Voluntary and involuntary ventilation do not alter the human inspiratory muscle loading reflex

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Murray NP, McKenzie DK, Gandevia SC, Butler JE. Voluntary and involuntary ventilation do not alter the human inspiratory muscle loading reflex. J Appl Physiol 109: 87–94, 2010. First published April 15, 2010; doi:10.1152/japplphysiol.01128.2009.—The reflex mechanism of the short-latency inhibitory reflex to transient loading of human inspiratory muscles is unresolved. Muscle afferents mediate this reflex, but they may act via pontomedullary inspiratory centers, other bulbar networks, or spinal circuits. We hypothesized that altered chemical drive to breathe would alter the initial inhibitory reflex if the neural pathways involved inspiratory medullary centers. Inspiration was transiently loaded in 11 subjects during spontaneous hypercapnic hyperpnea and matched voluntary hyperventilation. The latencies of the initial inhibitory response (IR) onset (32 ± 0.7 and 38 ± 1 ms for spontaneous and voluntary conditions respectively, P < 0.001) and subsequent excitatory response (ER) onset (80 ± 2.9 and 78 ± 2.6 ms, respectively, P = 0.46) were measured. Mean end-tidal PCO2 was 43 ± 1.5 Torr with dead space ventilation and was 14 ± 0.6 Torr with matched voluntary hyperventilation (P < 0.001). A mean minute volume >30 liters was achieved in both conditions. The absence of significant difference in the size of the IR suggested that the IR reflex arc does not transit the brain stem inspiratory centers and that the reflex may be integrated at a spinal level. In voluntary hyperventilation, an initial excitation occurred more frequently and, consequently, the IR onset latency was significantly longer. The size of the later ER was also greater during voluntary hyperventilation, which is consistent with it being mediated via longer, presumably cortical, pathways, which are influenced by voluntary drive.

hypercapnia; hypocapnia; occlusion reflex

IN CONTRAST TO THE LOADING-mediated excitation seen in limb muscles, inspiratory muscles show a profound, short-latency inhibition to transient airway occlusion that is likely to be mediated by afferents from inspiratory muscles acting on the chest wall (8, 11, 45, 50). Its latency is prolonged in asthma (9) and in obstructive sleep apnea, during which the prolongation is proportional to the severity of the disease (29). The inhibition is sufficiently powerful that, in response to a single occlusion of the airway, many subjects display a brief period during which there is a clear loss of electromyographic (EMG) activity (Fig. 1C). Investigation of this reflex offers insight into the neural control of ventilation and also the potential usefulness of the reflex in the assessment of respiratory diseases (44).

The reflex to airway occlusion is similar to the inhibitory reflexes of respiratory muscles evoked by electrical stimulation of the muscular afferents in humans and animals, including the phrenic-to-phrenic, phrenic-to-intercostal, and intercostal-to-phrenic reflexes (10, 12, 18–20, 27). However, the neural mechanisms underlying the inhibition remain unclear. It may simply be a segmental and largely autogenetic reflex with no integration of the response between the ventilatory muscles. Second, a spinal segmental response may be integrated via propriospinal projections passing cranially and caudally to different inspiratory motor nuclei. Such propriospinal projections are involved in the integration of spinal cord responses involving ventilatory (2, 28, 30, 33) and limb muscles (48) in humans and animals. A third possibility is that the reflex is integrated within the brain stem, perhaps in pontomedullary respiratory centers. This is consistent with the observation that tendon organ afferents from intercostal muscles directly inhibit some medullary inspiratory neurons (7).

Several observations argue against simple segmental pathways for the occlusion reflex. First, the latency of the onset of inhibition across scalene muscles, parasternal intercostal muscles, costal diaphragm, and crural diaphragm is broadly similar in humans, despite different peripheral conduction distances for each inspiratory muscle (50). In addition, electrical stimulation of a single intercostal or phrenic nerve in cats or humans evokes reflex inhibition of many inspiratory muscles, suggesting a propriospinal or supraspinal mechanism (10, 19, 20, 27, 59). The dorsal respiratory group (DRG) of inspiratory neurons is inhibited by electrical stimulation of phrenic and intercostal nerve group I and II afferents in the cat (53). For human scalene muscles, if it is assumed that the peripheral nerve length is ~10 cm, group I afferent velocities are as low as 70 ms−1 (37), motoneuronal conduction velocities are as low as 40 ms−1, and there are a minimum of two central synaptic delays, the latency of the onset of the initial reflex inhibition should not be longer than ~7 ms if the reflex inhibition is segmental. This prediction is much less than the mean measured onset latency of 34 ms for human scalene muscles (44). This comparison argues against a simple di- or oligosynaptic segmental reflex mediated by large-diameter muscle afferents. In fact, the latency of the onset of inhibition is long enough to allow central conduction to inhibit bulbospinal output or conduction via intersegmental paths.

Inspiratory corticospinal neurons, driving inspiratory motoneurons by fast, oligo- or monosynaptic connections, exist (26, 52), and it is believed that voluntary breathing, at least in part, is mediated by these neurons, although uncertainty about the organization of voluntary inspiration remains. Spontaneous breathing is driven by medullary circuits (22, 23). To assess the level of reflex integration in the motor axis, we aimed to measure the short-latency occlusion-mediated reflex of inspiratory muscles under conditions of maximized differential re-
cruitment of inspiratory bulbospinal efferents and inspiratory corticospinal efferents. The occlusion reflex was compared during CO2-driven hyperpnea and matched voluntary hyperventilation. We hypothesized that if the short-latency, loading-mediated inhibitory reflex is integrated within medullary inspiratory centers, then during increased activation of these centers by hypercapnia, reflex inhibition to inspiratory occlusion would be greater. Equally, during voluntary hyperventilation, any drive passing corticospinally would not be subject to inhibition. Conversely, if this inhibitory reflex is integrated outside the medullary inspiratory centers with the inhibitory projections acting more caudally, such as on propriospinal networks or at the motoneurons themselves, then biasing of the inspiratory motor axis toward volitional or automatic states should not affect the magnitude of the inhibitory response, because either drive would be equally subject to inhibition.

**METHODS**

**Subjects.** Eleven subjects (6 female) with no history of respiratory or neurological disease participated in the study. Their age, weight, and height were 32 ± 10 (SD) yr, 67 ± 12 kg, and 175 ± 9 cm. All procedures were approved by the Human Research Ethics Committee at the University of New South Wales, and the study was conducted according to the Declaration of Helsinki.

**Electromyography.** EMG was recorded from the scalene muscles bilaterally with surface electrodes (Cleartrace ECG electrode, ConMed, Utica, NY) according to a validated technique (44). The active electrode was placed in the posterior triangle of the neck at the transverse level of the cricoid cartilage, midway between the posterior border of the sternomastoid muscle and the anterior border of the trapezius muscle. The reference electrode was placed on the clavicle at a site indicated by an imaginary line descending the longitudinal axis of the scalene muscle group from the active electrode. The active electrode was placed on the clavicle at a site indicated by an imaginary line descending the longitudinal axis of the scalene muscle group from the active electrode. A ground electrode plate was placed over the right acromion. The surface electrocardiogram (ECG) was also recorded.

EMG signals were amplified 10,000 times (CED 1902, Cambridge Electronic Design, Cambridge, UK) and filtered online with a band pass of 16–1,000 Hz. Offline, further high-pass filtering was applied to the EMG recordings (>53 Hz).

**Protocol.** Each subject underwent two sets of experimental trials during the same session. In the first set, the subject breathed through an additional dead space of 1.02 liters to induce hypercapnia. To achieve hypocapnia in the second set, the subject breathed voluntarily through a low-volume mouthpiece following a visual display of actual inspiratory volume and a target inspiratory volume. The feedback controller used a “triangular,” linearly increasing target of inspiratory

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Fig. 1. Method of measurement of short-latency inhibitory reflex. A: reflex latencies and sizes measured from average of rectified electromyograms (EMG) for each set of 60 trials. Mean mouth pressure (Pm, cmH2O) and mean rectified scalene EMG activity (µV) are shown. Inhibitory response (IR) trough amplitude is given by x/z, and excitatory response (ER) peak amplitude is given by y/z; z is mean preocclusion baseline EMG. Mean amplitudes were also calculated from 10-ms periods centered on the IR trough and ER peak. IR area over the curve (AOC) is given by the obliquely hatched area normalized to z, and ER area under the curve (AUC) is given by the dark gray area normalized to the light gray area. Initial ER (ER0) AUC (in black) is defined as the AUC within a measurement pane bounded by 3 dashed lines (1 SD above the 50-ms preinspiratory mean, 20 ms after occlusion onset, and 32 ms after occlusion onset). B: time of onset of airway occlusion determined from the Pm trace, with a magnified gain for the y-axis, showing sharp inflection caused by balloon inflation. This was used to mark time of occlusion onset. All latencies are expressed relative to this time. C: right scalene raw EMG and flow signals for 1.5 ventilatory cycles. Vertical dashed line, inspiratory occlusion onset; *, clear IR. Inspiratory flow is in the negative direction.
volume to set the same mean tidal volume, respiratory rate, and inspiratory time that had been measured during the first set of trials over the period when end-tidal PCO₂ (PetCO₂) was stable. A 10-min break between sets of trials allowed the return of isocapnia. During the hypercapnic experiment, the subjects were instructed to breathe as they wished. During the hypocapnic experiment, subjects were instructed to follow the inspiratory target and to exhale as they wished to be ready for the next inspiration. Inspiratory occlusion was achieved with an in-line, inflatable balloon valve (inspiratory occlusion pressure valve and valve controller, Hans Rudolph, Kansas City, MO). For both sets of trials, subjects were told to “breathe through” the occlusion.

In each experiment, subjects were seated comfortably and breathed through a low-resistance, low-volume, in-line apparatus containing a microbiological filter (SureGard, Melbourne, Australia), balloon valve, and linear pneumotachograph (model 3813, Hans Rudolph). Each set of trials consisted of 60 inspiratory occlusions that lasted 250 ms and were delivered after the onset of inspiration during random, operator-selected breaths at an average rate of about one in three breaths. The occlusion was delivered without warning to halt inspiratory flow within 10 ms of the onset of balloon inflation. A hardware integrator (model FV 156, Validyne Engineering, Los Angeles, CA) processed the flow signal online to provide a resetting inspiratory volume signal. Mouth pressure (Pm) and PetCO₂ (Normocap, Datex-Ohmeda, Madison, WI) were measured near the mouthpiece.

For both conditions, before the loading stimuli were introduced, subjects breathed for ≥180 s until PetCO₂ was stable. During the hypercapnic experiment, a software-driven gating system was used to avoid contamination of the reflex response by the QRS complex of the ECG. Occlusion was gated first by a standard inspiratory volume and then by the QRS complex of the ECG. A different dual-gating system was used for the hypocapnic experiment, with the occlusion gated first by the QRS complex and then by the mean level of rectified scalene EMG, measured by a moving 30-ms window, and averaged for both sides of the neck. This aimed to match the mean scalene EMG at the onset of occlusion during the hypercapnic experiment.

Effect of EMG activity on reflex inhibition. Six of the 11 subjects took part in a third experiment, which was designed to examine the effect of the level of prestimulus EMG on the reflex inhibition to loading. The same apparatus described for the hypocapnia experiment was used. Subjects were given feedback of inspiratory flow only and asked to maintain a flow of 0.75 l/s for as long as was comfortable during each inspiration. The EMG gating system used in the main experiment triggered the inspiratory occlusion at five arbitrary mean voltages, between 2 and 50 μV depending on the subject. Instruction to the subject and the pattern of loaded breaths were otherwise as described for the main experiment.

Data analysis. All signals were monitored online and recorded to computer using an interface with a 2-kHz sampling rate (CED 1401 and Spike2, Cambridge Electronic Design). Trials of 400-ms duration, commencing 100 ms before occlusion, were collected offline. The collection frames were triggered for each occlusion by threshold-crossing measurement of the Pm channel at the perturbation induced by airway occlusion (Fig. 1B). EMG was rectified and then averaged across each set of 60 trials. A five-point smoothing was applied to the averaged EMG traces. As described in previous studies (8, 45, 50), the short-latency loading reflex consists of an early inhibitory response (IR), with a typical onset latency of ∼35 ms, followed by a later excitatory response (ER), with a typical onset latency of ∼115 ms. The rectified, averaged EMG for each set of trials was measured to provide the latencies of the IR onset, IR trough, ER onset, and ER peak and the EMG amplitudes of the IR trough, a 10-ms EMG average centered on the IR trough, the ER peak, and a 10-ms EMG average centered on the ER peak (Fig. 1). The IR area over the curve and the ER area under the curve (AUC) were also measured. All voltage measurements were normalized to the preocclusion EMG, measured as the mean of the rectified EMG over the 100 ms immediately preceding the occlusion, according to a validated protocol (44), resulting in units that are dimensionless or temporal (see Table 2). Measurements for each subject were averaged from both sides of the neck. An initial ER (ER₀) was seen frequently at ∼20 ms (Fig. 2). For the purpose of measuring the relative frequencies of this event in the two conditions, an ER₀ was deemed to occur if the rectified and averaged scalene EMG exceeded 3 SD above the preocclusion mean for >5 ms within a window of 20–32 ms after the occlusion onset. To quantify the ER₀, its magnitude was measured as the AUC, >1 SD above the preocclusion EMG and occurring within 20–32 ms following the stimulus onset. As the response was typically small, its onset was difficult to differentiate from the preocclusion scalene EMG. The preocclusion mean was measured over the final 50 ms for the definition of ER₀ events.

For the third experiment, in which the reflex to loading was compared at different preocclusion levels of EMG, IR trough size, 10-ms EMG average centered on the IR trough, and trough area over the curve were measured and normalized to the preocclusion EMG (as described above). These quotients were normalized to the corresponding quotient measured for each subject during the hypercapnic experiment. The size of the inhibitory reflex was then compared with the preocclusion EMG levels, expressed relative to the absolute preocclusion EMG measured for each subject in the hypercapnic experiment.

Statistics. For 9 of the 10 measures of reflex latency and size and, also, Pm, minute volume, PetCO₂, ER₀ area, and preocclusion EMG, paired t-tests were used to test for differences in reflex parameters
between hypercapnic hyperpnea and hypocapnic hyperventilation. For the one nonparametric data set (ER AUC), a Wilcoxon signed-rank test was used. For categorical data (ER0 frequency), a \( \chi^2 \) test was performed. Statistical significance was set at \( P < 0.05 \).

**RESULTS**

Rebreathing through an increased dead space resulted in hypercapnia and significant hyperpnea (Table 1). The feedback-driven voluntary hyperventilation resulted in good matching of the minute volume with the hypercapnic hyperpnea and successfully induced marked hypocapnia (Table 1). There was no statistical difference between the mean peak negative pressures resulting from the transient inspiratory occlusion in the two conditions (Table 1). This suggests that the mechanical effect of the occlusion was similar in the two conditions. All subjects completed the protocol.

**EMG reflex responses.** All subjects showed clear reflex responses, which consisted of an initial short-latency IR at 32 ± 2.3 ms (range 26–44) ms followed by a longer-latency ER at 117 ± 13 ms (range 77–143) ms. Figure 2 shows representative reflex responses to airway occlusion during the hypercapnic and voluntary experiments superimposed from two subjects and suggests little difference between the two conditions other than a more prominent ER0 in the voluntary condition. Neither the measures of size of the IR nor the latencies of the IR trough and ER onset differed significantly between the hypercapnic and voluntary conditions (Table 2). However, the latency of the IR onset was 6 ms longer in volitional hyperventilation (\( P < 0.001 \)). This reflected the increased prominence of ER0 during voluntary hyperventilation (Figs. 1 and 2).

The size of the normalized ER peak (0.69 vs. 0.51), the 10-ms EMG average centered on the ER peak (0.49 vs. 0.34), and the ER AUC (0.33 vs. 0.18) were significantly larger in voluntary hypocapnic ventilation (Table 2).

An ER0, with a typical latency of ~20 ms, occurred in 45% of the averaged responses from the voluntary experiment and 27% of the averages from the hypercapnic experiment (\( P = 0.17 \); Fig. 2, Table 2). The average size of the ER0 was larger in the voluntary experiment (normalized area of 1.5 vs. 0.66 ms, \( P = 0.009 \); Table 2). The more prominent ER0 in the hyperventilation is the likely explanation for the difference in the IR onset latency between the experiments.

**Differences in neural drive.** Despite attempts to match the level of ongoing scalene EMG at the time airway occlusion was initiated, the mean preocclusion EMG amplitude was greater during voluntary hyperventilation than hypercapnia (23 ± 4 vs. 18 ± 3 µV, \( P = 0.029 \)). Despite matching of the inspiratory volume, examination of the pattern of inspiratory activation of the scalene muscles in the two conditions showed that they received more inspiratory drive in the voluntary condition (Fig. 3). An assumption that the size of the inhibitory reflex response to airway occlusion can be compared across different levels of preocclusion EMG activity requires that the normalized reflex response sizes do not differ across a range of levels of EMG.

To assess this, we measured the reflex across a range of levels of muscle activity in a third experiment. At levels of muscle activation <70% of the level measured in the hypercapnic experiment, the normalized size of the reflex response was positively related to the preocclusion level of muscle activity (\( r^2 = 0.364, P = 0.006 \); Fig. 4). One subject failed to achieve the requisite level of preocclusion EMG seen in spontaneous hyperpnea, but, for the remaining five subjects the normalized amplitude and area of the IR became independent of preocclusion muscle activation (\( P < 0.05 \)).

**DISCUSSION**

If the short-latency inhibitory reflex to inspiratory muscle loading (IR) acts through the bulbospinal inspiratory neurons, then there should be decreased reflex inhibition under a condition of decreased activation of these neurons. The bulbospinal inspiratory neurons should be less active during voluntary hyperventilation, even if corticobulbospinal tracts are activated and even if bulbospinal afterdischarge occurs (16), because of the likely major contribution of corticospinal fibers under this voluntary condition (see below). If the medullary inspiratory neurons are not affected by loading-mediated inhibition and the

### Table 2. Responses to transient airway occlusion by experimental condition

<table>
<thead>
<tr>
<th>Experimental Condition</th>
<th>Hypercapnic Hyperpnea</th>
<th>Voluntary Hyperventilation</th>
<th>Statistical Index</th>
</tr>
</thead>
<tbody>
<tr>
<td>IR Onset latency, ms</td>
<td>32 ± 0.7</td>
<td>38 ± 1</td>
<td>-5.89</td>
</tr>
<tr>
<td>Trough latency, ms</td>
<td>80 ± 2.9</td>
<td>78 ± 2.6</td>
<td>0.697</td>
</tr>
<tr>
<td>Trough size, %</td>
<td>65 ± 2</td>
<td>67 ± 3</td>
<td>-0.686</td>
</tr>
<tr>
<td>10-ms mean trough size, %</td>
<td>60 ± 3</td>
<td>62 ± 4</td>
<td>-0.831</td>
</tr>
<tr>
<td>Area, ms</td>
<td>33 ± 2</td>
<td>35 ± 4</td>
<td>-0.673</td>
</tr>
<tr>
<td>ER Onset latency, ms</td>
<td>117 ± 3.8</td>
<td>114 ± 4.4</td>
<td>0.756</td>
</tr>
<tr>
<td>Peak latency, ms</td>
<td>142 ± 4</td>
<td>134 ± 5.2</td>
<td>1.63</td>
</tr>
<tr>
<td>Peak size, %</td>
<td>51 ± 8</td>
<td>69 ± 6</td>
<td>-3.15</td>
</tr>
<tr>
<td>10-ms mean peak size, %</td>
<td>34 ± 7</td>
<td>49 ± 5</td>
<td>-3.04</td>
</tr>
<tr>
<td>Area, %</td>
<td>18 ± 7</td>
<td>33 ± 3</td>
<td>0.015</td>
</tr>
<tr>
<td>ER0 Area, ms</td>
<td>0.92 ± 0.38</td>
<td>1.9 ± 0.40</td>
<td>-3.26</td>
</tr>
<tr>
<td>Frequency</td>
<td>6/22</td>
<td>10/22</td>
<td>0.009</td>
</tr>
</tbody>
</table>

Nonstatistical values are means ± SE derived from the 11 subjects. Areas for inhibitory response (IR) trough and initial excitatory response (ER) area have been normalized, such that their units are ms (see Fig. 1). Paired t-test was used for all comparisons, except excitatory response (ER) area, which was assessed by Wilcoxon’s signed-rank test, and ER0 frequency, which was assessed by \( \chi^2 \) test. *Significant difference between conditions (\( P < 0.05 \)).
IR acts through another supraspinal network or through spinal paths between or within the inspiratory motoneuron pools, then it should not be changed by different levels of activation of the bulbospinal efferents. As there were no major differences in the size of the IR in hypercapnia and hypocapnia, we conclude that the neural organization of the short-latency inhibitory reflex of inspiratory muscles does not critically depend on medullary respiratory centers. Hence, models of the reflex as autogenic, segmental, mediated by propriospinal projections, or mediated by brain stem neuronal pools outside the chemosensor-influenced respiratory groups should be favored.

Previous evidence of candidate inhibitory mechanisms. A number of previous findings suggest that short-latency inhibition might be mediated through the pontomedullary respiratory centers. Tendon organ (Ib) afferents from inspiratory muscles in the cat activate non-respiratory-modulated inhibitory interneurons adjacent to the inspiratory neurons in the brain stem (54). Electrical stimulation of group Ib and II afferents from external and intercostal muscles in the cat causes generalized inhibition of ventral respiratory group (VRG) and DRG inspiratory neurons supplying the phrenic and external intercostal motoneurons (53, 55). In the rat, upper cervical interneurons have been identified that integrate phrenic afferents and project to the VRG (31). Electrical stimulation of the phrenic nerve in the cat also increases activity in the Bötzinger complex (57), a region containing neurons that inhibit phrenic motoneurons (6, 41). High spinalization can modify inhibitory reflex influences on feline phrenic motoneurons (58), but other work shows the persistence of phrenic-to-phrenic inhibition in spinalized cats (27). On the basis of medullary recordings, it has been proposed that the supraspinal effect of phrenic afferent stimulation excites DRG premotor neurons but that this excitation is negated by segmental (or propriospinal) inhibition (58, 60). Overall, prior evidence probably favors a role for the medullary inspiratory centers in integrating the inhibitory inputs delivered by proprioceptive afferents.

Voluntary inspiration. To conclude that the relevant inhibitory afferents or interneurons project directly to the motoneu-
rons, rather than higher in the motor control axis of inspiratory muscles, assumes that voluntary inspiration bypasses inspiratory bulbospinal neurons; if voluntary drive acts through these pontomedullary neurons, then the results of this experiment allow no conclusions to be drawn about the site of reflex inhibition. Consequently, evidence about the mechanism of voluntary inspiration must be considered. It is known from human and animal studies of cortical stimulation and from neuronal labeling studies that there are monosynaptic corticospinal projections to inspiratory motoneurons (4, 5, 15, 32, 38, 49). In humans, they have a central conduction time of as little as 4 ms with a synaptic latency of 1 ms, consistent with a monosynaptic pathway that bypasses the inspiratory bulbospinal neurons (25, 26, 56). In cats, retrograde labeling has identified cortical neurons projecting to phrenic and intercostal motoneurons (34, 52). Premotor (Bereitschaft) cortical potentials occur prior to the onset of voluntary inspiration (35, 51). Functional imaging studies during voluntary breathing revealed inspiration-associated activity in the motor cortex (14, 40) and the rostrodorsal medulla (40), but the medullary activity could result simply from increased respiratory afferent input. Invasive medullary recordings in the cat, during electrical stimulation of the cortex, have not shown any evidence of short-latency excitatory corticobulbar inspiratory projections (5). When the human motor cortex is stimulated by a transcranial magnetic stimulus (TMS) during voluntary breathing in differential states of chemoreceptor-driven medullary respiratory activity, no difference in the diaphragmatic motor evoked potential is observed (17). Corfield et al. (17) state the caveats that must apply to interpretation of their results; nevertheless, this result favors the hypothesis that the cortical activation of the diaphragm by TMS “bypasses” the medulla. TMS in humans also has no effect on the respiratory rhythm (17, 43). Increased activation of the medullary respiratory centers is thought to cause air hunger as a result of corollary discharge to the sensory cortex (1, 3, 13, 24, 42), but air hunger is not a feature of voluntary hyperventilation. The cortical inhibition of automatic breathing in humans appears to be mediated via a complex supramedullary network (39), and inhibitory corticobulbar connections to medullary inspiratory premotor neurons are present in the cat (5, 46, 47). On balance, the evidence suggests that most, if not all, fast-conducting excitatory cortical pathways to inspiratory motoneurons do not pass via the bulbar inspiratory centers and that these corticospinal projections to inspiratory motoneurons are used in volitional ventilation. The design of this study requires only that a significant proportion of cortical inspiratory drive passes via corticospinal pathways.

Organization of afferent integration. If the short-latency inhibitory reflex is not integrated within the medullary inspiratory centers, then where is the region of integration of drive and afferent inhibition? Latency calculations address this question. The onset latency of the motor evoked potential in scalenes following TMS of the motor cortex is ~9 ms (Hudson, Anand, Gandevia, Taylor, and Butler, unpublished data).

Fig. 5. Known and hypothesized components of the inspiratory motor axis, with possible mechanisms for short-latency, loading-mediated inhibitory reflex of inspiratory muscles. Arrowheads indicate inhibitory projections. A: rapidly conducting corticospinal projection to inspiratory motoneurons, which is involved in voluntary inspiration. B: bulbospinal projections that drive automatic ventilation. C: inhibitory corticobulbar tracts that project to medullary inspiratory centers. Excitatory corticobulbar projections have been hypothesized but have not been documented. Inspiratory muscle afferents may inhibit inspiratory motoneurons segmentally or autogenetically (i). These afferents may, alternatively, be integrated within medullary inspiratory centers (ii). Propriospinal networks may integrate inputs from inspiratory muscle afferents within the cervicothoracic spinal cord (iii). Longer-latency inhibition from inspiratory muscle afferents could be driven by a transcortical reflex (iv).
As there is an ~10-ms central delay in the bulbocortical transmission of human inspiratory muscle afferents (36), the absolute minimal latency for a transcortical inhibitory propriospinal reflex for the scalenes would be ~30 ms. Because the diaphragmatic latency to motor cortical stimulation is 15–16 ms (26, 61) and the IR of the diaphragm is broadly simultaneous with that of scalene muscles (50), the latency to the onset of the IR in the diaphragm is too short to involve a transcortical pathway. Thus the earliest part of the IR could be mediated through the cortex for the scalenes, but not for the diaphragm. Also, our finding that the size of the IR is the same during hypercapnic hyperpnea and voluntary hypocapnic ventilation suggests that the motor cortex is not involved in the scalene short-latency inhibitory response to airway occlusion. That the short-latency inhibitory reflex commences at about the same time in all inspiratory muscles, despite large differences in the lengths of the afferent and efferent conduction paths (50), suggests that there is spinal or supraspinal integration that generates a coordinated reflex response. Given that spinal respiratory networks exist (2, 30) and that our result argues against a mechanism involving the brain stem inspiratory centers, we propose that an integrated propriospinal reflex system is involved (Fig. 5). A recent study in the dog, which shows that spinal cord stimulation at high thoracic levels elicits a coordinated output across inspiratory muscles and acts through motor nuclei above and below the site of stimulation, is consistent with the hypothesis of a propriospinal respiratory network (21).

Conclusion. The results obtained in this study show that the potent inhibitory response to occlusion in human inspiratory muscles is unchanged, whether descending drive is biased toward bulbospinal or corticospinal paths. The simplest interpretation is that the output of medullary inspiratory neurons is not altered by reflex inputs and that corticospinal and bulbospinal pathways converge on a common propriospinal output to the inspiratory motoneurons.

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DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the authors.

REFERENCES


