Task failure with lack of diaphragm fatigue during inspiratory resistive loading in human subjects

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Critical airway narrowing leads to progressive accumulation of CO₂ and respiratory arrest unless it can be reversed. However, it remains controversial whether this ventilatory failure is due primarily to failure of the inspiratory muscles to generate sufficient force (i.e., muscle fatigue) or whether it reflects a decline in the voluntary activation of the respiratory muscles or a decline in the drive from respiratory centers, possibly acting to delay or prevent the onset of muscular fatigue. The concept that inspiratory muscles may fatigue rapidly and therefore contribute to the development of acute ventilatory failure in patients with critical airway narrowing has gained wide acceptance (e.g., Refs. 8, 15, 28). In contrast, there is evidence that the inspiratory muscles of healthy subjects are resistant to fatigue induced by maximal “static” inspiratory contractions and that the diaphragm recovers from any fatigue ~10 times faster than the elbow flexors (23).

When healthy subjects breathe through graded inspiratory resistive loads, endurance time decreases as the load increases above a critical threshold (6, 9, 28, 29). This relationship between load and endurance time is typical of fatigue in isolated muscle preparations. However, in the initial studies in humans, neither maximal voluntary isometric force nor twitch forces were measured at the time of task failure (cf. Ref. 8). With critical inspiratory resistive loads, hypercapnia and hypoxemia develop and the subject fails to maintain ventilation (10). Changes in electromyographic (EMG) power spectra suggested that this failure resulted from inspiratory muscle fatigue (7, 16), but other objective data are lacking. Neurophysiological evidence of diaphragm fatigue has been provided for subjects performing combined inspiratory/expulsive maneuvers (1), expulsive maneuvers (5, 22), threshold loading (12), and whole body exercise (18), although in the latter two studies the reduction in diaphragm twitch pressure was small.

Studies of resistive loading in animals have yielded conflicting data concerning the relative importance of muscle fatigue and reduced central respiratory drive in the development of ventilatory failure and respiratory arrest (2, 3, 11, 19, 25, 32; for review, see Ref. 21). Some of these conflicting results may reflect differences in species, anesthesia, and the precise loading protocols.

The present study used maximal inspiratory pressures (MIP) to assess muscle performance before, during, and after inspiratory resistive loading. Particular attention was paid to use trained and untrained subjects and to blind the subject to the randomized presentation of both the level of the load and the addition of supplemental O₂. Each MIP maneuver was corrected for any change in pressure due to variation in the absolute lung volume at which it was performed (24). Bilateral phrenic nerve stimulation was also used to assess voluntary drive and peripheral fatigue of the diaphragm.

METHODS

Seven healthy subjects (4 men and 3 women; see Table 1) participated in the series of experiments. Four were aware of the general experimental hypothesis, and two had performed similar maneuvers previously. Three subjects were naive. All gave informed consent, and the procedures were approved by the institutional ethics committee.

Standard protocol. First, subjects performed tests of lung function in a body plethysmograph. These included at least 10 maximal inspiratory efforts against a closed shutter to practice the maneuvers and to obtain a relationship between maximal static inspiratory pressure and absolute lung volume. A second-order polynomial equation was fitted to the data points for mouth pressure and lung volume after deletion of clearly submaximal efforts. This equation was used to calculate the MIP expected for the lung volumes at which MIP maneuvers were performed during inspiratory loaded breathing (24). For each subject, the MIP was determined at a lung volume around functional residual capacity (FRC).

For the main experiments, six subjects were seated in the body plethysmograph with a noseclip on, and they breathed through a two-way valve with an inspiratory loading device on the inspiratory port. The loading device consisted of a plastic tube with an adjustable clamp that allowed compres-
to the subject nor was the presence of supplemental O2 or (see Fig. 1, Table 2). The magnitude of the load was not known to the subject nor was the presence of supplemental O2 or medical air added to the inspiratory line. Trials were ended at 20 min unless task failure occurred. Task failure in the trials was defined as the point at which the subject came off the mouthpiece or when the subject could no longer reach the target pressure throughout inspiration for three consecutive breaths. However, all subjects were still able to reach the target pressure at the point at which they came off the mouthpiece (see RESULTS).

After the first loaded breath of each trial, the mouthpiece was occluded at end expiration and the subject performed a maximal inspiratory effort. Thoracic gas volume and mouth pressure were measured on-line. After the MIP maneuver, the subject resumed breathing through the inspiratory load to the target pressure on each breath. At subsequent 1-min intervals, maximal inspiratory efforts were repeated and the trial continued until the subject either had performed the task for 20 min or was unable to continue the task (i.e., in <20 min). The subject signaled to the experimenters if unable to continue and then performed a final maximal inspiratory effort against the shutter before coming off the mouthpiece. After 30-s recovery, the subject breathed once more through the resistance to the target pressure and then performed an occluded maximal inspiratory effort.

During all MIP maneuvers, subjects were provided with a separate uncalibrated visual feedback of mouth pressure with the gain varied randomly between maximal efforts so that the subject had no knowledge as to whether MIP had changed during the task. During all trials end-tidal PCO2 (PETCO2) was measured from the expired port of the valve by using an infrared analyzer (Ametek), and O2 saturation and heart rate were monitored with a pulse oximeter (Ohmeda).

Phrenic stimulation and voluntary activation of the diaphragm. In four subjects, the protocol was repeated at one target pressure (70% with and without supplemental O2) with bilateral phrenic nerve stimulation during and after each MIP maneuver to assess diaphragm voluntary activation and peripheral fatigue. This inspiratory load was selected to provide a resistance that could not be sustained for 20 min, on the basis of the initial results, but that would allow data collection for >3 min. Respiratory pressures [esophageal pressure (Pes), gastric pressure (Pga), and transdiaphragmatic pressure (Pdi)] were measured by a multilumen gastroesophageal balloon catheter (22) inserted transnasally, and the phrenic nerves were stimulated bilaterally with supramaximal electrical stimuli (100-µs pulse width, 5- to 40-V or 5- to 100-mA stimulus intensity; Devices stimulator type 3072 or Digitimer DS7) delivered through fine-wire electrodes inserted in the neck at the level of the cricoid cartilage (17, 22). Supramaximality of the phrenic stimuli was checked throughout each experiment by monitoring the evoked compound muscle action potentials (CMAPs) that were recorded via surface EMG electrodes positioned on the chest wall overlying the costal diaphragm and by EMG electrodes on the multilumen catheter that recorded responses from the crural diaphragm. If the CMAP declined during a trial, the stimulus intensity was increased until the maximal amplitude was restored.

Before the resistive breathing trial was performed, a series of unfatigued MIP maneuvers was performed at different

Table 1. Subject data

<table>
<thead>
<tr>
<th>Subject</th>
<th>Gender</th>
<th>Height, cm</th>
<th>Weight, kg</th>
<th>Age, yr</th>
<th>Initial MIP, cmH2O</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>M</td>
<td>189</td>
<td>85</td>
<td>44</td>
<td>126.7</td>
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<tr>
<td>2</td>
<td>M</td>
<td>172</td>
<td>60</td>
<td>42</td>
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<td>3</td>
<td>M</td>
<td>178</td>
<td>75</td>
<td>26</td>
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<td>F</td>
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<td>168</td>
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<td>6</td>
<td>F</td>
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<td>65</td>
<td>24</td>
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<tr>
<td>7</td>
<td>M</td>
<td>178</td>
<td>76</td>
<td>30</td>
<td>136.0</td>
</tr>
</tbody>
</table>

MIP, maximal inspiratory pressure.

Fig. 1. Pressure profile for a typical subject during a 35% maximal inspiratory pressure (MIP) trial. Subject chose his own respiratory rate. After first loaded breath and at 1-min intervals, subject performed brief MIP maneuvers against a closed shutter.
lung volumes between residual volume (RV) and ~1.5 liters above FRC. This was to enable interpretation of results if any significant shift in end-expiratory level occurred during the loading trial. During the maximal inspiratory efforts, supramaximal bilateral stimuli were delivered to the phrenic nerves at the peak pressure. Approximately 1–2 s after each maximal effort the subject relaxed, while the shutter remained closed to maintain lung volume and the same stimuli were delivered to the relaxed diaphragm to evoke a control twitch of the diaphragm. Voluntary activation of the diaphragm was calculated from the ratio of the amplitude of the Pdi response evoked by the stimuli during the maximal effort to that of the control twitch (Pdi), converted to a percentage of the twitch of the diaphragm. The presence of such progressively increasing increments is conventionally known as central fatigue (22), but the test does not reveal the precise site for the impairment. It may be due to motoneuronal inhibition or reduced descending drive to motoneurons (from motor cortex, respiratory centers, and elsewhere). If a subject terminates a loading task, regardless of whether any discernible peripheral or central fatigue is present (as defined above), we refer to this as “task failure.” Both central fatigue and task failure may be influenced by motivational factors on the basis of the subject’s ability to perform or tolerate the different maneuvers or tasks.

In all trials, subjects rated their breathing discomfort or dyspnea at the point of task failure (or at 20 min) on a modified Borg scale. The descriptors on the scale were 0, dyspnea at the point of task failure (or at 20 min) on a diaphragm were assessed during and after the MIP maneuver, but the test does not reveal the precise site for the impairment. It may be due to motoneuronal inhibition or reduced descending drive to motoneurons (from motor cortex, respiratory centers, and elsewhere). If a subject terminates a loading task, regardless of whether any discernible peripheral or central fatigue is present (as defined above), we refer to this as “task failure.” Both central fatigue and task failure may be influenced by motivational factors on the basis of the subject’s ability to perform or tolerate the different maneuvers or tasks.

Statistics. Major comparisons between variables at the start and end of the resistive loading trials were made by using either Wilcoxon’s rank sum test or paired t-tests, depending on whether the data were normally distributed. $P_{ETCO_2}$ was assessed by paired t-test. Wilcoxon’s rank sum tests were used to compare final and initial MIP. The end of the trial was either at the point of task failure or when the subjects had sustained the inspiratory loading for 20 min. Trials performed with the addition of medical air were compared with those with supplemental O2 by using an analysis of variance. The possibility of progressive changes in lung volume during the trials was assessed using Pearson’s correlations.

RESULTS

The MIP obtained in the practice efforts before inspiratory loading for each subject is shown in Table 1. All subjects demonstrated relationships between load and endurance time that were similar to those published previously (e.g., Ref. 28): endurance time is short for high loads and long for low loads. Figure 2 shows the data from a single subject and for the group. There was a trend for longer endurance times in the trials performed with the supplemental O2, and, although not statistically significant, this trend was more apparent for the intermediate loads (50 and 75% MIP). Five of the six subjects who performed the standard protocol were able to sustain the 35% MIP inspiratory load for 20 min. In the 50% MIP trials, three subjects sustained the resistance for 20 min and three failed and came off

Table 2. Endurance data for inspiratory resistive loaded tasks

<table>
<thead>
<tr>
<th>Inspiratory Load*</th>
<th>Duty Cycle, median</th>
<th>Tension Time Index, median</th>
<th>Minute Ventilation, l/min</th>
<th>Endurance Time,** min</th>
</tr>
</thead>
<tbody>
<tr>
<td>90% MIP</td>
<td>56%</td>
<td>0.50</td>
<td>4.8</td>
<td>1.9 ± 1.1 (n = 12)</td>
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<td></td>
<td></td>
<td></td>
<td>6.1 ± 0.6 (n = 12)</td>
</tr>
<tr>
<td>75% MIP</td>
<td>60%</td>
<td>0.45</td>
<td>5.4</td>
<td>4.6 ± 0.5 (n = 12)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>6.0 ± 0.8 (n = 12)</td>
</tr>
<tr>
<td>50% MIP</td>
<td>52%</td>
<td>0.26</td>
<td>8.1</td>
<td>6.6 ± 4.0 (n = 7)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>5.4 ± 0.8 (n = 7)</td>
</tr>
<tr>
<td>35% MIP</td>
<td>24%</td>
<td>0.08</td>
<td>21.3</td>
<td>15.0 ± 2.8 (n = 2)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>6.1 ± 0.4 (n = 2)</td>
</tr>
</tbody>
</table>

Values are means ± SE; n = no. of tasks. $P_{ETCO_2}$ end-tidal Pco2. *Data for O2 and air trials combined (i.e., n = 12 for each load). **All trials were ended at 20 min if task failure had not occurred before this time.
the mouthpiece, and in the 75 and 90% MIP trials all subjects failed before 20 min. However, in none of the subjects did task failure occur because they were unable to sustain the required inspiratory target pressure. Breathing patterns, including duty cycle, tension-time indexes, and minute ventilation, chosen by the subjects for each load are given in Table 2.

To assess the presence of inspiratory muscle fatigue, all subjects performed MIP maneuvers at 1-min intervals during the inspiratory loading. Values for each subject were expressed as a percentage of the best maximal effort achieved just before the trial in that subject at a lung volume close to FRC. All MIP values were also expressed as a percentage of that expected for the lung volume at which each effort was performed (see METHODS). This corrected for any variation in the lung volume at which MIP maneuvers were performed during the resistive loading. Figure 3 shows data for two single trials (75 and 35% MIP) from a representative subject. Note that in this subject there is minimal change in lung volume across the trials. In some subjects, there was a trend for end-expiratory lung volume to decrease across the trial, but in the group data there was no significant change. Therefore, for the group, data are expressed as a percentage of the pretrial maximal pressure on the day, from which the resistive load was also determined. Maximal pressures were similar across days for each subject (mean coefficient of variation = 7.2%; range 4.2–11.1%). Conclusions based on the results did not differ whether results were normalized to this maximal value or to the initial MIP for each trial, or whether they were corrected for small variations in end-expiratory lung volume.

Data from all resistive loading trials are displayed in Fig. 4. For the pooled data, there was a slight but significant increase in MIP across the trial (P < 0.05), regardless of whether the data were expressed as a percentage of the best MIP or whether the pressures were corrected for the lung volume at which they were performed (see Fig. 4A). Even for the trials in which the subjects came off the mouthpiece before 20 min (n = 32 from a total of 48), there was no decline, but a slight increase, in MIP at the point at which task failure occurred (MIP increased from 90.2 ± 13.6 to 101.6 ± 17% of pretrial MIP).

Although evidence for peripheral muscle fatigue (assessed with maximal voluntary contractions) was not present, there was a significant increase in PETCO2. In the trials in which task failure occurred before 20 min, PETCO2 increased from 4.91 ± 0.69 to 5.88 ± 0.72% (P < 0.001), but when the load could be tolerated for 20 min...
there was no increase in the PETCO₂ [initial, 4.62 ± 0.6%; final, 4.52 ± 0.70%; not significant (NS)].

There was a significant increase in heart rate from 78.0 ± 9.9 to 90.6 ± 17.7 beats/min in all trials (P < 0.01). In the trials in which task failure occurred and with the addition of air, there was a significant decrease in O₂ saturation (from 97.5 ± 0.94 to 93.1 ± 5.5%, P < 0.01). These results were dominated by marked and relatively rapid changes observed near the time of task failure, especially for the higher inspiratory resistances. For the trials in which subjects sustained the trial for 20 min with air added, there was no significant change in O₂ saturation (from 97.4 ± 1.4 to 96.7 ± 1.6%, P = 0.392). There was no change in O₂ saturation in any trials with supplemental O₂.

During resistive loading trials in which task failure occurred (i.e., <20 min), the score on the Borg scale was near maximal at the point of task failure (mean 9.5 on a 10-point scale, range 9–10; see METHODS). When subjects were able to breathe through the resistance for at least 20 min, subjects scaled their dyspnea at the time of completion as a mean of 5.7 (range 3–10). A score of five on the scale corresponds to the descriptor “large amount” of breathing discomfort.

Phrenic stimulation and voluntary activation of the diaphragm. To determine directly whether peripheral muscle fatigue or failure of voluntary drive to the diaphragm occurred before or at task failure, four subjects repeated two trials of the resistive loaded breathing (70% MIP) with phrenic nerve stimulation (with and without supplemental O₂, 8 trials in total). Data from a single subject and the group are shown in Fig. 5. In six of eight trials, task failure occurred before 20 min and in these trials PETCO₂ increased from a mean of 4.94 ± 0.72 to 6.51 ± 1.05% (P < 0.01). There was no decrease in MIP (expressed as %pretrial maximum), which tended to increase from 100.6 ± 20.4 to 109.8 ± 17.5% (P = 0.256; NS). Voluntary activation of the diaphragm, which was initially slightly submaximal at a median of 94.7% (range 76.3–100%) increased to maximal (mean = 100 ± 0%), but the increase was not significant (P = 0.18). Because the end-expiratory lung volume did not change significantly in this study, the twitch amplitude was not corrected for lung volume. Twitch amplitude did not decline (initial 27.5 ± 15.6 cmH₂O; final 29.4 ± 13.3 cmH₂O; NS). The tension-time index for Pdi was >0.3 in all trials with task failure (mean 0.39 ± 0.1; range, 0.31–0.58), a value exceeding the accepted “threshold” for diaphragmatic fatigue (e.g., Ref. 6). In the two trials in which the task failure did not occur, there were no marked changes in mouth or Pdi pressure, end-expiratory lung volume, twitch amplitude, voluntary activation, or PETCO₂.

Influence of rebreathing CO₂ on task failure. To examine the effect of an increase in PETCO₂ on task failure, six subjects performed rebreathing with carbogen (5% CO₂-95% O₂) through a 65% MIP inspiratory load, and a control trial with the same load breathing air (Fig. 6). In the trials performed with air, all subjects were able to continue for 20 min. There was no significant change in mouth pressure during the trials, which started at 107.3 ± 11.8% pretrial initial maximum and decreased to 99.4 ± 11.5% (P = 0.054). In these trials there was no change in PETCO₂ or lung volume. By contrast, task failure occurred before 20 min (mean 3 min 48 s; range 1 min 50 s to 5 min 30 s) in all the trials when the subjects rebreathed carbogen through the same inspiratory load (65% MIP; see METHODS). In these trials, PETCO₂ increased from a mean of 4.78 ± 0.3% to 7.0 ± 1.3% at the point of task failure (P < 0.01). MIP, corrected for lung volume, increased
from 96.3 ± 21.9% of the pretrial maximum to 120.9 ± 32.4% in these rebreathing trials, although this increase was not significant (P = 0.277; NS).

At the end of the trial, subjects used Borg scales to give a score for inspiratory effort and a separate score for dyspnea. In rebreathing trials the subjective scores for effort (mean 8.8; range 8–9.5) and dyspnea (mean 8.3; range 7–9.5) were close to maximal on the Borg scale. These scores were greater than those in non-rebreathing trials (effort: mean 5.5, range 3–8.5; dyspnea: mean 3, range 0–7.5).

**DISCUSSION**

The present results confirm previous observations that hypoventilation and task failure occur when breathing through high linear inspiratory resistances. Endurance time decreases progressively as the target pressure (%MIP) increases (6, 28; see also Ref. 27). However, the development of hypercapnia and extreme dyspnea was associated with task failure, whereas there was no conventional evidence of inspiratory muscle fatigue or of failure of voluntary drive during brief occluded Mueller maneuvers.

The present results are at variance with several previous reports of studies involving inspiratory loading in human subjects that have provided evidence for the development of diaphragmatic (or inspiratory muscle) fatigue. However, those studies either have used indirect evidence for muscle fatigue such as a change in EMG power spectra (7, 16) or have involved different types of loading (see Ref. 8). Maneuvers that produce a marked elevation of Pga, such as expulsive or combined inspiratory/expulsive efforts, result in substantial diaphragmatic fatigue documented by electrophysiological techniques (1, 5, 14, 22). Such protocols are also accompanied by significant failure of voluntary activation of the diaphragm, accounting for up to one-half of the decline in pressure development (5, 22). We found no evidence for failure of voluntary activation of the diaphragm in this study. This is consistent with a study in rabbits (26) during inspiratory resistive loading, in which high firing rates of phrenic motoneurons were observed and no evidence for a lack of their recruitment was present.

Eastwood et al. (12) reported a small decline in diaphragmatic twitch pressure that was long lasting when subjects performed progressive inspiratory threshold loading up to MIP. However, complete recovery of endurance capacity occurred immediately after the subject came off the mouthpiece (i.e., they could repeat the entire protocol). Nevertheless, the authors concluded that low-frequency diaphragm fatigue had a role in determining the precise point of task failure (12). In the present study, the highest load attempted represented 90% of the MIP compared with the maximal (100%) threshold loading described above. With threshold loads, minute ventilation is also better maintained than with high resistive loads, and this possibly explains why the subjects in the study by Eastwood et al.
were able to continue to a point at which there was some peripheral fatigue of the diaphragm.

In the study by Eastwood et al. (12), no constraints were placed on ventilatory parameters in an attempt to maximize performance. Subjects in the present study were also free to control their own tidal volume and respiratory frequency (and hence duty cycle), whereas these variables have been controlled in many previous studies of inspiratory loading (e.g., Ref. 6; for review, see Ref. 8). Despite this freedom, which might have helped to minimize dyspnea, our subjects were unable to drive the diaphragm to the point at which peripheral fatigue could be observed.

When subjects in the present study breathed with tension-time indexes below the accepted threshold for producing muscle fatigue (i.e., <0.18; Ref. 6), they were able to sustain the inspiratory load for at least 20 min. The tension-time indexes for the failed trials were all >0.18 (based on mouth pressure, range 0.20–0.56, and on Pdi, range 0.31–0.64). Thus the lack of evidence of peripheral diaphragm fatigue cannot be attributed to the adoption of a breathing pattern that placed the inspiratory muscles (or diaphragm) below the fatigue threshold. Therefore, we must hypothesize that some mechanism other than inspiratory muscle fatigue was responsible for task failure. When subjects breathed through the 65% MIP inspiratory load with air, they were able to sustain their breathing through this load for at least 20 min. However, rebreathing 5% CO2 through this same load resulted in task failure well before 20 min. These results suggest that task failure may result from sensations related to progressive hypercapnia rather than from discomfort related only to the inspiratory load. In addition, a mild hypoxic stimulus developed in some trials that were terminated at 20 min.

Our conclusion that peripheral fatigue of the diaphragm did not occur is based on data from diaphragmatic twitches evoked by bilateral phrenic nerve stimulation and maximal voluntary efforts (equivalent to tetanic responses). Hence we have not assessed other portions of the force-frequency relationship. If there were only a shift in the midportion of the force-frequency relationship as a consequence of fatigue, our measurements would have been unable to detect a decrease in force production, but this mechanism seems unlikely. Measurements of MIP in this study were performed at lung volumes at or below FRC in most instances, and in this range of lung volume there is greater variability in the degree of voluntary drive.

Fig. 6. A: change in Pm, lung volume, and level of rise of PETCO2 during a trial with 65% MIP inspiratory resistance. There was no significant change in Pm or lung volume, although a slight increase in PETCO2 occurred over 20 min. B: responses during a trial with same resistive load (65% MIP) but while rebreathing 5% CO2. In all subjects, task failure occurred before 20 min. At task failure, Pm had increased slightly, there was no change in lung volume, and PETCO2 had increased.
during MIP maneuvers than at lung volumes above FRC (20). This variability may make a true decline in MIP difficult to detect. However, in the four subjects studied with phrenic stimulation here, voluntary activation of the diaphragm increased and was close to 100% at the point of task failure in all trials.

A change in thoracic gas volume between the maximal inspiratory effort and relaxation for the control twitch (Boyle's Law effect) may have caused a slight distortion in the calculation of voluntary activation. However, this error would probably be consistent across the trials because absolute lung volume did not change significantly. Furthermore, the lack of a decline in twitch amplitude was not due to any systematic reduction in end-expiratory lung volume over the duration of the loading trial.

The present documentation that severe hypercarbia and task failure can occur in the absence of overt inspiratory muscle fatigue is concordant with at least some of the animal literature. Awake infant monkeys developed profound hypoventilation during resistive breathing but with no evidence of diaphragmatic fatigue (32). A similar result has been observed in adult dogs exposed to cardiogenic shock (25). Using a dog model of respiratory arrest in acute severe bronchospasm, Yanos et al. (33) also found no evidence of respiratory muscle fatigue. By contrast, a number of other studies have found some evidence of peripheral respiratory muscle fatigue. By contrast, a number of other studies have found some evidence of peripheral respiratory muscle fatigue. However, this error would probably be consistent across the trials because absolute lung volume did not change significantly. Furthermore, the lack of a decline in twitch amplitude was not due to any systematic reduction in end-expiratory lung volume over the duration of the loading trial.

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The present documentation that severe hypercarbia and task failure can occur in the absence of overt inspiratory muscle fatigue is concordant with at least some of the animal literature. Awake infant monkeys developed profound hypoventilation during resistive breathing but with no evidence of diaphragmatic fatigue (32). A similar result has been observed in adult dogs exposed to cardiogenic shock (25). Using a dog model of respiratory arrest in acute severe bronchospasm, Yanos et al. (33) also found no evidence of respiratory muscle fatigue. By contrast, a number of other studies have found some evidence of peripheral respiratory muscle fatigue. By contrast, a number of other studies have found some evidence of peripheral respiratory muscle fatigue. However, this error would probably be consistent across the trials because absolute lung volume did not change significantly. Furthermore, the lack of a decline in twitch amplitude was not due to any systematic reduction in end-expiratory lung volume over the duration of the loading trial.

It has been proposed that hypercapnia contributes to fatigue of the diaphragm (30) but through a different mechanism from that involved in exercise-induced fatique. The hypercapnia is thought to decrease intracellular pH, which could decrease the binding of Ca2+ to troponin as well as impair function of the contractile proteins (13). Johnson and colleagues (18) found a decrease in the amplitude of Pdi twitches during whole body exercise. It was postulated that this fatigue may be due, in part, to diaphragm uptake of circulating lactate produced by limb muscles working under a high load (18). In the present study, we found no fatigue of the diaphragm despite increases in PETCO2 ranging up to 2% and subjective reports of near maximal dyspnea. Even in the trials performed with rebreathing 5% CO2 in which PETCO2 rose to 7.0 ± 1.3%, there was no evidence of inspiratory muscle fatigue at the point of task failure. However, it is possible that the increase in PETCO2 in this study, or the decrease in tissue pH, was not of sufficient magnitude to have an effect on diaphragmatic fatigability.

It is difficult to reconcile the development of profound ventilatory failure during resistive loading with the observations that both the force-generating capacity of the inspiratory muscles (and diaphragm, in particular) and voluntary drive to the diaphragm (assessed during brief occluded Mueller maneuvers) are both intact. Indeed, there was a trend for voluntary activation, MIP, and twitch pressure of the diaphragm to increase slightly during loading. There are several possibilities that might explain this slight increase in MIP. In some of the trials, the increase could reflect an increase in voluntary activation. In the studies performed with phrenic stimulation, voluntary activation became maximal after the first minute and then remained near maximal throughout the trial. The rise in MIP and the increase in the amplitude of the Pdi twitch in the relaxed diaphragm across these trials did not reach statistical significance. It is possible that some potentiation of diaphragm contractility occurred (e.g., Ref. 31), which was reflected in the trend for the twitch to increase. An alternative explanation for the trend for the MIP to increase is that the pattern of recruitment of inspiratory synergists altered as the trial progressed. If the intercostal/accessory muscles were recruited to a relatively greater extent in the MIP maneuvers performed later in the trials, such that the maximally activated diaphragm was lengthened (i.e., an eccentric contraction), the diaphragm would be capable of exerting additional tension beyond its isometric maximum. This notion is also consistent with the results of Clanton (8), for example, who suggested that activity in the rib cage muscles was the dominant inspiratory muscle activity when subjects breathed through inspiratory resistive loads. Although definitive data were not provided, this mechanism could provide an explanation for the relative lack of diaphragm fatigue with resistive loading tasks. However, even if this explanation were true, our results indicate that the overall function of inspiratory synergists was not significantly impaired.

The presence of hypoventilation implies inadequate "central" drive during resistive loading, but voluntary activation of the diaphragm during brief MIP maneuvers remained near maximal. These observations are relevant to the question of whether breathing during critical loading is predominantly voluntary or whether it remains under primary control of bulbopontine respiratory centers. The motor cortex is known to project powerfully to human inspiratory muscles, sufficient to activate all relevant motoneurons, whereas respiratory center output may not be able to activate the diaphragm fully during maximal chemical drive (for review, see Ref. 21). One hypothesis that might explain the apparent paradox is that the progressive hypercapnia during critical resistive loading cannot optimally recruit inspiratory motoneurons, whereas a transient voluntary input via the motor cortex is able to achieve maximal activation of the diaphragm.

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