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Review

Impact of diaphragm muscle fiber atrophy on neuromotor control☆

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ABSTRACT

In skeletal muscles, motor units comprise a motoneuron and the group of muscle fibers innervated by it, which are usually classified based on myosin heavy chain isoform expression. Motor units displaying diverse contractile and fatigue properties are important in determining the range of motor behaviors that can be accomplished by a muscle. Muscle fiber atrophy and weakness may disproportionately affect specific fiber types across a variety of diseases or clinical conditions, thus impacting neuromotor control. In this regard, fiber atrophy that affects a specific fiber type will alter the relative contribution of different motor units to overall muscle structure and function. For example, in various diseases there is fairly selective atrophy of type IIx and/or IIb fibers comprising the strongest yet most fatigable motor units. As a result, there is muscle weakness (i.e., reductions in force per cross-sectional area) associated with an apparent improvement in resistance to fatiguing contractions. This review will examine neuromotor control of respiratory muscles such as the diaphragm muscle and the impact of muscle fiber atrophy on motor performance.

1. Introduction

The final common effector of skeletal muscle neuromotor control is the motor unit consisting of a motoneuron and the group of muscle fibers it innervates (Liddell and Sherrington, 1925). With recruitment of additional motor units force increases (Fournier and Sieck, 1988; Sieck, 1988). In addition, for those units recruited, force increases with increasing discharge frequency (Iscoe et al., 1976). The muscle fibers comprising motor units express uniform contractile proteins that underlie distinction of different fiber types (Enad et al., 1989; Fournier and Sieck, 1988; Hamm et al., 1988; Nemeth et al., 1986; Sieck et al., 1989a, 1996). Specifically, the expression of different isoforms of myosin heavy chain (MyHC) corresponds with the classification of different muscle fiber types (Fig. 1) (Butler et al., 1999; Sieck, 1991, 1994; Su et al., 1997). The contractile and fatigue properties of motor units vary widely depending on their fiber type composition (Burke et al., 1973; Fournier and Sieck, 1988). The overall diversity of motor unit contractile and fatigue properties determines the range of function of a skeletal muscle.

The diaphragm muscle (DIAm) is the major muscle for inspiration in mammals, and in accomplishing this ventilatory behavior it is active ∼30–40% of the time (duty cycle) each day throughout life (Hensbergen and Kernell, 1997). However, ventilatory behaviors can be accomplished by activating only ∼10–25% of the total force-generating capacity of the DIAm (Mantilla et al., 2010; Mantilla and Sieck, 2011; Sieck, 1991; Sieck and Fournier, 1989). This level of force generation by the DIAm is accomplished by the recruitment of only fatigue resistant slow- and fast-twitch motor units. From a design standpoint it would be inefficient to repeatedly recruit more fatigable fast-twitch motor units to accomplish sustained ventilatory behaviors.

It is important to recognize that the DIAm is also activated during non-ventilatory motor behaviors such as coughing, sneezing, sighing, vomiting, defecation, vocalization and maintenance of posture (Butler et al., 2001; Mantilla et al., 2010, 2011; Milano et al., 1992). Forces generated by the DIAm are much greater during expulsive, airway-protective (clearance) behaviors (Mantilla et al., 2010; Mantilla and Sieck, 2011; Sieck, 1991; Sieck and Fournier, 1989). For instance, near maximal co-activation of the DIAm and abdominal muscles during coughing and sneezing is necessary to generate the large inspiratory effort and high intra-abdominal pressure that precedes diaphragm elevation and increased intra-thoracic pressure to "clear" the airway (Milano et al., 1992; Rybak et al., 2008; Shannon et al., 1998). Indeed, these non-ventilatory motor behaviors of the DIAm require activation of all motor unit types, but particularly more fatigable fast-twitch motor units.

In a variety of diseases or treatment conditions, there is muscle fiber wasting that affects the contractile and fatigue properties of

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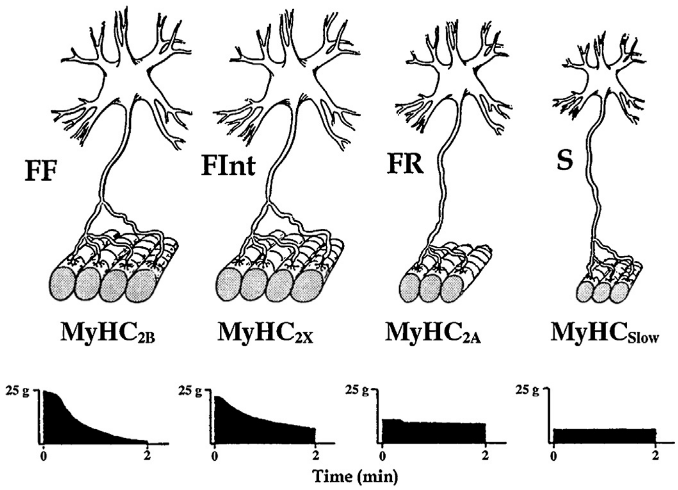

Fig. 1. Motor units display differences in their contractile and fatigue properties that underlie the most common classification scheme: type S, FR, FInt and FF. Importantly, muscle fibers in a motor unit share a homogeneous fiber type composition as determined by myosin heavy chain (MyHC) isoform expression ($MyHC_{Slow}$, $MyHC_{2A}$, $MyHC_{2X}$ and/or $MyHC_{2B}$ for type S, FR, FInt and FF units, respectively).
Reprinted with permission from Mantilla and Sieck (2013).

the DIAm. Specific fiber type atrophy is often noted that disproportionately affects the relative contribution of different motor unit types and possibly the ability to accomplish certain motor behaviors. This review will discuss various disease conditions where DIAm fiber atrophy occurs and the impact on performance of ventilatory versus non-ventilatory motor behaviors. Diseases that affect survival of respiratory motor neurons (e.g., amyotrophic lateral sclerosis) will affect neuromotor control directly as a result of motor neuron loss. Furthermore, if motor neuron loss is specific to certain motor unit types (Pun et al., 2006), perhaps reflecting specific vulnerability of certain motor neuron populations, then functional impairments will display the confounding contribution of motor unit types to muscle performance, as discussed herein.

2. Classification of muscle fiber and motor unit types

In the DIAm, four different types of motor units are classified based on the contractile and fatigue properties of their muscle fibers (Fig. 1) (Burke, 1981; Fournier and Sieck, 1988; Kernell, 2006; Sieck et al., 1989a). Based on their twitch contraction times, motor units are classified as slow-twitch (type S) or fast-twitch (type F). Motor units are also classified based on their fatigue resistance. All type S motor units are fatigue resistant, while fatigue resistance of type F units varies considerably. These contractile and fatigue properties of motor units correspond with the MyHC isoform composition of muscle fibers. Type S motor units comprise type I fibers that express $MyHC_{Slow}$. These type I fibers have smaller cross-sectional areas (Lewis and Sieck, 1990; Miyata et al., 1995; Prakash et al., 2000; Sieck et al., 1989b; Zhan et al., 1997), higher mitochondrial volume densities and higher capacities for oxidative phosphorylation (Enad et al., 1989; Sieck et al., 1996). Single fiber studies show that type I muscle fibers have slower maximum shortening velocities, consistent with slower cross-bridge cycling kinetics (Sieck and Prakash, 1997). Type I fibers also have lower specific force (force per cross-sectional area) (Geiger et al., 1999, 2000, 2001, 2002).

Type F motor units that are fatigue-resistant are classified as type FR and comprise type IIa fibers that express $MyHC_{2A}$. Type IIa fibers have smaller cross-sectional areas (Lewis and Sieck, 1990; Miyata et al., 1995; Prakash et al., 2000; Sieck et al., 1989b; Zhan et al., 1997), higher mitochondrial volume densities and higher oxidative capacities compared to other type II fibers (Enad et al., 1989; Sieck et al., 1996). Type IIa muscle fibers have faster maximum shortening velocities, consistent with faster cross-bridge cycling kinetics (Sieck and Prakash, 1997). The specific force of type IIa fibers is comparable to type I fibers (Geiger et al., 1999, 2000, 2001, 2002).

More fatigable type F motor units are classified as either fast-twitch fatigue intermediate (FInt) or fast-twitch fatigable (FF), although a continuum of fatigue resistance exists across these units. Type FInt and FF units comprise type IIx and IIb fibers that commonly co-express $MyHC_{2X}$ and $MyHC_{2B}$ isoforms, albeit in varying proportions (Sieck et al., 1996). Cross-sectional areas of type IIx and IIb DIAm fibers are usually larger than type I and IIa fibers (Greising et al., 2013a; Lewis and Sieck, 1990; Miyata et al., 1995; Prakash et al., 2000; Sieck et al., 1989b, 2012; Zhan et al., 1997). Mitochondrial volume densities and oxidative capacities of type IIx and IIb fibers are lower than type I and IIa fibers (Enad et al., 1989; Sieck et al., 1996). Type IIx and IIb fibers also have the fastest maximum shortening velocities and generate the greatest specific forces of all DIAm fiber types (Geiger et al., 1999, 2000, 2001, 2002).

Differences also exist in the force-Ca^{2+} relationships of type I, IIa, IIx and IIb fibers that underlie differences in their force-frequency responses (Geiger et al., 1999, 2000). At a given myoplasmic Ca^{2+} concentration, the force generated by type I DIAm fibers is greater than type II fibers, reflecting increased Ca^{2+} sensitivity, most likely due to the expression of a slow troponin C isoform. Correspondingly, the force-frequency response curve of type S motor units is shifted leftward compared to type F motor units. No differences in Ca^{2+} sensitivity exist across type F units. In agreement, motor units with lower recruitment thresholds (most likely type S units) have slower initial and peak discharge rates than type F motor units with higher recruitment thresholds.

The innervation ratio (i.e., the number of muscle fibers innervated by a motoneuron) of type FInt and FF motor units is greater than that of type S and FR units (Sieck, 1988). Thus, as a result of larger fiber cross-sectional areas, greater innervation ratios and greater specific forces, the overall force contributed by type FInt and FF DIAm motor units is substantially greater than that contributed by type S and FR units (Fig. 2) (Fournier and Sieck, 1988; Mantilla et al., 2010; Mantilla and Sieck, 2011; Sieck and Fournier, 1989).

3. Motor unit recruitment order

Based on recordings from ventral root filaments, it was shown that motor units that are recruited first display smaller amplitudes and slower conduction velocities than units recruited later (Henneman, 1957; Henneman and Olson, 1965; Henneman et al., 1965; McPhedran et al., 1965). Gasser had previously demonstrated a relationship between action potential amplitude, conduction velocity and axon diameter that reflects motoneuron size (Gasser and Grundfest, 1939). Consequently, Henneman formulated the "size principle", proposing that motor units are recruited in an orderly fashion according to intrinsic electrophysiological properties related to motoneuron size. Subsequently, the size principle was tested by demonstrating that the order of motor unit recruitment was consistently related to axonal conduction velocity (Henneman and Olson, 1965; Henneman et al., 1965; McPhedran et al., 1965). Those motor units recruited first (i.e., with lower threshold) displayed slower axonal conduction velocities compared to higher threshold motor units that were recruited later.

The size principle has been validated in a variety of muscles (Gordon et al., 2004; Mendell, 2005), including the DIAm (Dick et al., 1987). It has also been shown that the order of motor unit recruitment matches the mechanical and fatigue properties of motor units such that type S units are recruited first, followed by type FR, FInt