<td>Smoking 8 &amp; 24 wk</td>
<td>60 d cessation: soleus restored, gastrocnemius still lower mass</td>
<td>15</td>
</tr>
<tr>
<td>Mouse</td>
<td>Calf muscle complex ↓</td>
<td></td>
<td></td>
<td>Smoking 8–16 wk</td>
<td></td>
<td>16</td>
</tr>
<tr>
<td>Rat</td>
<td>EDL, type IIA and IIB fiber atrophy</td>
<td>Soleus: 8 wk = 16 wk ↓ EDL =</td>
<td></td>
<td>Smoking 8 wk</td>
<td>Effects only in high dose</td>
<td>14</td>
</tr>
<tr>
<td>Rat</td>
<td>Quadriceps, myosin loss</td>
<td></td>
<td></td>
<td>Smoking 4–12 wk</td>
<td>Lung lesions detectable after 12 wk</td>
<td>17</td>
</tr>
<tr>
<td>Human</td>
<td>VL, type I atrophy</td>
<td></td>
<td></td>
<td>Electrically evoked contractions</td>
<td>No correlation with physical activity (questionnaire)</td>
<td>11</td>
</tr>
<tr>
<td>Human</td>
<td>VL =</td>
<td></td>
<td></td>
<td>Electrically evoked contractions</td>
<td>No correlation with physical activity (questionnaire)</td>
<td>9</td>
</tr>
<tr>
<td>Human</td>
<td>VL, fiber atrophy</td>
<td>ACSA =</td>
<td></td>
<td>Repeated voluntary dynamic contractions</td>
<td>Monozygotic twin. Similar physical activity level. No differences in monozygotic nonsmoker-ex-smoker pairs</td>
<td>28</td>
</tr>
<tr>
<td>Human</td>
<td>VL =</td>
<td></td>
<td></td>
<td>Repeated voluntary dynamic contractions</td>
<td>Similar physical activity level</td>
<td>29</td>
</tr>
<tr>
<td>Human</td>
<td>Quadriceps =</td>
<td></td>
<td></td>
<td></td>
<td>Independent of physical functioning</td>
<td>7</td>
</tr>
<tr>
<td>Human</td>
<td>=</td>
<td></td>
<td></td>
<td></td>
<td>Independent of physical functioning</td>
<td>6</td>
</tr>
<tr>
<td>Human</td>
<td>Lean mass ↓</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>8</td>
</tr>
<tr>
<td>Human</td>
<td>Lean mass ↓</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>10</td>
</tr>
</tbody>
</table>

*Definition of abbreviations: ACSA = anatomical cross-sectional area; EDL = extensor digitorum longus; VL = vastus lateralis muscle. Equal signs indicate no change.*
be abolished by inhibition of nuclear factor-κB (NF-κB) (20). The following pattern thus emerges that substances in smoke stimulate p38 and ERK1/2 phosphorylation, which in turn enhances the expression of MuRF1 via NF-κB activation, and MAFBx independent of NF-κB activation (Figure 1). However, in mice exposed to cigarette smoke for 8 weeks, gastrocnemius muscle mass decreased without enhanced MuRF1-protein levels (15), indicating that also other pathways might be involved in smoke-induced muscle wasting. Indeed, besides stimulating protein degradation, smoke exposure may also inhibit anabolic pathways. Muscle protein synthesis, as assessed by the incorporation of labeled leucine, is decreased in the quadriceps muscle of smokers (19), which was associated with an increased expression of myostatin (19). Myostatin inhibits muscle growth by inactivation of protein kinase B (also known as Akt), a promoter of protein synthesis, and by hampering muscle cell renewal (21). In accordance, cigarette smoke exposure respectively reduces the presence of active Akt in mice skeletal muscle (15) and impairs the differentiation of cultured muscle cells into myotubes (17). It thus appears that smoking both stimulates protein breakdown and inhibits protein synthesis.

Cigarette smoke contains thousands of substances, and several of those potentially stimulate muscle protein breakdown and impair protein synthesis, as extensively reviewed in Reference 22. Among these constituents, aldehydes are capable of entering the circulation and directly affecting skeletal muscle tissue. Acetaldehyde exposure, for example, reduces protein synthesis rate in cultured human muscle cells (23). Another aldehyde, acrolein, induces atrophy and myosin breakdown in murine myotubes in a dose- and duration-dependent manner via p38 MAPK phosphorylation (24).

Circulating proinflammatory cytokines may also contribute to smoking-induced muscle wasting. Exposure of animals to cigarette smoke increases blood levels of proinflammatory cytokines, especially tumor necrosis factor (TNF-)α (16). In the circulation of smoking humans, IL-6 rather than TNF-α levels are higher than in nonsmokers (8, 19). Both TNF-α and IL-6 can induce skeletal muscle wasting by enhancing proteolysis and inhibiting protein synthesis (25). The exact origin of these circulating cytokines is unclear, but might include spill-over from the lung, activated leukocytes, and organ systems like bone marrow and skeletal muscle itself (26). Although in skeletal muscles of smoke-exposed guinea pigs and smoking humans no evidence of enhanced expression of cytokines has been found (6), the induction of TNF-α in skeletal muscle may be duration dependent. This is supported by the elevated expression of TNF-α in skeletal muscle from mice after 24 but not 8 weeks of cigarette smoke exposure (15). That muscle wasting in smoking mice depends...
on the action of TNF-α is supported by the attenuation of both atrophy and the IIa-III fiber type shift in smoking TNF-α receptor-2 knockout mice (27).

In summary, circulating constituents of cigarette smoke and cytokines can cause smoking-induced muscle wasting through activation of muscle proteolysis and inhibition of protein synthesis.

**Skeletal Muscle Fatigue Resistance in Smokers**

**In Vivo Evidence**

Muscle fatigue resistance, or endurance, is defined here as the ability of the muscle to maintain a given force or power output. Studies from Larsson and Orlander (28) and Orlander and colleagues (29) showed that neither isometric nor dynamic endurance was impaired in smokers compared with nonsmokers. More recently, however, Wüst and colleagues found a reduced fatigue resistance in the quadriceps muscle of smokers (12). The main difference between these studies is that the former used voluntary contractions, whereas the latter applied electrically evoked contractions to study muscle fatigability. Electrically evoked contractions have the advantage that motivational bias is circumvented, a factor that is particularly important during prolonged duration of contractile activity (30). In the context of smoking this is even more relevant, because muscle activation was ~4% higher during voluntary contractions in smokers than nonsmokers (9), which may result in delayed onset of fatigue during prolonged contractile activity in smokers. The enhanced ability of smokers to activate their muscles may be caused by nicotine. In fact, nicotine has been shown to improve exercise endurance, probably via a central mechanism (18). It is thus possible that an increased central drive during sustained or repeated voluntary contractions effectively overcomes any reduction in muscle fatigue resistance in smokers, whereas the electrically evoked fatigue reflects detrimental effects on intrinsic muscle contractility.

**Mechanisms of Smoking-induced Reduced Fatigue Resistance**

**Fiber type composition.** In general, muscle fatigue resistance is related to the oxidative capacity of the muscle (31). Accordingly, a fiber type transition from oxidative type I fibers to more glycolytic type II fibers may underlie the reduced fatigue resistance of smokers. Indeed, one of the earliest investigations reported that smokers had a lower proportion of type I fibers in the vastus lateralis muscle than nonsmokers (29). To exclude the impact of differences in genotype between individuals, Larsson and Orlander studied monozygotic discordant twins and found that the smoking twin had smaller and a lower proportion of type I fibers than the nonsmoking twin (28). Although this suggests that smoking itself causes these changes, the physical activity of the smoking twins tended to be lower. As disuse induces a slow-to-fast fiber type transition (5), it is possible that such changes in muscles from smokers are the result of disuse (28) rather than smoking itself. The potential importance of disuse is also reflected by two studies reporting a similar fiber type composition of the vastus lateralis muscle in activity-matched smokers and nonsmokers (11, 12). Despite the absence of a fiber type transition, the study from Montes de Oca and colleagues (11) still showed a reduced skeletal muscle oxidative capacity in smokers. Wüst and colleagues (12) did not observe significantly lower succinate dehydrogenase activity in skeletal muscles from smokers, but this could be explained by a lower smoke exposure in their subjects: average of 30 pack-years (>20 yr) (11) versus 12.9 pack-years (2.9–35) (12), respectively. Nevertheless, future studies should obtain a better indication of the physical activity level of their smoking participants or the smoking rodents.

**Skeletal muscle oxygen delivery.** Because the reduced muscle fatigue resistance observed in smokers (9, 32) is hardly explicable by changes in fiber type composition or oxidative enzyme activity (12), another factor must cause the reduced muscle fatigue resistance in smokers. Such a situation could occur when the oxygen delivery to the mitochondria, or the ability of the mitochondria to use the oxygen, is impaired (Figure 1).

The arterial vascular resistance increases (33) and the vasodilatory response in smokers worsens with duration of smoking (34). Consequently, the blood flow and hence oxygen delivery to the active muscle may be diminished and contribute to some of the increased muscle fatigability in smokers. As NO plays an important role in vasodilation, the reduced expression of neuronal and endothelial nitric oxide synthase in smokers (11) may underlie the reduced vasodilatory response. Despite the reduced vasodilatory response, muscle capillarization is not significantly affected by smoking (11, 12, 28).

Probably the most important factor in cigarette smoke that hinders the delivery of oxygen to the working muscle is CO. The affinity of hemoglobin for CO is 200-fold stronger than for oxygen. The association of CO with hemoglobin results in carboxyhemoglobin (COHb), which effectively reduces the oxygen carrying capacity of the blood. Smokers may have up to 9% COHb (35), which could thus be compared with a hypoxic condition. Yet, reducing the SaO2 to 80% by inhaling hypoxic air (inspiratory oxygen 12%) did not significantly reduce muscle fatigue resistance during repeated electrically evoked contractions (36). However, in addition to a reduction in the oxygen carrying capacity, the CO-induced left shift of the oxyhemoglobin dissociation curve impairs the delivery of oxygen to the mitochondria in the active muscle. That this is important is reflected by the increased oxygen extraction in hypoxic (inspiratory oxygen 9%) working dog muscles, whereas it is reduced with COHb (37). Raising the COHb to 6% in humans by inspiring CO acutely reduced fatigue resistance (38). In smokers, this is to some extent compensated for by an increased hematocrit, which can return to normal values within 3 days of smoking cessation (39). It thus appears that CO in cigarette smoke may diminish muscle fatigue resistance via formation of COHb that results in (1) a reduced oxygen carrying capacity of the blood, and (2) an impaired oxygen delivery consequent to the left shift of the Hb-dissociation curve.

Although the myoglobin (Mb) concentration of the muscle did not differ between smokers and nonsmokers (12), CO in cigarette smoke may combine with Mb and thereby hamper facilitated oxygen diffusion within the cell, even in the presence of an unaltered [Mb] (40). Ultimately, this may impair the delivery of oxygen to, in particular, the intermyofibrillar mitochondria.

**Mitochondrial function.** Although part of the reduced muscle fatigue resistance in smokers can be ascribed to impaired oxygen delivery to the muscle, interference of substances in cigarette smoke with the mitochondrial respiratory chain may hamper aerobic ATP production and hence...
result in increased muscle fatigability. For instance, cyanide, CO, and lung-secreted ceramides inhibit cytochrome-c oxidase (complex IV) in isolated mitochondria from skeletal muscle (41, 42), which may well underlie the lower complex IV activity in skeletal muscle mitochondria of active smokers (28, 29). This process is potentially rapid, as acute smoking (five cigarettes in 45 min) in healthy nonsmokers leads to an immediate decrease in complex IV activity in blood cells that normalized after as little as 24 hours’ smoking cessation (43). The ultimate significance of inhibition of these complexes has not yet been determined, but the final consequence is the loss of the capacity for the mitochondria to produce ATP (43). Obviously, this may be particularly harmful in high-energy–dependent tissues such as skeletal muscles, the brain, and the heart.

Furthermore, dysfunctional mitochondria are notorious producers of reactive oxygen species (44). Accordingly, mitochondrial dysfunction in lymphocytes from smokers is accompanied by increased membrane peroxidation (45). It seems therefore plausible that smoke-induced mitochondrial dysfunction in skeletal muscle cells (28, 29, 42) may also lead to increased reactive oxygen species generation and result in oxidative modifications of skeletal muscle proteins. In addition, it should be noted that cigarette smoke itself contains a host of free radicals (22). In line with this hypothesis, several skeletal muscle proteins involved in energy metabolism and contraction display oxidative modifications in the quadriceps of smoking humans compared with nonsmoking control subjects (6). Furthermore, 3 months of cigarette smoke exposure was sufficient to induce similar modifications in skeletal and respiratory muscles of guinea pigs (6). Oxidative stress can impair contractile protein function (46) and is therefore expected to contribute to smoking-induced muscle dysfunction.

**Effects of Smoking Cessation**

Much of the decrement in skeletal muscle fatigability in smokers is related to the acute effects of substances in smoke on oxygen delivery and the ability of the mitochondria to use oxygen. This is supported by the observation that the lower skeletal muscle fatigue resistance in smokers was not related to pack-years or cigarettes smoked per day (9) and that similar reductions in fatigue resistance can acutely be achieved by CO inhalation (38). If so, some of the smoking-related changes in skeletal muscle function should be rapidly reversible by smoking cessation. Studies in lymphocytes have reported that smoking cessation for as little as 24 hours to 7 days resulted in restored complex III and IV activities and oxygen consumption (43, 47). It is likely that such improvements with smoking cessation will occur also in skeletal muscle, but this has hitherto not been explored. It is expected that the restoration of normal function will take somewhat more time than that observed for blood cells that are more directly exposed to components in cigarette smoke than muscle tissue. In this context, it is encouraging to see that nonsmoking patients with COPD have a similar muscle fatigue resistance as activity-matched healthy people (48).

Another factor that may contribute to the improvement in fatigue resistance would be normalization of vascular resistance after smoking cessation as observed in former smokers (34). Also, the detrimental effects of smoking on muscle wasting are likely reversible, as a 60-day smoking cessation period was sufficient to normalize the muscle cell signaling alterations and reverse the loss of soleus muscle mass induced by 24-weeks’ cigarette smoke exposure in mice (15). This was, however, not the case for the gastrocnemius muscle, which might indicate that not all muscles respond similarly to smoking cessation. In postmenopausal women, 16 months of smoking cessation was associated with an increase in muscle mass (49), and the absence of atrophy in the ex-smoker sibling of monozygotic twins (28) also fits the notion that smoking cessation can reverse smoking-induced muscle wasting. In agreement, both skeletal muscle force-generating capacity and the lean body mass of formerly smoking subjects are not different from never-smoking control subjects (8), suggesting that the recovery of muscle mass is also associated with a normalized muscle function. This is further supported by the observation that nonsmoking patients with COPD do not show reduced muscle strength compared with age- and physical activity–matched healthy nonsmoking control subjects (48). Thus, although smoking-induced changes in the lung are irreversible (50), skeletal muscle may well recover from cigarette smoke–induced wasting, weakness, and increased fatigability by smoking cessation.

**Conclusions**

In summary, skeletal muscle weakness and reduced fatigue resistance exist in nonsymptomatic human smokers and cigarette smoke–exposed animals without overt pulmonary disorders. This indicates that cigarette smoke itself contributes to the development of skeletal muscle dysfunction, even before pulmonary problems are evident. Circulating cigarette smoke constituents seem to play an important role in the underlying molecular mechanisms, as these induce muscle wasting, reduce oxygen delivery, and impair mitochondrial function. There is some evidence that skeletal muscle may recover from cigarette smoke–induced impairments, but future studies should establish whether smoking cessation indeed restores muscle function. For example, muscle function could be evaluated in a cohort of subjects who participate in quit-smoking programs. Promising results are at least expected in terms of normalization of vascular and mitochondrial function, because these impairments occur rapidly. If indeed smoking cessation has immediate beneficial effects on mitochondrial, vascular, and muscle function, this may provide an important extra stimulus to stop smoking and thereby avert the “explosion of the smoking time bomb” in later life.

**Author disclosures** are available with the text of this article at www.atsjournals.org.

**References**


