HIGHLIGHTED TOPIC  | Muscle Dysfunction in COPD

Neuromotor control in chronic obstructive pulmonary disease

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Mantilla CB, Sieck GC. Neuromotor control in chronic obstructive pulmonary disease. J Appl Physiol 114: 1246–1252, 2013. First published January 17, 2013; doi:10.1152/japplphysiol.01212.2012.—Neuromotor control of skeletal muscles, including respiratory muscles, is ultimately dependent on the structure and function of the motor units (motoneurons and the muscle fibers they innervate) comprising the muscle. In most muscles, considerable diversity of contractile and fatigue properties exists across motor units, allowing a range of motor behaviors. In diseases such as chronic obstructive pulmonary disease (COPD), there may be disproportional primary (disease related) or secondary effects (related to treatment or other concomitant factors) on the size and contractility of specific muscle fiber types that would influence the relative contribution of different motor units. For example, with COPD there is a disproportionate atrophy of type IIX and/or IIb fibers that comprise more fatigable motor units. Thus fatigue resistance may appear to improve, while overall motor performance (e.g., 6-min walk test) and endurance (e.g., reduced aerobic exercise capacity) are diminished. There are many coexisting factors that might also influence motor performance. For example, in COPD patients, there may be concomitant hypoxia and/or hypercapnia, physical inactivity and unloading of muscles, and corticosteroid treatment, all of which may disproportionately affect specific muscle fiber types, thereby influencing neuromotor control. Future studies should address how plasticity in motor units can be harnessed to mitigate the functional impact of COPD-induced changes.

diaphragm muscle; fiber type; motor control; motor unit; respiratory muscles

IN SKELETAL MUSCLES, the final common pathway for neuromotor control is the motor unit, comprising a motoneuron and the group of muscle fibers it innervates. Muscle force is increased by the recruitment of additional motor units (15, 53) or by increasing the discharge frequency of those units recruited (frequency coding) (30). The contractile and fatigue properties of motor units can vary widely (6, 15), depending on the number of muscle fibers innervated and the contractile protein expression and mitochondrial density within muscle fibers. The range of motor unit contractile and fatigue properties is critically important in determining the functional diversity of a skeletal muscle in accomplishing different motor tasks. Motor unit contractile and fatigue properties generally match the fiber type composition of the unit (7, 54, 56, 64). Importantly, within a single motor unit, fiber type and thus the contractile and fatigue properties of muscle fibers are relatively uniform (14, 59). The range of forces generated by a muscle during different motor behaviors reflects the combined contractile and fatigue properties of those motor units recruited and their relative contribution (9).

CLASSIFICATION OF MOTOR UNIT TYPES

Motor units are classified into four different types based on the contractile and fatigue properties of their muscle fibers (Fig. 1) (5, 15, 33, 59). Importantly, in adults, all muscle fibers within a motor unit are the same fiber type (14, 15, 24, 43, 60).

Motor units that display slower-twitch contraction times are classified as type S, and they are also fatigued resistant. Muscle fibers comprising type S motor units are classified as slow or type I fibers, and express a slow myosin heavy chain isoform (MyHCslow). These type I fibers tend to have smaller cross-sectional areas compared with other fiber types (35, 42, 49, 61, 68), but they also have higher mitochondrial volume densities and higher capacities for oxidative phosphorylation (14, 60), most likely accounting for their greater fatigue resistance. In single-fiber studies, it has been shown that these type I muscle fibers also have slower maximum velocities of shortening, reflecting slower cross-bridge cycling kinetics (62). Type I fibers also generate less force per cross-sectional area (specific force) (17–20), perhaps reflecting an intrinsic property of the MyHCslow isoform.

There are three types of motor units that display faster-twitch contraction times but vary in their resistance to fatigue. Motor units that have faster-twitch contraction times and are fatigued resistant are classified as type FR. Muscle fibers com-
prprising type FR motor units are classified as type IIa, and express the MyHC2A isoform. Similar to fatigue-resistant type I fibers, these type IIa fibers tend to have smaller cross-sectional areas (35, 42, 49, 61, 68) and have higher mitochondrial volume densities and oxidative capacities compared with fibers comprising more fatigable fast-twitch motor unit types (14, 60). Single-fiber studies have shown that these type IIa muscle fibers have faster maximum velocities of shortening, reflecting faster cross-bridge cycling kinetics (62), and generate greater specific force compared with type I fibers (17–20).

Motor units that have faster-twitch contraction times and are more fatigable are classified as either fast-twitch fatigable (FF) or fast-twitch fatigue intermediate (FInt). Type FF motor units comprise type IIX or IIB muscle fibers that express either MyHC2B and/or MyHC2X isoforms. In contrast, type FInt motor units comprise muscle fibers that express only the MyHC2X isoform. The cross-sectional areas of both type IIX and IIB fibers are larger than type I and IIa fibers (35, 42, 49, 61, 68). The mitochondrial volume densities and oxidative capacities of type IIX and/or IIB fibers are lower compared with type I and IIa fibers (14, 60). Type IIX and IIB fibers have the fastest maximum velocities of shortening and generate greater specific force compared with type I and IIa fibers (17–20).

There are also differences in the force-Ca\(^{2+}\) relationship between type I and type II (all types) fibers that affect the force-frequency responses of these fibers (19, 20). Type I fibers are more sensitive to myoplasmic Ca\(^{2+}\) concentration compared with type II fibers (all types) due to the expression of a slow troponin C isoform in type I fibers. As a result, the force-Ca\(^{2+}\) curve is shifted to the left in type I fibers compared with type II fibers. Accordingly, the force-frequency response curve of type S motor units is leftward shifted compared with type FR, FInt, and FF units. It has been shown that motor units with lower recruitment thresholds (most likely type S units) have slower initial and peak discharge rates compared with motor units with higher force thresholds.

Other important differences among motor unit types also contribute to their distinct mechanical properties. For example, the number of muscle fibers innervated by a motoneuron (i.e., innervation ratio) varies across motor unit types, with greater innervation ratios at type FInt and FF motor units than at type S or FR units (53). Taken together, the larger fiber cross-sectional areas, greater specific forces, and greater innervation ratios of type FInt and FF motor units result in their contributing substantially greater forces when recruited compared with type S and FR units (Fig. 1) (38).

**MOTOR UNIT RECRUITMENT**

In 1957, Elwood Henneman demonstrated that in recordings from ventral root filaments those motor units recruited first had smaller amplitudes than those recruited later (26). Given the relationship between action potential amplitude, conduction velocity, and axon diameter reported by Gasser (16), Henneman concluded that motor units are recruited in order of motoneuron size—the “size principle.” In 1965, Henneman and colleagues (27, 28, 40) tested this hypothesis by assessing the relationship between motor unit recruitment and axonal conduction velocity. They demonstrated that those motor units recruited first (lower threshold) had slower axonal conduction velocities compared with motor units recruited later (higher threshold).

A number of subsequent studies have reported that motor units in a variety of muscles are recruited in an orderly fashion, based on the intrinsic size-related electrophysiological properties of motoneurons (21, 41). For the same synaptic input, smaller motoneurons are more excitable due to their higher input resistance and lower capacitance. Smaller motoneurons also have smaller axons and slower axonal conduction velocities. The order of motor unit recruitment also matches their mechanical and fatigue properties: type S, followed by FR, FInt, and FF units (6, 41, 65), and force development strongly predicts recruitment order for individual motor units (67). This recruitment order has been subsequently demonstrated in diaphragm motor units: those with slower conduction velocities are recruited first during inspiratory efforts (13, 31, 32).

Models of motor unit recruitment have been developed for limb and respiratory muscles (38, 39, 55, 58, 66). For example, in the case of diaphragm (58) and medial gastrocnemius motor units (66), a model of motor unit recruitment was developed (Fig. 2) based on 1) an orderly recruitment of motor units (type S followed by type FR, then FInt and FF last), 2) maximal activation of each motor unit, 3) specific force developed by type-identified motor unit muscle fibers (17–20, 53, 58, 66), 4) cross-sectional areas of type-identified muscle fibers (35, 42, 49, 61, 68), 5) proportion of different fiber types, and 6) innervation ratio for each motor unit type (14, 15, 53, 59, 60). By comparing the forces developed by the orderly recruitment of different motor unit types in such a model to the forces generated across different motor behaviors, it is possible to examine the possible impact of different pathophysiological conditions (including COPD) on the motor performance of different muscles (39). For instance, in the case of the diaphragm muscle, demands imposed by ventilatory behaviors such as eupnea and exposure to 10% O\(_2\) and 5% CO\(_2\) (i.e., hypoxia and hypercapnia) could be accomplished by recruitment of only type S and FR motor units in rats (38), cats (54, 58), and hamsters (56). Similarly, for the cat medial gastrocnemius muscle, forces generated during standing, walking, and
Running are also accomplished by recruitment of only fatigue-resistant motor units (66). During whole body exercise, ventilatory forces generated by the diaphragm and running/biking/walking forces generated by limb muscles are accomplished by the recruitment of fatigue-resistant motor units. These behaviors will only be compromised if the forces generated by these fatigue-resistant motor units are affected.

In the diaphragm muscle (38, 54, 56, 58), expulsive airway clearance behaviors (e.g., sneezing or coughing) require greater force generation accomplished only by near maximal recruitment of all motor units. Because of the recruitment of highly fatigable motor units, these expulsive behaviors are inherently short-duration and infrequent. Similarly, in limb muscles such as the medial gastrocnemius, jumping and other explosive behaviors also require the recruitment of more fatigable units (66). Conditions that selectively affect the force contribution of more fatigable, fast-twitch motor units will clearly compromise the ability to generate the near maximal forces required by these behaviors.

**MOTOR UNIT CHANGES IN COPD**

Many studies have examined muscle fiber type changes in animal models of COPD and in human patients (c.f., Ref. 10). Other papers in this Highlighted Topic series address muscle changes in COPD. However, few studies have addressed issues related to motor control of respiratory or limb muscles. Indeed, limited information on motor control in COPD patients is available for respiratory muscles (11, 63), with scant information being available for limb muscles.

Respiratory muscles. Animal models of COPD have been used to examine adaptations in neuromuscular properties across multiple studies. For example, elastase treatment is commonly used to induce emphysematous changes in the lung of male hamsters. In this model, Lewis and colleagues reported a 30% increase in the cross-sectional area of type II diaphragm muscle fibers and increased succinate dehydrogenase activity across all fibers (36). Noticeably, they reported a ~25% reduction in maximum specific force. As expected, optimal fiber length was shortened following 6 mo of emphysematous changes induced by elastase treatment in hamsters. No evidence of a change in fiber type distribution was present. Emphysematous lung changes induced by elastase treatment in mice also resulted in shortened diaphragm muscle length and impaired relaxation, but did not affect specific force or the force-frequency response (37). This report is consistent with previous observations of diaphragm muscle fiber length adaptation (decrease in number of sarcomeres in series) in the hamster model of emphysema (36). Accordingly, despite an emphysema-induced increase FRC and a consequent shortening of diaphragm muscle length, optimal sarcomere length is maintained.

Several studies have examined the diaphragm muscle of COPD patients (12, 34, 44–47). Single diaphragm muscle fibers obtained from patients with moderate to severe COPD mostly represent a slow-twitch phenotype. In addition, single fibers commonly display hybrid properties with coexpression of contractile and energetic protein isoforms (e.g., myosin heavy chain or sarcoplasmic-endoplasmic reticulum Ca\(^{2+}\) ATPase pumps) that are expressed differentially across fiber types in the diaphragm muscle (44, 45). Furthermore, a decrease in maximum single fiber isometric specific force in both type I and IIa fibers has been reported consistently (34, 47). Of note, although fiber CSA is slightly increased in both fiber types, myosin heavy chain content per half-sarcomere is reduced (47). Thus, when force is normalized for myosin heavy chain content per half-sarcomere, no differences in maximum force generation are observed, suggesting that diaphragm muscle weakness relates to the loss of contractile proteins. In addition, Ca\(^{2+}\) sensitivity is reduced in both type I and IIa fibers in the diaphragm muscle of COPD patients. A reduction in Ca\(^{2+}\) sensitivity would compromise submaximal activation and thereby affect the force-frequency response of motor units. Last, cross-bridge cycling kinetics are slower in both type I and IIa diaphragm muscle fibers in these patients.

Fine wire recordings are useful for determining the activation patterns of single motor units and have been used in human patients with COPD. During eupnea, motor units recorded from the diaphragm muscle of patients with severe COPD displayed higher discharge frequencies than motor units recorded from healthy control subjects (11). Unfortunately, only a few motor units can be recorded simultaneously from each electrode pair, and recordings become more challenging (indeed impossible) once more demanding tasks are imposed (e.g., during coughing). In this sense, it would be useful to derive specific information about motor unit recruitment from more global measures of motor unit activation such as the compound EMG. In a recent study, nonstationarity of the diaphragm EMG signal was used to determine motor unit recruitment across a range of ventilatory and nonventilatory behaviors in rats (50a). It seems likely that similar analytical tools can be used in humans. In particular, it seems important...
to determine whether the onset of additional recruitment of motor units is changed as motor behaviors become more demanding and as disease progresses in patients with COPD. Such indexes could be used to determine patients with more limited reserve capacity and thus at greater risk for respiratory complications following surgery.

The compound diaphragm muscle EMG can also be used as an index of mechanical activity in the muscle. In a recent study in rats, the forces generated by the diaphragm muscle (measured by Pdi) and the peak root-mean-square (RMS) amplitude of the EMG signal showed a robust correlation across motor behaviors (38). Indeed, the progressive increase in Pdi from eupnea to hypoxia (10% O2-hypercapnia (5% CO2), airway occlusion, and sneezing was consistent with changes in RMS EMG amplitude, when Pdi was expressed as a percent of maximum Pdi obtained by bilateral supramaximal phrenic nerve stimulation.

One important consideration for human studies relates to the ability to place electrodes for single motor unit recordings from the diaphragm muscle. In this regard, the costal and crural regions of the diaphragm muscle display similar activity and fiber type composition (48, 50, 53). Furthermore, several studies have used esophageal placement and even intramuscular electrode via laparoscopy (2–4, 25).

**Limb muscles.** In general agreement with respiratory muscles such as the diaphragm, the cross-sectional area of type IIx fibers from the vastus lateralis muscle was reduced ~40% in patients with COPD compared with control subjects (22, 23). No atrophy was evident for other fiber types.

A number of confounding factors merit attention when interpreting studies in human COPD patients. First, studies in human patients with COPD primarily reflect investigations of muscle biopsy material. In evaluating this information, it is important to determine sarcomeric length for measurements of fiber CSA. In addition, the limited number of muscle fibers in the biopsy does not provide a representative sample to reflect fiber type proportions within the muscle. In addition, there may be regional variations within the muscle, further complicating sampling errors. Therefore, cautious interpretation of any findings using biopsy material is necessary. These issues may account at least in part for the varying results of changes in fiber type proportions and CSA in human COPD patients. Second, human COPD patients are afflicted by a number of comorbid conditions including older age, corticosteroid use, malnutrition, deconditioning (inactivity and unloading), as well as other diseases associated with chronic smoking such as peripheral vascular and cardiac disease. Again, these issues may account for widely varying results reported in the literature.

Comparing the results of animal and human studies reveals multiple areas of discrepancy that may reflect adaptive changes rather than primary effects of COPD on motor unit properties (10). In this regard, it is important to realize that the adaptations to the disease will depend on a number of factors including the activation patterns of that specific muscle group. For instance, patients with severe COPD display increased diaphragm activation (as measured by RMS EMG activity) during eupneic breathing, yet no change in Pdi compared with healthy subjects (63). In contrast, deconditioning and reduced endurance (i.e., time to task failure) are likely associated with limited exercise tolerance and thus reduced activity of limb muscles including the vastus lateralis muscle.

The multiple mechanisms that contribute to motor dysfunction in patients with COPD may also differ across muscle groups (8). For example, in patients with moderate to severe COPD [based on measurements of forced expiratory volume in 1 s (FEV1) and forced vital capacity (FVC)], muscle biopsies obtained from the diaphragm and vastus lateralis muscles showed different levels of inflammatory cell infiltration compared with healthy control subjects (1). Whereas the number of immunohistochemically detected leukocytes and macrophages increased in vastus lateralis biopsies from COPD patients, such an increase was not evident in the diaphragm muscle.

**IMPACT OF COPD-RELATED MUSCLE FIBER CHANGES ON MOTOR PERFORMANCE**

COPD is associated with a relatively selective effect on the cross-sectional areas and function of type IIx and/or IIb fibers. In the case of the diaphragm muscle, forces generated during ventilatory behaviors can be accomplished by the recruitment of only type S and FR motor units (38, 54, 56, 58). However, expulsive airway clearance behaviors that require greater force generation are almost certainly impaired since they require recruitment of more fatigable motor units. In limb muscles, forces generated during standing, walking and running behaviors that are accomplished by recruitment of only fatigue-resistant motor units (66) would not be compromised in patients with COPD. However, it is unlikely that more explosive, short-duration motor behaviors (e.g., jumping) can be accomplished by COPD patients. Unfortunately, there is no information available on the performance of such behaviors in COPD patients. However, it has been demonstrated that maximum limb muscle strength is reduced (29, 51, 52). At the whole body level, ventilatory forces generated by the diaphragm and running/biking/walking forces generated by limb muscles during exercise can be accomplished since they require recruitment of only fatigue-resistant motor units. However, since gas exchange and oxygen delivery to tissues are impaired by COPD, the ability to sustain aerobic behaviors may be compromised not due to limited muscle performance per se but to provision of adequate metabolic substrates. Thus disease severity (e.g., based on FEV1 alone or normalized for FVC in patients with COPD) will clearly compromise the integrative response to exercise.

**MUSCLE FATIGUE AND ENDURANCE**

It is important to recognize that muscle fatigue and endurance are not the same and reflect different aspects of motor performance. Intrinsic muscle fatigue is a property of muscle fibers that varies with contractile protein expression that distinguishes different muscle fiber types. This is evident by the fatigue resistance of motor units that are composed of these different fiber types (Fig. 1). In contrast, endurance is a measure of the ability to perform a motor task and is usually defined in units of time to task failure. Endurance can be measured at various levels of motor unit recruitment and activation including maximum efforts and submaximal efforts. Typically, endurance is measured at submaximal activation, which complicates interpretation since the extent of motor unit recruitment (muscle fiber activation) is unknown. Endurance
may also be influenced by CNS mechanisms that are involved in activating motor neurons and would thus be independent of and unrelated to intrinsic muscle fiber fatigue. Unfortunately, the literature does not consistently address and recognize these distinctions, and muscle fatigue and endurance are often conflated.

The relatively selective effects of COPD on type IIx and/or IIb muscle fibers that comprise more fatigable motor units may lead to confusion about the impact of COPD on muscle fatigue vs. endurance. With a decreased contribution of more fatigable motor units to muscle force, there will be an improvement in the apparent fatigue resistance of the entire muscle, whether it be the diaphragm or limb muscles. This effect is misleading since the capacity of the muscle to generate force (i.e., muscle strength) has been diminished. Thus recruitment of additional motor units may be required to generate a given level of force required during a submaximal motor effort. Accordingly, endurance will be diminished. Thus assessments of endurance are even more confounded by this “paradox” since endurance depends on the motor behavior being tested. For example, ventilatory behaviors of the diaphragm muscle are accomplished primarily by recruitment of fatigue-resistant motor units. Thus all ventilatory behaviors are intrinsically high-endurance, and ventilation per se is rarely limited by neuromotor performance; what fails is gas exchange and oxygen delivery to tissue (a function of capillarity, muscle blood flow, and cardiac output). Even high-endurance motor units will fail under hypoxic or hypercapnic conditions. This is not reflected in neuromotor assessments of muscle fatigue. The parallel conditions in limb muscles will be standing and walking behaviors that are generally accomplished by the recruitment of fatigue-resistant motor units. In COPD patients, limitations in the performance of these low-level motor behaviors are also likely related to compromised gas exchange and oxygen delivery rather than compromised muscle endurance.

MECHANISMS OF MOTOR CONTROL DYSFUNCTION IN COPD

Regardless of the underlying factors accounting for fiber type-specific changes observed in patients with COPD, the impact of COPD on diaphragm muscle is predominantly on fibers comprising higher threshold, more fatigable fast-twitch motor units (type IIx and FF). Accordingly, it appears that ventilatory functions that require lower levels of diaphragm force generation are preserved at the expense of nonventilatory behaviors that require higher levels of force generation and that are important in airway clearance and other expulsive maneuvers (e.g., coughing, sneezing). This is consistent with the increased incidence of comorbidities that could be associated with impaired airway clearance such as infectious complications (pneumonia, bronchitis) and inflammatory responses (increased mucus secretion, airway hyperreactivity, etc.).

Limb muscle weakness may also affect the range of motor behaviors that can be accomplished. Standing and walking are lower force-generating behaviors that may be less affected in COPD, where muscle fibers comprising lower threshold motor units (type I and IIa fibers) are generally less affected than fibers comprising higher threshold motor units (type IIx and/or IIb fibers). Jumping is a higher threshold motor behavior (54, 57, 66), and in COPD patients this motor behavior is likely compromised although no study has directly examined the ability to perform such high force-generating behaviors. As the disease worsens, not only is gas exchange affected, but the ability of limb muscles to generate forces necessary to accomplish these higher threshold behaviors can be affected. This may contribute to the ever-increasing exercise intolerance and decreasing activity levels of these patients as the severity of the disease progresses (Fig. 3). The disease condition of COPD may thus accelerate inherent age-related decline in respiratory function, impacting both quality of life and survival.

CONCLUDING REMARKS AND CLINICAL IMPLICATIONS

Future studies should address how the COPD-induced changes in the cross-sectional areas and specific forces of higher threshold motor units comprising type IIx and/or IIb fibers can be ameliorated and/or reversed. Resistance exercise that is focused on increasing muscle strength may be effective; however, most studies have focused on endurance exercise. Anabolic steroid or growth hormone treatment may also target fibers comprising higher-threshold motor units and thus may be effective in treating the neuromotor symptoms of COPD. Other therapies specifically designed to promote the maintenance of type IIx and/or IIb fiber size and contractility (e.g., gene therapy or proteasome inhibition) may mitigate the impact of COPD on neuromotor control. Importantly, assessing the potential beneficial impact of any therapeutic intervention will be obscured if only ventilatory capacity is examined, as has been the case in most previous studies. It must be recognized that the target of these therapies should be motor units comprising type IIx and/or IIb fibers that are likely involved only in nonventilatory airway clearance behaviors. Thus assessments of forces generated during coughing and sneezing will provide far greater insight into the therapeutic benefit of rehabilitative interventions. Another airway clearance behavior that could be assessed are deep sighs in which a substantial Pdi is generated, requiring recruitment of the more fatigable motor units.
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