Novel method for physiological recruitment of diaphragm motor units after upper cervical spinal cord injury

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EACH YEAR, approximately 11,000 people in the United States suffer cervical spinal cord injury that results in partial or complete diaphragm muscle paralysis with an annual expense of more than $3 billion. Those unable to maintain adequate ventilation due to diaphragm muscle paralysis become dependent on mechanical ventilators, a situation associated with ongoing problems related to pulmonary clearance, infections, and lung injury that lead to significant morbidity and increased mortality. Therefore, restoration of diaphragm muscle activity and the ability to accomplish ventilatory and nonventilatory motor behaviors (e.g., cough) would dramatically impact the quality of life of mechanical ventilator-dependent patients with cervical spinal cord injury.

For some time, functional electrical stimulation of the phrenic nerve has been used to restore diaphragm muscle activity and thereby ameliorate patient dependency on mechanical ventilation. However, due to the intrinsic electrophysiological constraints associated with electrical stimulation of peripheral nerves, over 50% of potentially eligible patients fail to obtain adequate diaphragm activation to sustain full-time ventilatory support. Moreover, electrical activation of only the diaphragm muscle misses the normal physiological advantage of stabilizing the chest wall through mechanical coupling of diaphragm and intercostal muscle activity. The study by DiMarco and Kowalski (4) in the *Journal of Applied Physiology* presents a novel stimulation technique that restores more normal physiological activation of the diaphragm muscle as well as coordinated activation of the diaphragm and intercostal muscles. This important proof of principle study represents the beginning stage of a therapeutic approach that may reduce morbidity and mortality associated with mechanical ventilation, thus restoring quality of life to thousands of spinal cord injury patients.

To better understand the significance of this study, it is important to understand normal recruitment of motor units, the fundamental building blocks of neuromotor control. Liddell and Sherrington (7) originally proposed that neural control of muscle force generation results from a combination of an orderly recruitment of motor units together with changes in motoneuron discharge frequency. Later, Henneman et al. (6) proposed that orderly recruitment of motor units was due to the intrinsic, size-related electrophysiological properties of motoneurons such that with similar synaptic input currents, smaller motoneurons with smaller axons, and thus slower axonal conduction velocities, are recruited before larger motoneurons (“size principle”). Dick and colleagues found that during spontaneous breathing in cats, those phrenic motoneurons recruited first had slower axonal conduction velocities compared with motoneurons recruited later (3), thus confirming the size principle in the diaphragm. A relationship between recruitment order and the mechanical properties of motor units has also been demonstrated (Fig. 1), which forms the basis for classifying different motor unit types (1, 5, 9, 11). Smaller motoneurons innervate slow-twitch muscle fibers (i.e., type I fibers comprising type S motor units) that generate lower maximum tetanic force, have a leftward-shifted force-frequency response curve, and display greater fatigue resistance during repetitive stimulation. Larger motoneurons innervate fast-twitch muscle fibers (type II muscle fibers) that generate greater maximum tetanic force, have a rightward-shifted force-frequency response curve, and display lesser fatigue resistance during repetitive stimulation.

![Diagram](http://www.jap.org)  

**Fig. 1.** A: schematic showing different motor unit types (see text). Motor units are normally recruited in an orderly fashion. Smaller slow-twitch (S) units are recruited before larger fast-twitch units, which are recruited in accordance with their fatigue-resistance properties (fatigue-resistant (FR), followed by fatigue-intermediate (Flnt), and last, fatigable (FF) units). Electrical stimulation of the phrenic nerve elicits an inverse recruitment order that leads to fatigue with sustained activation. B: motor unit recruitment varies across different ventilatory and nonventilatory behaviors such that during resting breathing (eupnea) only type S and FR units are recruited. Increasing ventilatory demands (e.g., during hypercapnia or tracheal occlusion) result in the additional recruitment of type Flnt units, and only during expulsive behaviors (e.g., sneezing, coughing) are FF units recruited.
frequency response curve, but display varying fatigue resistance. Among fast-twitch motor units, fatigue-resistant (FR; innervating type IIa fibers) units have the lowest recruitment threshold, followed in rank order by fatigue-sensitive (Flnt; innervating type IIX fibers) and highly fatigable (FF; innervating type IIb fibers) units (1, 11, 12). Thus size-related motor unit recruitment order is directly related to mechanical and fatigue properties of muscle unit fibers. The nervous system takes advantage of the mechanical and fatigue properties of motor units to accomplish different behavioral tasks (1, 10). For example, activation of highly-fatigable FF motor units in the diaphragm would not be desirable during normal quiet breathing (eupnea), nor during even greater breathing efforts stimulated by hypoxic or hypercapnic conditions, since fatigue would soon result and these behaviors could not be sustained. Accordingly, normal physiological recruitment of type S and FR diaphragm motor units provides a distinct advantage to sustain lung ventilation. Recruitment of more fatigable FF and Flnt motor units would be necessary only during short-duration nonventilatory behaviors that require higher force levels (e.g., sneezing or coughing). However, normal physiology is difficult to replicate with electrical stimulation of peripheral nerves, such as the phrenic, since electrical stimulation results in activation of larger axons first. Thus, with electrical stimulation of the phrenic nerve, motor unit recruitment order is reversed, and more fatigable motor units are activated first. It would be far better to take advantage of the normal intrinsic properties of phrenic motor neurons to provide more effective diaphragm muscle pacing, and it is this very issue that is addressed by the novel method reported by DiMarco and Kowalski (4).

In addition to descending premotor excitatory drive from the medulla, phrenic motoneurons also receive excitatory intraspinal input. It is generally thought that this excitatory afferent input is widely distributed such that the timing of phrenic motoneuron activation is primarily due to intrinsic, size-related properties. In the method validated by DiMarco and Kowalski (4), they employ stimulation of intraspinal pathways located in the ventrolateral column (8) to asynchronously activate phrenic motor neurons presumably following a physiological recruitment order, dependent on intrinsic size-related properties of phrenic motor neurons. Future studies using this novel method should validate size principle-dependent recruitment order of diaphragm motor units following stimulation (e.g., based on axonal conduction velocity). Although the authors did not directly assess the functional advantage of their novel method with respect to improved fatigue resistance, they report that continuous stimulation was effective in sustaining ventilation for up to 6 h, with continued functional reserve. This is very encouraging for spinal cord injury patients.

Another very important feature of the stimulation method validated by DiMarco and Kowalski (4) is that both phrenic and intercostal motor units were recruited, thereby activating diaphragm and chest wall intercostal muscles in a coordinated fashion. Under normal physiological conditions, the chest wall is stabilized to afford greater mechanical advantage for diaphragm muscle contractions (2). Chest wall stiffening, due to intercostal muscle contraction, increases the afterload for diaphragm muscle contraction, thereby increasing diaphragm muscle force and transdiaphragmatic pressure generation, and increasing stimulated lung volumes to near inspiratory capacity. With coordinated activation of diaphragm and intercostal muscles, it is also important to recruit motor units in a physiological order to avoid fatigue.

In summary, the novel method validated by DiMarco and Kowalski (4) more closely replicates normal physiology compared with phrenic nerve pacing methods currently in use. A major advantage is that diaphragm muscle activity is restored and adequate ventilation can be provided for a much longer period of time without fatigue. In addition, functional reserve capacity is maintained to accomplish important nonventilatory motor behaviors (e.g., cough). Important next steps are to extend these results for longer periods of time in animals and conduct phase II/III clinical trials. If successful, the development of this novel method will improve the quality of life for cervical spinal cord injury patients that are now tethered to mechanical ventilators.

REFERENCES


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