Effect of diaphragm fatigue on neural respiratory drive

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Luo, Y. M., N. Hart, N. Mustfa, R. A. Lyall, M. I. Polkey, and J. Moxham. Effect of diaphragm fatigue on neural respiratory drive. J Appl Physiol 90: 1691–1699, 2001.—To test the hypothesis that diaphragm fatigue leads to an increase in neural respiratory drive, we measured the esophageal diaphragm electromyogram (EMG) during CO2 rebreathing before and after diaphragm fatigue in six normal subjects. The electrode catheter was positioned on the basis of the amplitude and polarity of the diaphragm compound muscle action potential recorded simultaneously from four pairs of electrodes during bilateral anterior magnetic phrenic nerve stimulation (BAMPS) at functional residual capacity. Two minutes of maximum isocapnic voluntary ventilation (MIVV) were performed in six subjects to induce diaphragm fatigue. A maximal voluntary breathing against an inspiratory resistive loading (IRL) was also performed in four subjects. The reduction of transdiaphragmatic pressure elicited by BAMPS was 22% (range 13–27%) after 2 min of MIVV and was similar, 20% (range 13–26%), after IRL. There was a linear relationship between minute ventilation (VE) and the root mean square (RMS) of the EMG during CO2 rebreathing before and after fatigue. The mean slope of the linear regression of RMS on VE was similar before and after diaphragm fatigue: 2.80 ± 1.31 vs. 3.29 ± 1.40 for MIVV and 1.51 ± 0.31 vs 1.55 ± 0.31 for IRL, respectively. We conclude that the esophageal diaphragm EMG can be used to assess neural drive and that diaphragm fatigue of the intensity observed in this study does not affect respiratory drive.

It has been assumed that respiratory drive to the diaphragm increases to sustain appropriate ventilation when the diaphragm is fatigued (26, 27). It has been difficult to test this hypothesis because of the lack of reliable methods to assess neural respiratory drive. The diaphragm electromyogram (EMG) during spontaneous breathing recorded from an esophageal electrode has been used to investigate neural respiratory drive (18, 19). However, this technique was questioned after the assertion that the amplitude of the diaphragm compound muscle action potential (CMAP) changes with change in lung volume as a result of substantial movement of the electrode, up to 8 cm during deep breathing (11).

In a previous study (20), our laboratory demonstrated that the diaphragm crus is relatively stable and that the diaphragm CMAP is independent of changes in lung volume and can be accurately recorded by positioning the esophageal electrode at the centre of the electrically active region of the diaphragm (EARDi) (21). Recently, Beck et al. (2) demonstrated that the root mean square (RMS) of the voluntary diaphragm EMG recorded from a multipair esophageal electrode is not artifactually influenced by change in lung volume. These studies suggest that the esophageal diaphragm EMG may be useful to assess neural respiratory drive.

The effect of diaphragm fatigue on neural respiratory drive has been assessed by the ventilatory response to CO2 (23, 37). However, contradictory results have been reported. For example, Yan and co-workers (37) showed no alteration in the ventilatory response to CO2 after inspiratory muscle fatigue, whereas Mador and Tobin (23) reported that the slope of the ventilatory response to CO2 was significantly decreased by inspiratory muscle fatigue. Nevertheless, the effect of diaphragm fatigue on neural drive assessed by the esophageal diaphragm EMG has not been reported. Moxham and co-workers (27) showed that neural drive to the sternomastoid muscle was increased to sustain the required force when low-frequency fatigue occurred in this muscle. We hypothesized that diaphragm fatigue may increase neural drive to the diaphragm. To test this hypothesis, we investigated the effect of diaphragm fatigue on neural drive by recording the diaphragm EMG during CO2 rebreathing before and after maximal isocapnic voluntary ventilation (MIVV) and inspiratory resistive loading (IRL).

**METHODS**

**Subjects.** Six healthy volunteers (4 men and 2 women) aged 26–37 yr (mean age 32 yr) participated in the study. All subjects had experience of performing MIVV, and most were staff of the respiratory muscle laboratory. The study was approved by the ethics committee of King’s College Hospital, and all subjects gave their informed consent.

**Bilateral anterior magnetic stimulation of the phrenic nerves.** Bilateral anterior magnetic stimulation (BAMPS) was performed by using two 43-mm figure-eight coils powered by Magstim 200 stimulators (Whitland, Dyfed, UK). The coils were placed anterolaterally on each side of the neck over the phrenic nerves (20). One hundred percent of maximal
magnetic stimulator output was applied throughout the study except at the stage of positioning the esophageal electrode, when 80% of maximal output was used. Phrenic nerve stimulation was performed at functional residual capacity (FRC) with the subject seated upright in a chair.

**Esophageal electrode and its positioning.** We used a multi-pair esophageal electrode catheter with the same configuration as previously reported (20). In brief, the electrode catheter consisted of seven copper coils (coil 1 being proximal and coil 7 distal) that were positioned close to the esophageal hiatus. Four electrode pairs were created from the seven coils with an interelectrode distance of 3 cm within a recording pair. *Pair 1* consisted of electrodes 1 and 3, *pair 2* of electrodes 2 and 4, *pair 3* of electrodes 3 and 5, and *pair 4* of electrodes 5 and 7. Electrode 6 was connected to ground. The esophageal electrode was passed through the nose and swallowed into the esophagus. Electrode 3 was positioned at the center of the EARdi at FRC on the basis of the amplitude and polarity of the diaphragm CMAP recorded from the four pairs of electrodes during BAMPS (20). The ideal position of the electrode was characterized by a large CMAP amplitude from the diaphragm CMAP recorded from the four pairs of electrodes, with opposite polarity, and a small CMAP recorded from electrode *pair 4* because it is 3 cm away from the crus of the diaphragm. After the ideal positioning of the electrode was achieved, the catheter was securely taped at the nose. The diaphragm EMG signals were amplified and band-pass filtered between 40 Hz and 1 kHz (Magstim).

**MIVV.** Diaphragm fatigue was induced by 2 min of MIVV as previously described (28). The subject inhaled from a 6-liter anesthetic bag that was kept inflated by delivering medical air (21% O₂-79% N₂) and 100% O₂ from cylinders. We also added CO₂ to the bag to maintain the end-tidal Pco₂ at 5 kPa.

**CO₂ rebreathing.** CO₂ rebreathing was performed by using a method similar to that described by Read (31) except the baseline gas composition was 5% CO₂-95% O₂ (7). Subjects were studied in the seated posture and initially breathed room air through a mouthpiece connected to an open breathing circuit for a few minutes. When subjects were familiar with breathing with a mouthpiece, the rebreathing bag with 5% CO₂ was introduced. CO₂ rebreathing was terminated when the end-tidal CO₂ concentration was ~9%.

**Signal recordings.** End-tidal CO₂ was monitored by a capnograph (model 455, P. K. Morgan, Kent, UK). Flow was measured with a pneumotachograph (Fleisch no. 4, Lauzanne, Switzerland) connected to a Mercury CS660000 spectrometer (G. M. Engineering, Kilwinning, Scotland, UK). Esophageal pressure (Pes) and gastric pressure (Pga) were recorded by using commercially available balloon catheters. The balloons was positioned in the conventional manner, and pressures were measured by differential pressure transducers (model MP45, Validyne, Northridge, CA). Pdi was calculated by digital subtraction of Pes from Pga. The Pdi elicited by BAMPS at FRC with the airway closed was termed twitch Pdi. The Pdi obtained during maximum sniff maneuvers was also recorded and termed sniff Pdi. Pdi was measured in all subjects but one (subject 4) who had nasal obstruction, which prevented the positioning of the balloon catheters.

The spontaneous diaphragm EMG recorded from the four esophageal electrode pairs, Pes, Pga, respiratory flow, and end-tidal CO₂ were recorded simultaneously using PowerLab 8s hardware and software (ADInstruments, Castle Hill, Australia) combined with a Power Mac computer. The sample rate was 2 kHz for EMG signals and 200 Hz for all other signals. Signals were displayed in real time and stored in the computer hard disk for further off-line analysis.

**Protocol.** CO₂ rebreathing was done 15 min before and 15 min after MIVV. Twitch Pdi and sniff Pdi were measured immediately before and 10 min after MIVV to avoid twitch potentiation and assess diaphragm fatigue. Five twitches and five to seven sniffs were performed on each occasion.

**Additional study: diaphragm fatigue induced by IRL.** To observe whether IRL caused more severe diaphragm fatigue, and possibly a greater effect on neural drive, four subjects were asked to inspire through an inspiratory resistance. No load was added during expiration. Subjects were asked to achieve maximal voluntary Pdi and to maintain this pressure as a square wave throughout inspiration with a duty cycle of 0.66. Subjects were vigorously encouraged to make a maximal effort, with each breath, for 5 min. To seek to achieve substantial fatigue, three consecutive inspiratory loading runs were performed. A 10-min rest period was allowed between runs. Twitch Pdi was measured before the first run and 10 min after the last run to document diaphragm fatigue. CO₂ rebreathing was performed before the first run and 15 min after the third run to assess the effect of such severe inspiratory loading on the relationship between RMS and ventilation.

**Data analysis.** Data were analyzed off-line. The RMS with a time constant of 100 ms was calculated by computer. The peak RMS of inspiration cycles was measured, and the mean of five consecutive breathing cycles was calculated. To avoid the influence of the electrocardiogram on the diaphragm EMG, RMS was measured from the segments between QRS complexes. Minute ventilation (Vₐ) and tidal volume (Vₜ) were calculated by integrating flow from five consecutive breaths. Twitch Pdi was the average of the three to five twitches. Diaphragm fatigue was defined as a reduction of twitch Pdi >10% after MIVV or IRL, as suggested by Mador and co-workers (22). The difference in sniff Pdi before and after MIVV was assessed by a paired t-test. The Mann-Whitney U-test was used to assess the difference in the reduction of Pdi between MIVV and IRL groups. The relationship between ventilation (Vₐ and Vₜ) and RMS was assessed by correlation. An F-test was performed to assess the difference in slopes of the two regression lines. Unless otherwise stated, the RMS reported was from the electrode pair with largest EMG amplitude at the beginning of CO₂ rebreathing.

**RESULTS**

**Spontaneous EMG amplitude.** The electrode pair that recorded the greatest amplitude CMAP at FRC was usually the same as that recording the largest amplitude spontaneous EMG during resting breathing and CO₂ rebreathing (Fig. 1). The electrode pair that recorded the maximal EMG during resting breathing was the same as at the end of CO₂ rebreathing except in one subject in whom the electrode pair that recorded the maximal EMG changed from *pair 1* to *pair 2*. *Pair 4* always recorded the smallest EMG during CO₂ rebreathing (Fig. 1), even at the end of CO₂ rebreathing when Vₜ was 3.0 liters.

**Relationship between ventilation and RMS.** RMS increased with increasing Vₜ and Vₐ. There was a linear relationship between RMS and ventilation for all pairs
of electrodes, including pairs 2 and 4, although these only recorded a small EMG signal (Fig. 2). This relationship did not change after 2 min of MIVV (Table 1).

Diaphragm fatigue induced by MIVV. The mean twitch Pdi was reduced by 22 ± 3% after 2 min of MIVV. The reduction of twitch Pdi was >10% in all subjects. Sniff Pdi changed little (Table 1).

Linear regression analysis of RMS, V̇E, and V̇t. Figure 3 shows a typical example of the relationship between RMS and ventilation before and after MIVV. The mean slopes of linear regression of RMS on V̇E or V̇t were not significantly different before and after MIVV (P > 0.05) (Table 1).

Additional study: diaphragm fatigue induced by IRL. After 30–40 s of maximal voluntary inspiratory resistive breathing, Pdi and voluntary diaphragm EMG were reduced, although the subjects continued to attempt to achieve maximal inspiration (Fig. 4). The mean maximal reduction of EMG was 30% (range 12–54%). All subjects were exhausted after three consecutive loaded runs. Mean twitch Pdi was 31 and 25 cmH₂O before and after loading, respectively. In all
subjects, the reduction of twitch Pdi was 10% after loading, indicating diaphragm fatigue. There was a good correlation between V\dot{E} and the RMS. The correlation coefficients were 0.96 ± 0.02 before and 0.98 ± 0.01 after loaded breathing. The slope of the regression of RMS on V\dot{E} was similar before and after IRL breathing (Fig. 5, Table 2).

DISCUSSION

In the present study, we found a linear relationship between ventilation and RMS of the diaphragm EMG. This linear relationship was not changed by diaphragm fatigue. Our results do not support our original hypothesis.

Electrode movement. It is important to consider the extent of possible electrode movement relative to the crus of the diaphragm during spontaneous breathing. The esophageal electrode catheter was fixed securely at the nose. Therefore, any movement of the electrode relative to the crus would be due to movement of the diaphragm. It has been observed that the dome of the diaphragm can move 1–2 cm in normal resting breathing and up to 8–10 cm when breathing from residual volume to total lung capacity. Data on the movement of the crus in humans are much more difficult to obtain. The recommendation has been to use a balloon-stabilized esophageal catheter to allow the electrode to track the crus of the diaphragm and to fix the distance

Table 1. Twitch Pdi, sniff Pdi, R between RMS of EMG and \( \dot{V}E \) and VT, and slope of regression of RMS on \( \dot{V}E \) and VT before and after MIVV

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<th>Sniff Pdi, cmH(_2)O</th>
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<th>RMS-V\dot{E} Post</th>
<th>RMS-VT Pre</th>
<th>RMS-VT Post</th>
<th>RMS-V\dot{E} Pre</th>
<th>RMS-V\dot{E} Post</th>
<th>RMS-VT Pre</th>
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<th>R RMS-V\dot{E} Post</th>
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Pdi, transdiaphragmatic pressure; R, correlation coefficient; RMS, root mean square; V\dot{E}, minute ventilation; VT, tidal volume; MIVV, maximum isocapnic voluntary ventilation; pre, before 2 min of MIVV; post, after 2 min of MIVV.
of the electrode from the diaphragm (12). Gandevia and McKenzie (11) reported that a balloon-stabilized electrode catheter could move up to 8 cm during deep breathing on the basis of fluoroscopic observations. Subsequently, electrode movement was considered a major cause of artifact and unreliability when the diaphragm EMG was recorded with an esophageal electrode. However, the movement of the balloon-stabilized electrode may be more related to movement of the dome than the crus. Indeed, Gandevia and McKenzie further reported that electrode movement was directly proportional to the vertical displacement of the diaphragmatic dome. Similarly, Daubenspeck et al. (6) observed that the movement of the esophageal electrode was proportional to the movement of the diaphragm, on the basis of fluoroscopy. Beck et al. (3) judged the crus of the diaphragm to move less than 4 cm with respect to the electrode, on the basis of the change of the optimal electrode pair for recording the diaphragm EMG. The small movement of the electrode shown by Beck and co-workers was explained by the suggestion that the electrode catheter moved with the diaphragm because it was firmly gripped by the esophagus, as first suggested by Schweitzer et al. (32). We recently demonstrated that the position of the crus of the diaphragm was relatively stable when lung volume changed from residual volume to FRC plus 2.0 liters (20). In the present study, we found that the electrode pair that recorded the maximal amplitude of the EMG when VT was 1 liter was usually the same as at the end of CO₂ rebreathing when the VT was 3 liters. If the position of the crus changes with lung volume, the optimal electrode pair for recording the maximal EMG will also change. For example, the EMG recorded by electrode pair 1 will become smaller and the EMG recorded by pair 4, which is 3 cm away from the diaphragm, will become larger as VT increases. That this was not the case suggests that the crus of the diaphragm did not move beyond the span of one recording electrode pair. Furthermore, the EMG recorded from pair 2 commonly remained smaller than that from pair 1 and pair 3, suggesting the level of the EARdi center did not change with respect to the esophageal electrode. These results are similar to our laboratory’s previous study (20) and further support the view that the crus of the diaphragm is relatively stable. The difference in results between our study and that of Beck et al. (3) may be due to the different electrode configuration, in particular the positioning of the electrodes. We positioned the catheter on the basis of the CMAP produced by BAMPS at FRC, whereas the positioning by Beck and colleagues was determined by a cross-correlation method using signals from the multipair electrode (3).

**Diaphragm fatigue with MIVV.** It is important to be confident that significant diaphragm fatigue was present when the effect of fatigue on ventilation was assessed. In the present study, the reduction of twitch Pdi was >10% in all subjects, indicating diaphragm fatigue had been induced according to the criteria suggested by Mador and co-workers (22). Previous studies have shown that 2 min of MIVV cause diaphragm fatigue, as indicated by a reduction of twitch Pdi (8, 13). For example, Hamnegard and co-workers (13) showed that the mean twitch Pdi, elicited by cervical magnetic stimulation of the phrenic nerves, was reduced by 23% after MIVV, with a range of 11–40%, which was similar to the reduction of twitch Pdi in the
The reduced twitch Pdi signifies low-frequency fatigue, which can last for many hours (16).

**Neural drive assessed by diaphragm EMG.** The esophageal diaphragm EMG has previously been used to assess neural respiratory drive (18). However, the method was criticized after it was found that lung volume could have a significant influence on the diaphragm EMG recorded from balloon-stabilized electrodes (11, 34). As already discussed, our laboratory has shown that a relatively stable CMAP, little affected by lung volume, can be recorded when the esophageal electrode is accurately positioned at the level of the diaphragm (20). Animal studies have also shown that there is little effect of lung volume on diaphragm CMAP (12, 15). In humans, Beck et al. (2) have found a good relationship between diaphragm contractility and RMS recorded from a multipair esophageal electrode. In keeping with the results of previous work (18, 30), in the present study we found a good relationship between RMS and ventilation during CO₂ rebreathing. These results suggest that, when carefully positioned, the esophageal electrode is useful for recording the spontaneous diaphragm EMG.

**Neural respiratory drive before and after diaphragm fatigue.** There is a good correlation between the RMS of the diaphragm EMG, an index of drive, and ventilation (18). Therefore, the effect of diaphragm fatigue on neural drive may be reflected by ventilation. Although respiratory muscle fatigue has been assumed to be a cause of ventilatory failure, the available data are contradictory. Aubier et al. (1) and Hussain et al. (14) showed respiratory muscle fatigue and ventilatory failure in animal models of shock, whereas Nava and Bellemare (29), studying shock in dogs, found no evidence of diaphragm fatigue. In fact, overt respiratory muscle fatigue in clinical settings is relatively uncommon (10). It has been suggested that diaphragm fatigue can contribute to weaning failure, on the basis of

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**Fig. 4.** EMG recorded from 4 pairs of electrodes during maximal inspiratory resistive loading. A large amplitude EMG was recorded from pairs 1 and 3. Pair 2 recorded a slightly smaller EMG than pairs 1 and 3. Pair 4 only recorded a small EMG. Left: at the beginning of maximal inspiratory resistive loading. Right: 1 min after maximal loading; maximal transdiaphragmatic pressure (Pdi) is reduced, and the amplitude of EMG recorded from all 4 pairs of the electrode is also reduced. The simultaneous reduction of EMG and Pdi suggests that the reduction of diaphragmatic contractility during maximal loading could be due to reduction of neural drive to the diaphragm.
the observation of a decrease in the high-to-low ratio of the EMG power spectrum in patients during unsuccessful weaning attempts (5). However, this may be unreliable because EMG spectral analysis is not a specific method to diagnose diaphragm fatigue (33). Consistent with these findings, a study of infant monkeys (36) showed that ventilatory failure as a result of inspiratory resistive loading was not associated with inspiratory muscle fatigue. Additionally, Elliot et al. (9) failed to find any relationship between the improvement in arterial PCO2 and an increase in inspiratory muscle strength in patients with stable chronic obstructive pulmonary disease successfully treated with noninvasive ventilation. More recently, Laghi and colleagues (17) showed that most patients in the intensive care unit undergoing a weaning trial did not develop diaphragm fatigue, on the basis of twitch Pdi, whether the trial was a success or failure. These observations suggest that respiratory muscle fatigue may not, in some circumstances, be clinically important and may not affect ventilation. A number of studies in normal subjects have shown that diaphragm fatigue does not affect ventilation. Our laboratory has shown that in normal subjects MIVV was the same before and after fatigue (8). Yan et al. (37) demonstrated that diaphragm fatigue did not reduce ventilation and that the ventilatory response to CO2 was not altered by diaphragm fatigue, although they did not record the diaphragm EMG. Mador and Tobin (23) showed that the ventilatory response to CO2 rebreathing 5 and 40 min after fatigue did not significantly differ from that before fatigue. These studies are consistent with the findings of the present study that fatigue does not alter neural drive.

The failure of respiratory muscle fatigue to reduce ventilation suggests that, even with high levels of ventilation, there is sufficient reserve of ventilatory muscle capacity to compensate. Such compensation would require an increase in motoneuron firing frequency or recruitment of additional motor units. The lack of an increase in diaphragm EMG suggests either that diaphragm fatigue was not severe enough to induce a detectable change in EMG or that recruitment of other respiratory muscles (37) is increased.

Because of the possibility that the diaphragm fatigue induced by 2 min of MIVV was not severe enough to significantly alter neural drive, we sought to increase the severity of fatigue by an IRL protocol. Although all subjects felt profound exhaustion after the three consecutive runs, the twitch Pdi reduction of 20% (range 13–26%) after loaded breathing was the same as that produced by 2 min of MIVV (22%, range 13–27%). It is of interest to consider why it is difficult to produce more severe fatigue. It has been suggested that human inspiratory muscles are resistant to fatigue. McKenzie and co-workers (24) reported that they had difficulty in producing diaphragm fatigue in normal subjects who

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**Table 2. Twitch Pdi, R between RMS of EMG and V˙E and slope of regression of RMS on V˙E before and after 3 runs of maximal inspiratory resistive loading**

<table>
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breathed with 75 or 90% of maximal inspiratory pressure during resistive breathing trials. It has been recognized that fatigue is more difficult to induce in the human diaphragm than in the quadriceps. For example, diaphragm fatigue does not occur when the diaphragm contracts with a tension-time index of 0.18, whereas this tension-time index causes substantial quadriceps fatigue (35). Although the diaphragm is a skeletal muscle, central control of the diaphragm differs from that of limb skeletal muscles. McKenzie et al. (25) showed that central fatigue was more important in the diaphragm than in limb muscle. Bellemare and Bigland-Ritchie (4) found that central fatigue played an important role in the reduced performance of the diaphragm during IRL breathing. They also found that motor drive to the diaphragm progressively declined during repeated maximal efforts. In the present study, we found that the EMG amplitude measured from the esophageal electrode was reduced during IRL, as was Pdi, although the subjects were ostensibly making maximal efforts (Fig. 4). We also observed that all subjects could regenerate maximal EMG after several breathing cycles with reduced EMG. There were alternating maximal and submaximal EMG responses during IRL trials. Reduction of the diaphragm EMG suggests decreased central respiratory drive because IRL breathing does not cause failure of neuromuscular transmission (4). The reduction of neural drive to the diaphragm during IRL breathing may serve to protect the diaphragm from more severe peripheral fatigue. Indeed, it is difficult to intensify diaphragm fatigue. Our laboratory has shown that multiple 2-min MIVV trials do not produce more profound fatigue than does a single 2-min MIVV trial (8).

In conclusion, the diaphragm crus is relatively stable during CO2 rebreathing and there is a linear relationship between ventilation and RMS of the diaphragm EMG. This relationship does not change with diaphragm fatigue, at least of the magnitude induced in this study. The failure of diaphragm fatigue to reduce ventilation may be due, at least in part, to a sufficient reserve of ventilatory muscle capacity to compensate for the fatigue.

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