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Spinal cord injury and diaphragm neuromotor control

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Abstract

Introduction: Neuromotor control of diaphragm muscle and the recovery of diaphragm activity following spinal cord injury has been narrowly focused on ventilation. By contrast, the understanding of neuromotor control for non-ventilatory expulsive/straining maneuvers (including coughing, defecation and parturition) is relatively impoverished. This variety of behaviours is achieved via the recruitment of the diverse array of motor units that comprise the diaphragm muscle.

Areas covered: The neuromotor control of ventilatory and non-ventilatory behaviors in health and in the context of spinal cord injury is explored. Particular attention is played to the neuroplasticity of phrenic motor neurons in various models of cervical spinal cord injury.

Expert opinion: There is a remarkable paucity in our understanding of neuromotor control of maneuvers in spinal cord injury patients. Dysfunction of these expulsive/straining maneuvers reduces patient quality of life and contributes to severe morbidity and mortality. As spinal cord injury patient life expectancies continue to climb steadily, a nexus of spinal cord injury and age-associated comorbidities is likely to occur. While current research remains concerned only with the minutiae of ventilation, the major functional deficits of this clinical cohort will persist intractably. We posit some future research directions to avoid this scenario.

Keywords

phrenic motor neurons; motor unit; recruitment; contusion; hemisection; neural circuit; skeletal muscle

1. Introduction

For far too long diaphragm neuromotor control has been slavishly focused on breathing and the response of ventilation to a variety of interventions. While undoubtedly worthwhile with

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regard to central pattern generation control of eupnea and responses to ventilatory challenge, misguided reductionists have led to the adoption of the idea that diaphragm motor units are merely the homogeneous and monolithic intermediates (the 'inspiratory motor neurons') between brainstem respiratory centers and the generation of tidal volumes. In reality, the diaphragm muscle forms the posterior partition for the thoracic cavity and the anterior partition of the abdominal cavity and comprises a mixed motor unit population that allows for generation of transdiaphragmatic pressures (P_{di}) [1]. These pressures (negative in the thorax and positive in the abdomen), are essential to a variety of behaviors, with quiet breathing accounting for ~15% of the maximum pressure generating capacity of the diaphragm muscle (P_{dimax}) in almost all species assessed [1, 2], including humans [1, 2, 3]. In the context of spinal cord injury, the nature of functional impairments may differ along with the therapeutic approach and consequences.

Here we take a nuanced view of diaphragm neuromotor control across four key areas relevant to spinal cord injury: i) distinguishing the three broad categories of diaphragm behavior and the requirements for recruitment of different motor unit types; ii) identifying how different models of spinal cord injury disrupt motor circuitry; iii) exploring the different neuroplastic responses of phrenic motor neurons to various spinal cord injury models; and iv) quantifying the functional outcomes and motor-unit specific underpinnings of deficits observed in different spinal cord injury models, and a brief exploration of therapies designed to improve non-ventilatory activities in patients.

2. Neuromotor control of diaphragm motor units

In addition to its non-trivial role as an anatomic barrier between the thoracic and abdominal cavities [1], the diaphragm muscle serves to effect three main behavioral functions: i) to ventilate the lungs for gas exchange (i.e., breathing); ii) to facilitate pressure generation for effective expulsive maneuvers (e.g. coughing sneezing, parturition and defecation); and iii) to accomplish social, language and emotional tasks (e.g. vocalizations or calls in all mammals and speech and musicianship in humans).

The indefatigable requirement for tidal breathing necessitates generation of nonfatiguing P_{di}, at a high duty cycle (time active versus inactive) approaching 40% [4, 5] that is sustained for the entirety of one's life. This is achieved via the generation of small negative intrathoracic pressures (P_{th}) resulting from relatively moderate caudal excursions of the diaphragm muscle [6, 7]. Typically, expiration is passive during eupnea, driven by the elastic recoil of the lungs and chest wall that generate a positive P_{ab} [6]. The P_{di} necessary for ventilation of the lung is generally around 15% of P_{dimax} during eupnea and approaches 30-40% P_{dimax} during maximal ventilatory efforts against an occluded airway [3, 4, 5, 8]. Indeed, during maximum voluntary hyperpnea with controlled CO_2, P_{di} does not exceed 60% P_{dimax} [9, 10]. Thus, ventilatory requirements for diaphragm muscle activation are submaximal with considerable reserve capacity for force generation.

The second category of diaphragm muscle activation is during expulsive behaviors that often involve coordinated co-contractions of the diaphragm with abdominal and/or upper airway muscles or lower sphincter muscles [11, 12, 13, 14, 15, 16], depending on the orifice of

ejection [1]. These behaviors are driven by central pattern generators that are likely distinct from but interact with the respiratory pattern generator responsible for ventilation [2, 11, 13, 17, 18, 19]. It is important to recognize that these expulsive behaviors are far less frequent, are of shorter duration (i.e., a lower duty cycle), and involve recruitment of more fatigable diaphragm motor units in order to generate higher P_{di}, that at times approach P_{dimax}. Thus, they may involve selective/distinct inputs to larger phrenic motor neurons that comprise more fatigable diaphragm motor units.

The social and emotional functions of the diaphragm muscle also require coordinated activation with other muscles such as the tongue and laryngeal muscles. The functional requirements during these motor behaviors do not require additional diaphragm motor unit types, but rather pattern generators and premotor inputs that are distinct from the ventilatory pattern generator. However, the seamless interruption of breathing during speech and vocalisation indicates interactions with the ventilatory pattern generator and/or premotor circuits, as well as with sympathetic and parasympathetic motor pathways [20, 21]. In humans, speech extends the post-inspiratory phase and reduces duration of the inspiratory phase, allowing for speech to occur relatively unpunctuated [20, 22].

2.1 Diaphragm motor units

To accommodate the diverse pressure generation requirements of these motor behaviors, the diaphragm muscle comprises different motor unit types: slow (type S), fast fatigue resistant (type FR), fast fatigue intermediate (FInt) and fast fatiguable [1, 2, 5, 10, 23, 24, 25, 26] (Figure 1). These mixed motor unit types furnish two broad groups of motor units whose properties denote their behavioral functions: a first set of lower force but highly fatigue resistant motor units (type S and FR) that efficiently generate adequate P_{di} to sustain breathing even under more extreme conditions [10, 27], and a second set of higher force but more fatigable motor units (type FInt and FF) that are optimally primed for short duration bursts of force generation approaching P_{dimax} [1]. The first set of inspiratory-related motor units is best considered as ‘the tidal pool’, responsible for generating the tidal volume during eupnea. The FInt and FF diaphragm motor units are not required for ventilation, despite their motor neurons residing in the phrenic pool and their constituent muscle fibers being distributed throughout the diaphragm muscle [28].

Type S diaphragm motor units comprise type I muscle fibers (expressing the slow myosin heavy chain – $MyHCs_{low}$ – isoform) that generate less force but are fatigue resistant and have a higher oxidative capacity (increased mitochondrial volume density) [23, 24, 29, 30, 31, 32]. It is likely that smaller phrenic motor neurons innervate type S motor unit fibers (Figure 1) [33, 34, 35], although this has not been directly established. Type FR diaphragm motor units comprise type IIa fibers (expressing the $MyHC_{2A}$ isoform) that also generate lower specific force compared to other type II fibers but greater than type I fibers and have a higher oxidative capacity accounting for their fatigue resistance (Figure 1) [23, 24, 29, 30, 31, 32]. It is likely that smaller phrenic motor neurons also innervate type FR motor unit fibers [33, 34, 35]. Type FR motor units are more functionally similar to type S motor units than to either type FInt of FF motor units (Figure 1) [1, 5, 10].

More fatiguable type FInt of FF motor units comprise type IIx and/or IIb diaphragm muscle fibers (co-expressing $MyHC_{2X}$ and $MyHC_{2B}$ isoforms in varying proportions) with larger cross-sectional areas (Figure 1) [4, 23, 25, 30, 31, 32, 36]. Single fiber studies have shown that type IIa, IIx and IIb diaphragm fibers generate greater specific forces compared to type I fibers [4, 23, 25, 29, 30, 31, 32, 36]. However, type IIx and/or IIb diaphragm muscle fibers have much lower oxidative capacities that contribute to their increased susceptibility to fatigue [4, 23, 25, 29, 30, 31, 32, 36]. Thus, although the contribution of type IIx and/or IIb fibers to total diaphragm muscle force is proportionately greater, their force contribution cannot be sustained. Phrenic motor neurons innervating type FInt and FF units are also likely to be larger than those of S and FR units [33, 34, 35] and this distinction is important in the appropriate recruitment of motor units during different behaviors (Figure 1).

2.2 Phrenic motor neurons and their recruitment

Phrenic motor neurons are located in the cervical spinal cord (C_3-C_6 depending on species). In rodents there are ~200-240 on each side [34], providing a total of ~450 diaphragm motor units. In the adult rat, phrenic motor neuron sizes vary, with somal surface areas ranging from ~500 to 8,000 μm^2 [34, 37]. This size variability plays an important role in motor control, with the orderly recruitment of diaphragm motor units being highly dependent on the total neuronal membrane surface area (capacitance). For a given synaptic input, the change in membrane potential ($\Delta Vm/\Delta t$) of smaller (lower capacitance) motor neurons is greater leading to earlier generation of action potentials (i.e., they are more excitable and recruited earlier) compared to larger (higher capacitance) motor neurons with lower intrinsic excitability – the Size Principle [5, 38, 39]. The size of motor neurons is also reflected by axonal diameters and axonal conduction velocities. Indeed, the Size Principle first proposed by Henneman was based on the observation that earlier recruited motor units displayed slower conduction velocities (i.e., smaller axonal diameters) [38, 39]. This distinction in the recruitment order of diaphragm motor units based on axonal conduction velocities was later validated by Dick et al [40]. Importantly, within a given motor unit type, the intrinsic properties of motor neurons are less variable, including properties such as axonal conduction velocity, discharge rates, somal surface areas, dendritic arborization and innervation ratio [34, 35, 40, 41, 42, 43, 44, 45, 46]. Accordingly, we introduced a model of diaphragm motor unit recruitment that assumes an orderly recruitment of type S, then type FR, followed by type FInt and FF units to accomplish increasing P_{di} generation across different behavioral requirements (Figure 1) [1, 5, 10, 26, 40, 46, 47].

There are five main circuit components that are included in the neuromotor control of diaphragm muscle during different motor behaviors (Figure 2): i) phrenic motor neurons; ii) central pattern generator responsible for the timing of diaphragm activation (and co-activation of other muscles) during the specific motor behavior; iii) premotor neurons responsible for transmitting the output of the central pattern generator and integrating sensory and other inputs; iv) interneurons (both local and ascending) responsible for modulating premotor neuron and/or phrenic motor neuron excitability; and v) direct cortical premotor input to phrenic motor neurons via the corticospinal pathway.

The neuromotor circuitry involved in activation of the diaphragm muscle during ventilatory behaviors has been very well-described (Figure 2). These previous studies reflect an intense focus on the ventilatory central pattern generator in the PreBötzinger complex, which represent the spontaneously active ‘kernel’ of neurons for the metronomic drive for inspiratory activation of the diaphragm [2, 48]. The location of inspiratory premotor neurons in the ventrolateral medulla (ventral respiratory group) and dorsomedial medulla (dorsal respiratory group) has been well documented. These medullary premotor neurons provide a predominantly ipsilateral monosynaptic drive to phrenic motor neurons during inspiration (Figure 3) [49, 50, 51, 52, 53, 54, 55]. If this descending bulbospinal presynaptic input is uniformly distributed, the recruitment of phrenic motor neurons would solely depend on intrinsic, size-dependent electrophysiological properties of motor neurons (i.e., the Size Principle). However, in a recent study, we found that glutamatergic presynaptic terminal density is higher on smaller phrenic motor neurons [37], that likely innervate type S and FR motor units that are involved in ventilatory behaviors. Similarly, we recently reported that expression of glutamatergic NMDA and AMPA receptors depends on phrenic motor neuron size with smaller motor neurons having a greater density of NMDA and AMPA receptor mRNA transcripts compared to larger motor neurons [56]. Thus, in addition to intrinsic motor neuron properties, the recruitment of fatigue resistant type S and FR motor units is guaranteed by the differential distribution of excitatory bulbospinal glutamatergic drive to smaller phrenic motor neurons (Figure 3).

Peripheral and central chemoreceptors are found in the carotid bodies and brainstem, respectively, and increase ventilatory drive in response to hypoxia and/or hypercapnia, respectively [2]. Lung mechanoreceptors are sensitive to lung inflation and act to prevent airway over-inflation [2]. Local inhibition of phrenic motor neurons from interneurons within the spinal cord has also been characterized [57, 58]. Additionally there are direct corticospinal inputs [59, 60] that allow for the voluntary control of ventilation or expulsive maneuvers, as well as during social and emotional activities [21, 61].

By stark contrast to the neural control of breathing, the circuits involved in expulsive/straining behaviors remain poorly characterised (Figure 2) [1, 2]. In expulsive maneuvers such defecation, vomiting, coughing and childbirth, the diaphragm muscle is often co-activated with upper airway, chest wall and/or abdominal muscles. The pattern generators (reflex centers) for these expulsive/straining behaviors are poorly defined but are likely located in the brainstem or spinal cord, similar to other pattern generators for vomiting [11, 12], sigh [62], swallowing [63], locomotion [64], micturition [65, 66] and ejaculation [67]. In addition, how these neural circuits interact or perhaps share common components with the ventilatory circuits [11, 13, 17, 18, 19, 68] or instead project directly to phrenic motor neurons [69, 70, 71] is obscure. Regardless, these expulsive/straining behaviors require the recruitment of the higher pressure generating but more fatigueable FInt and FF diaphragm motor units, with P_{di} often in excess of 200 cm H_2O [72, 73, 74, 75]. Perhaps our best knowledge of the neuromotor circuitry associated with these behaviors comes from studies investigating spinal cord injury and neuroplasticity in both animal models and clinical patients. The remainder of this review is concerned with these insights.

3. Models of spinal cord injury

Almost 17,000 new cases of spinal cord injury are diagnosed in the USA each year. The majority of these injuries involve the cervical spinal cord and result in significant impairment of diaphragm muscle activity [76]. A subset of these patients are unable to maintain adequate ventilation and become dependent on mechanical ventilation, a situation associated with substantial morbidity and mortality [77, 78]. Most spinal cord injuries are incomplete (~70%), with incomplete tetraplegia (cervical injury) accounting for 20.4% of spinal cord injury since 2015, with complete tetraplegia accounting for 11.5% of all injury [79]. Incomplete injuries largely affect only ipsilateral injury side portions of the descending bulbospinal excitatory inspiratory drive from the medulla to the phrenic motor neuron pool, although high level lesions (C_2) can affect both sides of the diaphragm muscle and chest wall [80]. These defects cause partial or complete paralysis of one side of the diaphragm during eupnea [76]. Post injury, variable recovery of ventilatory-related diaphragm muscle activity is observed [81], although the precise mechanisms underlying recovery of ventilatory function are not fully described. Overall, deficits in ventilatory activity following spinal cord injury range from 40-60% of expected forced vital capacity [76, 82], however, the contribution of diaphragm muscle alone to these deficits is confounded by increased airway secretions, reduced chest wall stiffness, reduced chest wall compliance, atelectasis and altered abdominal muscle tone, impairing P_{di} generation [76]. The impact of spinal cord injury on expulsive/straining behaviors is poorly understood, but dysfunction of these behaviors underlies diminished quality of life for spinal cord injury patients. Two models of spinal cord injury are routinely used to explore the mechanisms underlying diaphragm muscle dysfunction and recovery, namely, contusion injury and cervical spinal hemisection.

3.1 Cervical contusion injury model

Contusion injuries are the most common type of spinal cord injury, with substantial effects on long-term morbidity as well as mortality [76]. Animal studies of traumatic spinal cord injury commonly employ cervical contusion models [83, 84], including unilateral lesions [85, 86, 87, 88, 89, 90]. These models typically involve a cervical dorsal laminectomy, followed by collision with an impactor (with varying tip sizes ~1-2 mm) producing an impact force of 100-400 kDy. In addition to a range of forces, contusion models also differ in their placement, with midline and unilateral lesions employed. Despite faithful recapitulation of various histopathological hallmarks of spinal cord injury [86, 91], cervical contusion models are inconsistent in demonstrating alterations in diaphragm motor unit activity and ventilatory or non-ventilatory behaviors [83, 84, 85, 87, 88, 90, 92]. Inconsistencies in the effects of contusion models relate to differences in the extent of phrenic motor neuron and interneuron death, as well as the involvement of white matter tracts (ascending, descending and segmental) [86] that play major roles in neuromotor control of diaphragm motor units (see Figure 3) [1, 2]. The inconsistencies in these models limit their utility to provide mechanistic insight or as a key prognostic indicator for human functional outcomes [93]. For example, we showed that following unilateral mid-cervical contusion injury in rats, there is extensive loss of ~50% of phrenic motor neurons on the affected side [86, 88, 89, 90, 94] and a ~30% decrease in P_{dimax} evoked by bilateral phrenic stimulation [85]; yet there is very little effect on the performance of ventilatory behaviors

[86, 88, 89, 90, 94]. Indeed, unilateral denervation of the diaphragm muscle with total unilateral paralysis does not affect the performance of ventilatory behaviors [95]. This is not surprising since ventilatory behaviors of the diaphragm muscle require less than 50% of P_{dimax} [1, 4, 10, 85]. Importantly, without a clear loss of ventilatory function in the contusion model, the ability of this model to provide insight for the development of therapeutic approaches to promote functional recovery is severely limited. However, with a decrease in neural output to the diaphragm (reflected by a decrease in evoked P_{dimax}), it is likely that there are deficits in expulsive/straining behaviors of the diaphragm muscle in contusion models of spinal cord injury. Unfortunately, deficits in these expulsive/straining diaphragm muscle behaviors have not been adequately demonstrated.

3.2 Cervical spinal hemisection model

In 1895, John Porter introduced the cervical spinal hemisection animal model to investigate neuroplasticity of diaphragm muscle neuromotor control following spinal cord injury [96]. The cervical spinal hemisection technique is commonly performed at the C_2 level, rostral to the phrenic motor pool, thereby disrupting ipsilateral premotor input to phrenic motor neurons. Similarly to the contusion model, this model involves a dorsal laminectomy followed by unilateral transection transecting anteriolateral projections, specifically the ipsilateral bulbospinal pathways (Figure 3) [49, 50, 51, 52, 53, 54, 55]. Despite the presence of a modicum of contralateral descending inputs in addition to ascending columns projecting to cervical motor pools (Figure 3) [2], unilateral paralysis of eupneic diaphragm muscle activity ensues following transection [96, 97, 98, 99, 100, 101, 102, 103, 104, 105, 106, 107, 108, 109]. The absence of inspiratory-related diaphragm muscle EMG activity is validated at the time of surgery, providing a clear marker for the subsequent spontaneous recovery of ventilatory function over time (neuroplasticity) [101, 102, 103, 104, 105, 106, 107, 109, 110, 111]. A number of laboratories have used the cervical spinal hemisection model, and thus it is well-characterized and lacks many of the vagaries (scarring, inflammation, penumbra of injury) of the contusion model. Importantly, there is no loss of phrenic motor neurons in the cervical spinal hemisection model of injury, despite unsubstantiated reports from some laboratories. Furthermore, axotomy of the descending corticospinal and bulbospinal tracts does not result in marked death of premotor neurons [112, 113, 114, 115]. Recently, we did report that by two weeks following C_2 spinal cord hemisection, the size (somal surface areas) of phrenic motor neurons decreases, consistent with an increase in excitability that may underlie functional recovery.

4. Phrenic motor neurons and spinal cord injury

The primary prognostic determinant of neuromotor deficits following cervical spinal cord injuries is the extent of motor pathway disruption [76, 116]. For diaphragm motor units, the types of functional deficits present are largely dependent on the extent of bulbospinal disruption and the extent of phrenic motor neuron loss [76, 86]. There is a substantial capacity for neuroplasticity exhibited by the diaphragm neuromotor control system that may be harnessed for recovery. This plasticity is provided for by multiple substrates, including axonal sprouting of spared bulbospinal or interneuronal tracts, altered intrinsic properties of phrenic motor neurons (e.g., morphological changes) and enhancement of neurotrophic

signaling pathways (e.g., brain-derived neurotrophic factor – BDNF/tropomyocin-receptor kinase B – TrkB).

4.1 Presynaptic neuroplasticity at phrenic motor neurons following spinal cord injury

There is considerable regenerative neuroplastic capacity in the neural inputs onto phrenic motor neurons following spinal cord injury. These involve inputs from contralateral bulbospinal projections, local segment interneurons and ascending projections from more caudal regions of the spinal cord [52, 99, 101, 102, 103, 104, 109, 111, 117, 118, 119]. In cases where ventilatory behaviors are impaired, such as in the cervical spinal hemisection model, synaptic stripping occurs for the axotomized inputs, with a marked reduction in the number of excitatory glutamatergic pre-synaptic terminals remaining on phrenic motor neurons [120]. In a preliminary study from our group, we found that following unilateral cervical spinal hemisection, the extent of loss of glutamatergic presynaptic terminals (synaptic stripping) is much greater on smaller phrenic motor neurons. This obsevation confirms that descending inspiratory presynaptic drive for ventilatory behaviors is primarily ipsilateral [49, 50, 51, 52, 53, 54, 55] and further suggests this drive is distributed disproportionately to smaller phrenic motor neurons. It is possible, that a signficant proportion of presynaptic drive for expulsive /straining behaviors does not emanate from a supraspinal origin. In limb locomotor control, the central pattern generator and presynpatic neurons are located segmentally in the spinal cord [1]. This may also be the case for expulsive/straining behaviors of the diaphragm [11, 13, 17, 18, 19, 68], particularly those that involve co-activation of chest wall and abodminal muscles (Figure 3).

4.2 Postsynaptic neuroplasticity of phrenic motor neurons following spinal cord injury

Postsynaptic neuroplasticity of phrenic motor neurons may be divided into alterations of intrinsic neuronal properties, primarily through morphological adaptations, and alterations of neurotransmitter receptors and/or the expression of various subtypes.

Phrenic motor neurons display a wide range of neuronal surface areas, with their intrinsic excitability dictated by their capacitance (see section 1.2), as determined by the overall neuronal membrane surface area. Following spinal cord injury, the somal and dendritic compartments respond to alter intrinsic excitability. In the cervical spinal cord hemisection model, phrenic motor neurons exhibit reduced somal surface areas [121] and maintenance of the dendritic compartment surface area [121]. These changes are consistent with increased excitability of phrenic motor neurons thereby promoting recovery of eupneic activity. Alterations in somal or dendritic morphology following contusion injury have not been systematically examined. There is little reason to expect that contusion injury would have a selective size-dependent loss of phrenic motor neurons. By comparison, other conditions where phrenic motor neurons loss occurs over a longer time period affect primarily larger motor neurons [2, 33, 34, 122].

In addition to the remarkable structural neuroplasticity that is evident subsequent to spinal cord injury, modulation of receptor expression plays a key role in priming phrenic motor neurons for recovery. As mentioned above, smaller phrenic motor neurons have a greater density of NMDA and AMPA receptor mRNA transcripts compared to larger motor neurons

[56]. Early evidence for receptor-mediated neuroplasticity came from ultrastructural studies documenting increased synaptic apposition and double synapses [123, 124]. More recently, we reported a robust up-regulation of NMDA glutamatergic receptor mRNA expression in phrenic motor neurons that was associated with spontaneous recovery of eupnea following cervical spinal hemisection [119, 125]. Enhanced serotonergic signalling has also shown to be of importance in the recovery of diaphragm muscle ventilatory behaviors following cervical spinal hemisection [125, 126, 127, 128, 129] and contusion [92]. The precise interactions between phrenic motor neuron size, recovery of ventilatory behaviors and the neuroplastic enhancement by neurotrophins (including BDNF) [101, 102, 103, 109, 110, 111] is not fully determined. To this end, recent preliminary work by our group shows that smaller phrenic motor neurons express a greater amount of TrkB receptor compared to larger phrenic motor neurons. This finding may account for the ~30% spontaneous recovery from cervical spinal hemisection of ventilatory efforts and the robust effectiveness of neurotrophic enhancements in this particular model.

5. Diaphragm muscle functional deficits following spinal cord injury

The functional outcomes from the differing models of spinal cord injury depend on the model being assessed. In the case of cervical contusion models, the indiscriminate loss of phrenic motor neurons innervating type S, FR, FInt and FF motor units leads to an overall decrease in the generation of P_{dimax}, with no deficit in the performance of diaphragm muscle function. Unknown, but likely, deficits arise in the performance in the performance of expulsive/straining behaviors [85, 86, 94]. Importantly, the performance of expulsive/straining maneuvers by the diaphragm muscle display very little reserve capacity, with these behaviors necessitating recruitment of almost all diaphragm motor units [1, 2, 5, 10, 26, 27]. These observations are consistent with those in human clinical cohorts, with impaired Valsalva maneuvers [130], weak cough [131, 132, 133, 134], defecation difficulties (constipation, increased transit time) [135, 136, 137] and parturition difficulties (particularly stage 2 of labor) [138]. In patients, increased airway secretions, changes in lung and chest wall mechanics and reduced abdominal muscle activity may impair ventilation, particularly during high cervical injuries [76]. These factors all contribute to a ventilatory phenotype without requiring substantial alterations of S and FR diaphragm motor units.

Although ventilatory efforts of the diaphragm muscle are absent or markedly attenuated following cervical spinal hemisection, P_{dimax} is preserved. Unfortunately, functional deficits in the performance of higher force expulsive/straining behaviors of the diaphragm have not been examined. However, ventilatory behaviors that require greater P_{di} generation (e.g., efforts against an occluded airway) are less impacted by cervical spinal cord hemisection. Instead, the functional changes are primarily in the ventilatory pattern and unilateral diaphragm muscle paralysis during ventilation [51, 96, 99, 101, 102, 103, 104, 110, 111, 117, 119, 139, 140, 141, 142, 143], consistent with the selective disruption of ipsilateral bulbospinal respiratory glutamatergic drive [49, 50, 51, 52, 53, 54, 55]. Spontaneous recovery (~40% by 14 days post-injury) following cervical spinal hemisection does occur, although not to pre-injury levels [103, 104, 110, 117, 139, 140, 141, 142, 143]. The substrate for the recovery of diaphragm muscle activity are latent contralateral, segmental and

ascending inputs (Figure 3) [99, 101, 102, 103, 104, 109, 111, 117, 119, 144], although the precise motor unit specifics and pre- versus post-synaptic potencies remain undescribed.

Clinically, a variety of rehabilitative strategies have been developed in order to improve diaphragm muscle function following spinal cord injury. Ventilatory assistance is more common in the acute phase post-injury, related to spinal shock, excessive airway secretions and immediate flaccid paralysis of muscles below the level of injury, including intercostal muscles [82, 133, 145, 146, 147]. This latter results in the ribcage collapsing with negative intrathoracic pressures, substantially impinging on the effectiveness of lung ventilation [82]. However, with little changes in $PaCO_2$ between cervical and lower injuries [148] and only 10% of all spinal cord injury patients being hypoxaemic [149], mechanical ventilation weaning is a priority in all but the most severe cases of diaphragm paralysis following spinal cord injury. In the longer term, and with the goal of providing for expulsive/straining behaviors, a variety of treatment options exist, including manually assisted cough, mechanical insufflation/exsufflation devices and functional electrical stimulation of abdominal muscle. Manually assisted cough and the successful operation of insufflation/exsufflation devices requires the assistance of trained caregivers, which is often expensive or inconvenient. Furthermore these techniques are fail to produce peak cough flows > 4.5 l/s [150, 151], necessary to reduce risk of acute respiratory failure [152]. By contrast, functional electrical stimulation of abdominal muscle results in peak cough flows of >7 l/sec [153, 154], albeit in patients with implanted electrodes, although reasonable peak flows are achieved using surface electrodes ~3L/s, that are improved with muscle training [155]. Aside from the cost of the technology, the adoption of stimulation methods is limited to those who have intact motor neurons in the spinal pools innervating the abdominal muscles. While functional electrical stimulation of abdominal muscles does improve cough effectiveness, it does little to improve the function of the diaphragm muscle, whose inspiratory action is of greater importance than expiratory muscles, as low volumes of inspired air decrease cough capacity, regardless of the effectiveness of active expiratory muscles [156, 157]. Although pressure generation of the oesophagus and gastric compartments remain the best measure of cough effectiveness and muscle strength [4, 85, 158, 159, 160], they are often overlooked in favour of flow measures [161].

6. Conclusions

Diaphragm neuromotor control is about far more than just breathing, with diaphragm muscle activation required to accomplish a wide assortment of expulsive/straining maneuvers. As the emergency and ongoing care of patients with spinal cord injury steadily improves, there will be an increased onus on pre-clinical and clinical researchers to preserve these higher-force airway defence behaviors that are highly correlated with mortality and morbidity. Thus studies in neuromotor control of the diaphragm muscle should be of interest beyond the usual coterie of ventilation-centric studies.

7. Expert opinion

There are two major hindrances to increasing the translational potential of recent discoveries in the neuroplasticity of diaphragm motor units. The first problem is the lack of real data on

the burden of expulsive/straining deficits in the spinal cord injury clinical population. To date there have been no exhaustive studies or surveys of abdominal pressure generation in clinical cohorts with spinal cord injury, with the prime clinical assessment being the ability to ventilate. As the life expectancy of spinal cord injury sufferers continues to improve [162], and as the inclusivity of this cohort to activities such as pregnancy and childbirth increase [138], there remains an immediate need for some baseline quantifications of non-ventilatory maneuvers in these patients. Many other conditions of the diaphragm muscle selectively afflict the type FInt and FF diaphragm motor units, including age-associated weakness and atrophy (sarcopenia) [4, 31, 34, 163], malnutrition [36] and chronic obstructive pulmonary disease [164]. The FInt and FF motor units are activated to perform the expulsive/straining maneuvers that we know the least about in spinal cord injury patients. It behoves us a research community to address this issue, as these co-morbidities are going to become much more common as life span and quality of life expectations increase in the spinal cord injury cohort. Additionally, these concerns are not limited to the subset of patients with a cervical injury.

The second problem remains the obdurate focus of preclinical research into the minutiae of ventilation and ventilatory control. In many cases of cervical spinal cord injury, similar to the contusion models, there is little long-term compromise of eupnea. However, the substantial risk of airway infections remains, due to the lack of airway defence and effective clearance [76, 77]. It is important that issues such as weaning from mechanical ventilation continue to be addressed, but these constitute the minority of cases and are likely intractable in the absence of any paradigm-shattering advance.

Over the next five years, an adequate description of the specific motor unit types afflicted in various spinal cord injury models is necessary, along with a precise description of the specific functional deficits associated with injury. Similarly, the effect of therapies and interventions must be assessed in light of the motor units and type of behaviour affected. For too long, successful intervention has been defined as being a return to the normal pattern and tidal volume generation during eupnea. It is essential that assessment of non-ventilatory expulsive/straining maneuvers becomes *de rigueur* in the testing of interventions aimed at improving diaphragm muscle function. For enrolment of patients, eligibility criteria would not be exclusive to those with a cervical injury. Patients could be funnelled into pressure-generation assessments based on anecdotal histories (i.e., previous complaints of constipation or weak cough). At first blush, a cross-sectional study would provide some actionable data regarding abdominal pressure generation efforts, to be followed up by longitudinal studies and stratification by age and gender. For preclinical studies, various efforts outlined in this review to classify the effectiveness of intrinsic and circuit (input) substrates for recovery in a size-dependent manner are a reasonable start. We wait with bated breath for a wider adoption of motor unit diversity in the design and characterisation of future spinal cord injury research.

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Papers of special note have been marked as of considerable interest (*) to readers.

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Article highlights

- Neuromotor control of the diaphragm muscle is important for both ventilatory and non-ventilatory behaviors.
- The neuromotor circuitry that is integrated by phrenic motor neurons is likely to be different for different types of behaviour.
- Cervical spinal cord injuries and models of cervical spinal cord injury have differential effects on ventilatory and non-ventilatory behaviour
- Non-ventilatory expulsive/straining maneuvers cause the majority of morbidity and mortality in the spinal cord injury population, but very little quantitative data exists regarding these deficits.
- We outline some of the urgent pre-clinical and clinical directions to address non-ventilatory outcomes of spinal cord injury.

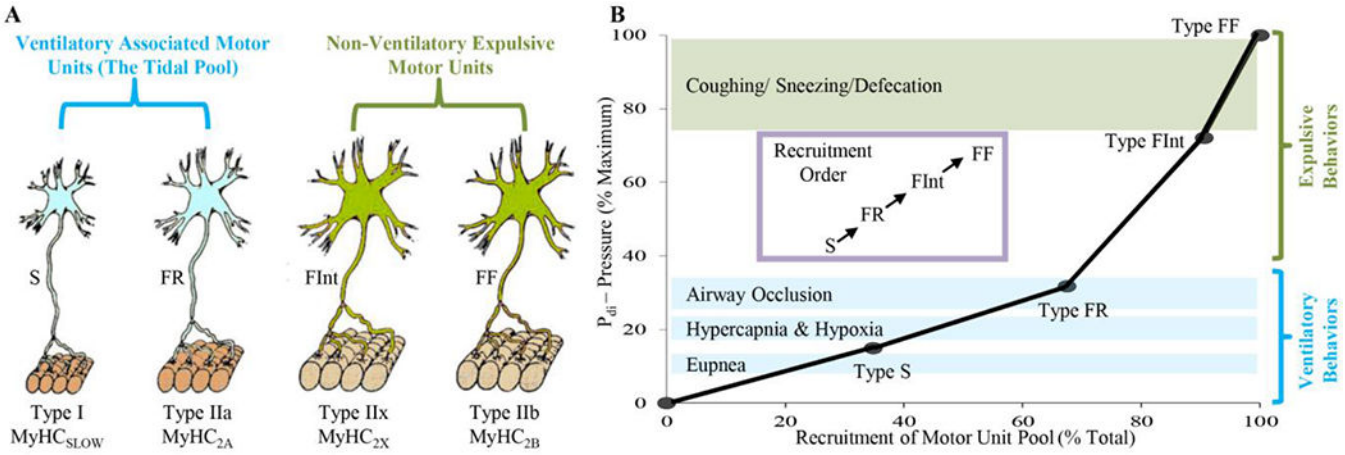

Figure 1:

Different diaphragm muscle motor unit types are distinguished by their intrinsic, mechanical, and fatigue properties, and are classified as type S, FR, FInt, and FF. Within an individual motor unit, all constituent muscle fibers exhibit homogeneous myosin heavy chain (MyHC) expression. In the diaphragm muscle of most species, type I and IIa muscle fibers have smaller cross-sectional areas than those of type IIx and/or IIb fibers. Forces produced by type I fibers are less than forces produced by type IIa fibers that are less than forces produced by IIx and/or IIb fibers. Recruitment of diaphragm muscle motor units is in an orderly fashion, necessary to accomplish a range of motor behaviors. Ventilation is accomplished by recruitment type S and FR motor units, whereas higher-force airway clearance behaviors and straining/expulsive manoeuvres require recruitment of more fatigueable type FInt and FF motor units.

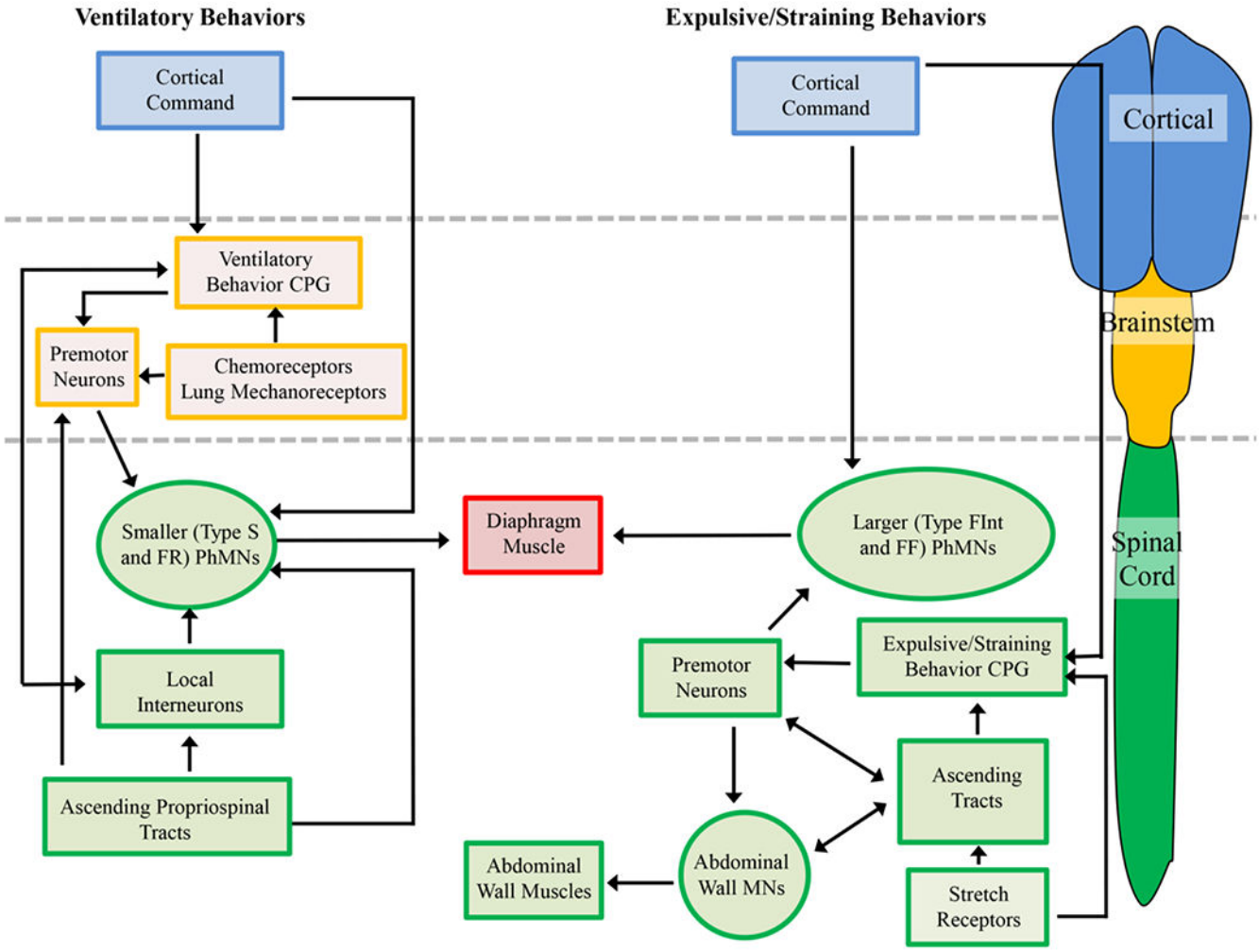

Figure 2:

Neuromotor control of diaphragm muscle ventilatory and expulsive/straining behaviors requires cortical (blue boxes), brainstem (orange boxes) and spinal cord (green boxes) centers. Ventilatory behaviors are the well characterized and require the recruitment of predominantly type S and FR motor units. Cortical pathways are able to modulate the eupnic rhythm by interactions with the ventilatory central pattern generator (CPG) or directly via synapses onto phrenic motor neurons (PhMNs). The ventilatory CPG activates brainstem premotor neurons that in turn innervate the PhMNs. Activity of PhMNs during ventilation is also modulated (directly and indirectly) by spinal cord ascending tracts and interneurons. Brainstem chemoreceptors and lung mechanoreceptors regulate the activity of premotor neurons, and act to increase premotor neuron discharge (and thus PhMN activity) during hypoxia/hypercapnia. In the case of expulsive/straining behaviors, the majority of control centers are located within the spinal cord, and recruitment of type FInt and FF motor units (higher-force producing units) is necessitated. Some cortical control of the PhMNs and spinal expulsive/straining CPG may be evident, but rectal and vaginal stretch receptors also elicit strong P_{ab} generation. There may be shared spinal premotor neurons within the spinal

cord for co-activations of PhMNs and abdominal muscle MNs, with a variety of ascending projections coordinating these activities.

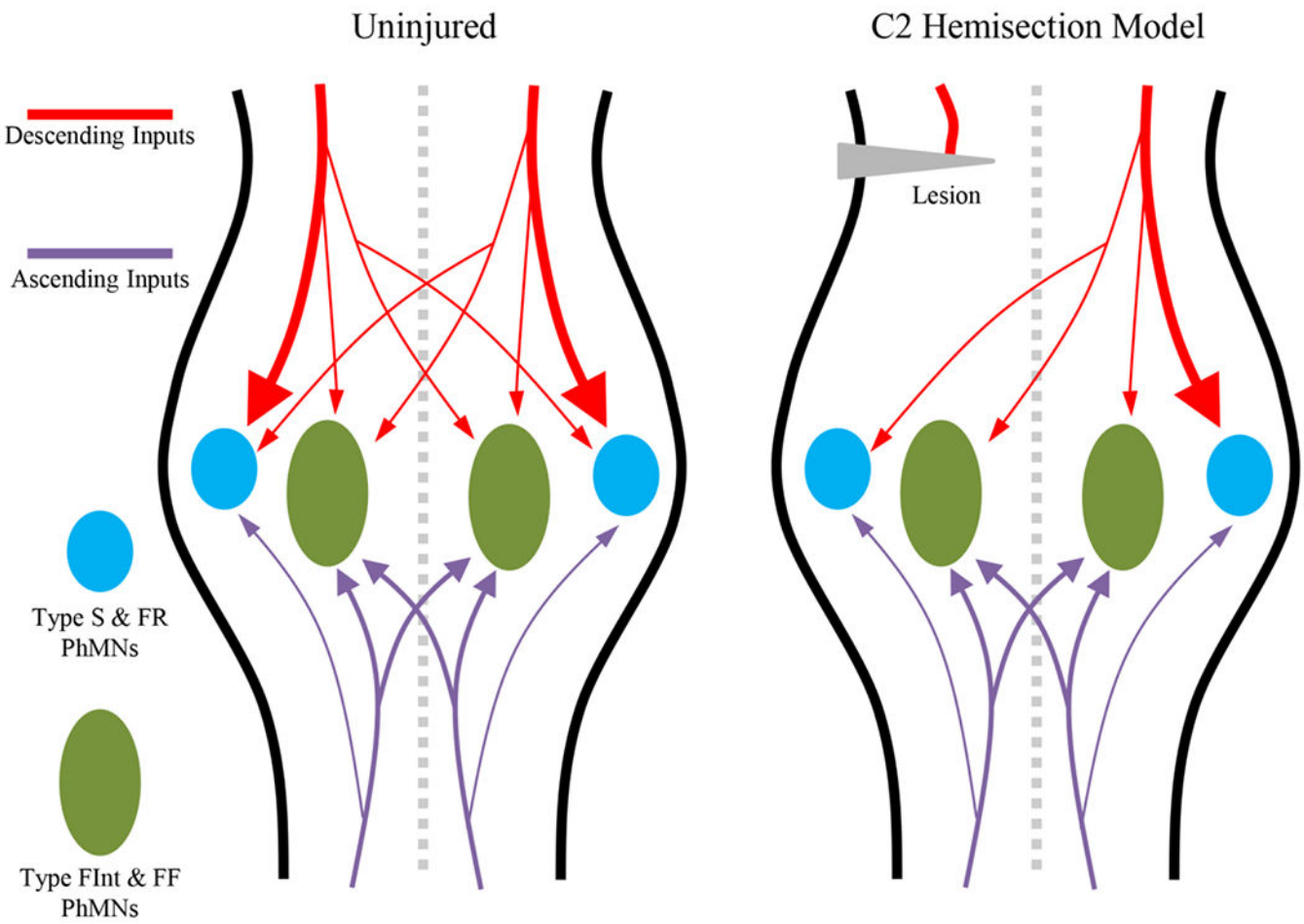

Figure 3:

The majority of phrenic motor neuron glutamatergic inputs are derived from descending (red) and ascending (purple) tracts. In the uninjured spinal cord, the majority of the bulbospinal descending inputs are distributed ipsilaterally to type S and FR phrenic motor neurons (PhMNs, blue), with small amounts of contralateral input to type S and FR PhMNs and a modicum of ipsi- and contralateral inputs to type FInt and FF motor units (green). Ascending inputs are primarily activated by co-contractions with abdominal muscles and both ipsi- and potentially contralateral inputs are predominantly on type FInt and FF PhMNs. Following unilateral C_2 cervical hemisection, the inputs transected are the ipsilateral bulbospinal descending projections onto type S and FR PhMNs, accounting for impairments in ventilatory behaviors. In this model, the majority of inputs to type FInt and FF PhMNs remain, accounting for the preserved P_{dimax}.