Bilateral Anterolateral Magnetic Stimulation of the Phrenic Nerves Can Detect Diaphragmatic Fatigue*

M. Jeffery Mador, MD; Saadat Khan, MD; and Thomas J. Kufel, MD

Background and study objectives: Measurement of twitch transdiaphragmatic pressure (TwPdi) during bilateral phrenic nerve stimulation is presently the best method to detect diaphragmatic fatigue in humans. The stimulation methods that are currently employed (ie, transcutaneous electrical stimulation [TES] and cervical magnetic stimulation [CMS]) have limitations. Bilateral anterolateral magnetic stimulation of the phrenic nerves (BAMPS) was recently described. The purpose of this study was to determine whether BAMPS can reliably detect diaphragmatic fatigue, and to compare the results with BAMPS with those obtained with the other stimulation techniques.

Subjects: Twelve healthy subjects participated in the study.

Methods: TwPdi was measured during TES, CMS, and BAMPS before and 10, 30, and 60 min after a potentially fatiguing task. Voluntary hyperpnea to task failure was used as the fatiguing task because this task has previously been shown to reliably produce contractile fatigue of the diaphragm. To determine the reproducibility of BAMPS, TwPdi was measured before and after a nonfatiguing task in 10 of the subjects.

Results: TwPdi fell significantly after the hyperpneic task with all three stimulation techniques, and the amount by which TwPdi fell after hyperpnea was not significantly different for the different stimulation techniques. The percentage fall in TwPdi after hyperpnea was significantly correlated between stimulation techniques (CMS vs BAMPS, r = 0.72; TES vs BAMPS, r = 0.84; and TES vs CMS, r = 0.67). The mean (± SE) within-subject, between-trial coefficient of variation for TwPdi during BAMPS was 5.1 ± 0.1%.

Conclusion: BAMPS is highly reproducible and at least as good at detecting diaphragmatic fatigue as the other stimulation techniques.

Key words: diaphragm; muscle fatigue; phrenic nerve; respiratory muscles; transcutaneous nerve stimulation

Abbreviations: ANOVA = analysis of variance; BAMPS = bilateral anterolateral magnetic stimulation of the phrenic nerves; CMS = cervical magnetic stimulation; MVV = maximum voluntary ventilation; Pdi = transdiaphragmatic pressure; Pes = Esophageal pressure; Pga = gastric pressure; PTP = pressure-time product; TES = transcutaneous electrical stimulation; TwPdi = twitch transdiaphragmatic pressure; TwPes = twitch esophageal pressure; TwPga = twitch gastric pressure; Ve = minute ventilation

Measurement of twitch transdiaphragmatic pressure (TwPdi) during bilateral phrenic nerve stimulation is presently the best method to detect diaphragmatic fatigue in humans.1 The “gold standard,” transcutaneous electrical stimulation (TES), is often difficult to apply because it can be difficult to accurately locate and supramaximally stimulate the phrenic nerves, particularly in subjects who are obese or who have short, thick necks. Minor changes in the location of the stimulating electrodes can result in submaximal stimulation. Cervical magnetic stimulation (CMS) is an alternative technique whereby the phrenic nerves are stimulated with a 90-mm circular magnetic coil.2 CMS is technically easy to perform and is highly reproducible. However, CMS provides a relatively diffuse stimulus that can stimulate additional chest wall muscles. It has been suggested3 that the analysis of CMS twitch pressures can be used to detect both diaphragmatic and rib cage muscle fatigue. Thus, CMS and TES may not be precisely equivalent. The phrenic nerves also can be magnetically stimulated by an anterolateral approach.3 Bilateral anterolateral magnetic stimulation of the phrenic nerves (BAMPS) may more
closely resemble TES than CMS. The purpose of this study was to determine whether BAMPS can reliably detect diaphragmatic fatigue and to compare the result with BAMPS with those obtained with the other stimulation techniques. Diaphragmatic fatigue was elicited by voluntary hyperpnea to task failure. This task previously has been shown to reliably produce contractile fatigue of the diaphragm. In addition, we evaluated the reproducibility of TwPdi during BAMPS following a nonfatiguing hyperpneic task.

**Materials and Methods**

**Subjects**

Twelve healthy subjects (eight men and four women) with a mean (± SE) age of 27.7 ± 2.0 years participated in the study. The mean height and weight of the subjects were 1.76 ± 0.03 m and 83.4 ± 5.3 kg, respectively. The study was approved by the appropriate institutional review boards, and informed consent was obtained from all subjects.

**Phrenic Nerve Stimulation**

The phrenic nerves were stimulated by the following three different techniques: TES, CMS, and BAMPS. Gastric pressure (Pga), esophageal pressure (Pes), and transdiaphragmatic pressure (Pdi) were measured with two balloon catheters using standard techniques, as previously described. TES: TES was performed with a pair of surface, bipolar, stimulating electrodes (model 13L36; Dantec; Allendale, NJ) that had felt tips and were 6 mm in diameter. The technical details of this procedure have been described previously. M waves were recorded with surface electrodes placed in the seventh and eighth intercostal spaces, 2 to 3 cm from the costal margin. The electromyogram signals were amplified and band pass-filtered (bandwidth, 20 Hz to 2 KHz). To ensure that the stimulus intensity remained supramaximal, the current was increased by an additional 20 to 50% during all experimental studies. Because lung volume can affect twitch amplitude, all twitches were performed at the same end-expiratory lung volume (ie, functional residual capacity), as inferred from the end-expiratory Pes. Before nerve stimulation, the mouthpiece was occluded via a mouth shutter (model 4200C; Hans Rudolph; Kansas City, MO) to prevent any change in volume during nerve stimulation. M waves from each hemidiaphragm were digitized and stored on a disk using computer software (Windaq; Dataq Instruments, Inc; Akron, OH). The peak-to-crest amplitude (ie, the M-wave height) was measured from the computer tracing. Individual twitches were rejected from analysis if any of the following conditions occurred: (1) a >20% decrease in M-wave amplitude (right or left) compared with the M-wave amplitude obtained during the initial control period; (2) a failure to initiate the twitch near functional residual capacity, as determined by the end-expiratory Pes; (3) an inability to analyze the M wave because of the superimposition of the ECG; (4) esophageal peristalsis during or just before the initiation of the twitch; and (5) a lack of diaphragmatic relaxation, as demonstrated by diaphragmatic electromyogram activity and/or a Pga in excess of baseline values before twitch onset.

CMS: CMS was performed with a commercial magnetic stimulator (Magstim 200; Magstim Co Ltd; Whitland, Dyfed, Wales, UK) using a circular 90-mm coil. To stimulate the phrenic nerve roots, the neck was flexed and the coil was placed over the C7 spinous process. The coil then was moved up and down the midline between C5 and C7 positions, and the position where the largest Pdi response was elicited was marked. All subsequent twitches were obtained from this coil position. BAMPS: BAMPS was performed using two 45-mm figure-of-eight coils, each of which was connected to a magnetic stimulator (Magstim 200; Magstim Co, Ltd.). The two magnetic stimulators were connected to allow simultaneous stimulation of the phrenic nerves on each side. The coils were placed at the posterior border of the sternomastoid muscle at the level of the cricoid cartilage. When the optimal position of the coil was located, the position was marked and used for all subsequent twitches.

**Experimental Protocol**

For magnetic stimulation, all twitches were performed at 100% power output of the stimulator. A series of eight twitches with each stimulation technique were obtained before and 10, 30, and 60 min after the same hyperpneic run. The order in which the three stimulation techniques were performed was randomly allocated. On a separate occasion, five twitches were obtained at 60%, 70%, 80%, 85%, 90%, 95%, and 100% power output (n = 10) to determine whether BAMPS maximally stimulated the phrenic nerves. A plateau in the TwPdi with increasing power output would indicate that the phrenic nerves were maximally stimulated. During magnetic stimulation, the M wave often was obscured by a large stimulus artifact. For this reason, we did not use M-wave amplitude as a criterion for twitch acceptance during magnetic stimulation. Otherwise, we used the same criteria to determine twitch acceptability as were employed during TES.

**Hyperpneic Run**

The subject’s maximum voluntary ventilation (MVV) was measured over 12 s using standard pulmonary function equipment (P.K. Morgan; Chatham, Kent, UK). At least three MVV maneuvers were performed, and the highest MVV was chosen for analysis. After a 3-min acclimatization period to the breathing circuit, subjects were asked to breathe at 60% of their MVV until task failure, which was defined as the inability to maintain minute ventilation (Ve) of >55% of the MVV. When the subjects’ Ve slipped below the target, they were verbally exhorted to increase their ventilation. When subjects were unable to maintain a Ve of >55% of the MVV despite verbal encouragement, task failure was said to have occurred and the run was terminated.

During hyperpnea, subjects breathed through a two-way nonrebreathing valve of low resistance and dead space (model 2700; Hans Rudolph). Inspiratory flow was measured with a pneumotachograph (model 3813; Hans Rudolph) and a ±5 cm H2O differential pressure transducer (MP 45; Validyne Corp). Tidal volume was obtained by integration of the flow signal. The inspiratory limb of the breathing circuit was connected to a 200-L bag filled with an air-O2-CO2 mixture. Expired CO2 was sampled at the mouthpiece and was analyzed by an infrared CO2 analyzer (Medical Gas Analyzer LB-2; Beckman Coulter; Fullerton, CA). The relative proportions of air and O2-CO2 gas mixture added to the bag were adjusted throughout the hyperpneic run to keep the end-tidal CO2 level between 4.0% and 5.5%.

To determine whether anterolateral magnetic stimulation was reproducible over time, control runs were performed in 10 subjects. Subjects breathed at a target ventilation of 25 L/min for 10 min. The average (± SE) Ve during the control runs represented 13.8 ± 0.7% of the subject’s MVV, a percentage that is clearly nonfatiguing.

Ve was measured continuously throughout the hyperpneic run.
Breathing pattern and respiratory pressures were measured for 10 consecutive breaths at the middle and during the penultimate minute of the run.

All signals were digitized and stored on disk using computer software (Windaq; Dataq Instruments).

Data Analysis

For each individual trial, a fall in TwPdi after hyperpnea of 15% was considered to be indicative of diaphragmatic fatigue. Changes in TwPdi after hyperpnea were analyzed by repeated-measures analysis of variance (ANOVA) and paired t test with Bonferroni correction. Simple linear regression was used to compare the values for TwPdi given by the different stimulation techniques. The data are expressed as the mean ± SE.

Results

Effect of Hyperpnea on Twitch Pressures

TwPdi values from before and after hyperpnea to task failure are shown in Figure 1. TwPdi fell significantly after hyperpnea with all three stimulation techniques. In three subjects, maximal stimulation could not be achieved with transcutaneous stimulation. These subjects were not included in the analysis of the transcutaneous TwPdi data. Expressing the TwPdi after hyperpnea as a percentage of the baseline value (to normalize for differences in baseline TwPdi between stimulation techniques), the amount by which the TwPdi fell after the hyperpneic trial was not significantly different for the three stimulation techniques (Fig 2). The fall in TwPdi after hyperpnea was due to decreases in both the twitch Pes (TwPes) and the twitch Pga (TwPga) with all the stimulation techniques.

In individual subjects, a 15% fall in TwPdi from the baseline value was used as the threshold to distinguish fatiguers from nonfatiguers. Congruent results (ie, same classification with the different stimulation techniques) were achieved in 10 of the 12 subjects (approximately 80%). Nine of 12 subjects were classified as fatiguers with BAMPS, 7 of 12 subjects were classified as fatiguers with CMS, and 6 of 9 subjects (the three subjects with submaximal TwPdi levels during TES were not included in the analysis) were classified as fatiguers with TES.

The percentage fall in TwPdi after hyperpnea (from the baseline value) was significantly correlated among the three stimulation techniques (Fig 3). The r values were 0.72 for CMS and BAMPS, 0.84 for TES and BAMPS, and 0.67 for TES and CMS.

For the group as a whole, the TwPes/TwPga ratio did not change significantly after hyperpnea by any of the three stimulation techniques. However, changes in the TwPes/TwPga ratio after hyperpnea were observed in some of the subjects. The criteria for CMS outlined by Similowski and colleagues to detect preferential rib cage fatigue, preferential di-

![Figure 1](http://example.com/figure1.png)

**Figure 1.** TwPdi values before and 10, 30, and 60 min after hyperpnea to task failure for the three stimulation techniques are shown. TwPdi fell significantly after hyperpnea with all three stimulation techniques. * = significant difference from baseline value.

![Figure 2](http://example.com/figure2.png)

**Figure 2.** TwPdi values expressed as a percentage of the baseline value before and 10, 30, and 60 min after hyperpnea to task failure are shown. The percentage fall in TwPdi after hyperpnea was not significantly different between stimulation techniques. * = significant difference from baseline value.
phrenic, or global inspiratory muscle fatigue were applied to our data. After hyperpnea, predominant diaphragmatic fatigue was observed in four subjects, predominant rib cage fatigue was observed in five subjects, global inspiratory muscle fatigue was observed in one subject, and no inspiratory muscle fatigue was observed in two subjects. For the subjects with predominant diaphragmatic fatigue, the TwPdi fell after hyperpnea by $16.7 \pm 4.7\%$ during CMS, by $24.6 \pm 5.2\%$ during TES, and by $27.0 \pm 4.2\%$ during BAMPS (differences were not significant by ANOVA). For the subjects with predominant rib cage fatigue, the TwPdi fell after hyperpnea by $18.0 \pm 3.4\%$ during CMS, by $14.8 \pm 2.1\%$ during TES, and by $18.9 \pm 3.2\%$ during BAMPS (differences were not significant by ANOVA).

Reproducibility and Validity of TwPdi With BAMPS

The TwPdi was not significantly different from the baseline value at any time after the control hyperpneic run (Fig 4). The within-subject, between-trial coefficient of variation for TwPdi during BAMPS was $5.1 \pm 1.0\%$. The coefficient of variation for its component parts was $7.1 \pm 1.5\%$ for TwPes and $8.2 \pm 0.9\%$ for TwPga.

Twitch pressure with increasing power output is shown in Figure 5. The TwPdi initially increased with increasing power output but then plateaued at around 85% of power output. A similar plateau was seen for both TwPes and TwPga (Fig 5). The TwPdi at 100% power output was obtained at both the beginning and the end of the run to ensure that the twitches obtained at lower power outputs did not potentiate subsequent twitches at higher power outputs. The TwPdi at 100% of power output at the beginning of the run ($27.9 \pm 2.2$ cm H$_2$O) was not significantly different from that obtained at the end of the run ($26.9 \pm 2.3$ cm H$_2$O).

In the fresh state, the TwPdi was similar during CMS ($32.0 \pm 2.1$ cm H$_2$O) and BAMPS ($31.6 \pm 1.8$ cm H$_2$O). The TwPdi during TES ($25.6 \pm 2.2$ cm H$_2$O) was significantly lower than during BAMPS ($p < 0.001$) and CMS ($p < 0.01$). The difference in TwPdi was solely due to differences in TwPes, whereas TwPga was not significantly different with the three techniques. The Pes/Pga ratio was significantly higher during CMS compared with TES.
The Pes/Pga ratio during BAMPS was between those obtained during CMS and TES and was not significantly different from either.

**Breathing Pattern During Hyperpnea**

Endurance time averaged 12.3 ± 2.0 min. The Ve averaged 97.7 ± 4.1 L/min, which represented 58.6 ± 1.6% of the 12-s MVV. The respiratory rate was 71.4 ± 5.7 breaths/min, while the peak inspiratory flow was 4.1 ± 0.2 L/min. The mean inspiratory Pes and Pdi were 30.8 ± 1.4 and 15.9 ± 1.4 cm H2O, respectively. The respiratory duty cycle was 0.55 ± 0.01. Pressure-time products (PTPs) from the esophageal and the diaphragmatic pressure curves were calculated as mean pressure × inspiratory time × respiratory frequency and equaled 1,011 ± 67 and 511 ± 40 cm H2O/s/min, respectively. A tension-time index from the Pes curve was calculated as the mean inspiratory Pes/maximal Pes × respiratory duty cycle and equaled 0.15 ± 0.01 during hyperpnea. Abdominal muscle contraction during expiration occurred in all subjects. Expiratory Pga swings averaged 28.4 ± 3.6 cm H2O. The Ve during the control hyperpnea runs averaged 24.7 ± 1.0 L/min. The esophageal PTP and the diaphragmatic PTP were 201 ± 12 and 230 ± 28 cm H2O/s/min, respectively.

**Discussion**

The major findings of this study are the following: (1) TwPdi during BAMPS is as good at detecting diaphragmatic fatigue as the other stimulation techniques; (2) TwPdi during BAMPS is reproducible; (3) the results of measuring TwPdi during BAMPS in the fresh state were similar to those observed during CMS but were larger than those observed during TES; and (4) twitch pressure during BAMPS plateaued at power outputs well below the maximum.

**BAMPS Technique:** BAMPS proved to be quite simple to use, and, once the stimulating coils were placed in the suggested position,4 minimal to no repositioning of the coils was required. In contrast, TES can be quite difficult to perform, particularly in obese individuals. A slight movement of the patient’s neck can completely alter the orientation of the stimulating electrodes, which then require extensive repositioning. In this study, we had three subjects, all of whom were obese and in whom we had considerable difficulty finding the optimal position for TES. In these subjects, although it appeared that the compound motor action potential plateaued with increasing stimulus current, TwPdi was low, ranging from 13.2 to 14.4 cm H2O. TwPdi was markedly larger during CMS (32.5 ± 2.0 cm H2O) and BAMPS (31.1 ± 1.2 cm H2O), clearly demonstrating that TwPdi during TES was submaximal in these subjects. No such difficulties were encountered during BAMPS. A plateau in TwPdi during TES occurred at a power output from the magnetic stimulator of ≤ 85%. In contrast, during CMS TwPdi does not appear to plateau until approximately 95% of power output.5,7 Thus, it is much easier to document that stimulation is maximal with BAMPS.
During CMS, flexion of the neck is required to obtain maximal stimulation. When this is not possible, BAMPS would be a suitable alternative. In patients with fatty deposits at the back of their neck, as in patients with Cushing’s syndrome, the results of CMS are unlikely to be maximal and BAMPS would be a better choice. Patients with severe COPD are sometimes placed on long-term steroid therapy that, obviously, can produce Cushingoid features.

In our study, we had one obese female subject with a prominent fatty deposit at the back of her neck. Although the TwPdi during CMS was within the normal range, it was considerably lower than that obtained during TES and BAMPS. Thus, patient anatomy should be considered when determining the optimal method to obtain the TwPdi.

The TwPdi obtained during CMS is larger than that obtained during TES. CMS provides a more diffuse stimulus that activates the chest wall muscles, stiffening the upper rib cage, which improves the transformation of diaphragmatic force into negative pleural pressure. The TwPdi obtained during BAMPS was also significantly higher than that obtained during TES but was not significantly different from that obtained during CMS. During CMS, the TwPes/TwPga ratio is often significantly higher than that during TES, as was observed in this study. The TwPes/TwPga ratio during BAMPS was intermediate between the values obtained during TES and CMS, and was not significantly different from either value. BAMPS may more closely resemble TES than does CMS.

TwPdi during BAMPS was highly reproducible (5.1 ± 1.0%; Fig 4), with a within-subject, between-trial coefficient of variation that was similar to that observed in our laboratory for TES and CMS.

**Ability to Detect Fatigue:** The TwPdi fell significantly following voluntary hyperpnea to task failure with all three stimulation techniques (Fig 1). For the group as a whole, the percentage fall in TwPdi after hyperpnea was not significantly different for the three stimulation techniques (Fig 2). In individual subjects, based on a threshold of a 15% fall in TwPdi after hyperpnea (from the baseline value) to distinguish fatigues from nonfatigues, congruent results were obtained in 10 of 12 subjects. Thus, it appears that all three techniques are acceptable methods to detect diaphragmatic fatigue. When the percentage fall in TwPdi after hyperpnea was compared for the three techniques, significant correlations were obtained. BAMPS was significantly correlated with TES and CMS, and TES and CMS were also significantly correlated.

The degree of fatigue elicited by voluntary hyperpnea was relatively modest as, on average, TwPdi fell by 21% after hyperpnea. The range for the between-trial, within-subject coefficient of variation is 5 to 8% for the different stimulation techniques. For each correlation, we compared changes in two signals with significant noise compared with the magnitude of the expected change. Thus, it is not surprising that the correlations are not extremely tight. If the degree of fatigue elicited by hyperpnea had been greater (ie, improving the signal-to-noise ratio), the correlations between the stimulation techniques might have been better.

We have previously shown that during voluntary hyperpnea to task failure, the pattern of respiratory muscle recruitment can vary between subjects. While all inspiratory and expiratory muscles are recruited, the amount of rib cage and expiratory muscle recruitment (compared to diaphragmatic recruitment) varies among subjects. Depending on respiratory muscle recruitment patterns during hyperpnea, at task failure subjects may have predominant diaphragmatic fatigue, predominant rib cage fatigue, global inspiratory muscle fatigue, or no inspiratory muscle fatigue (in patients with no inspiratory muscle fatigue, task failure must be due to either expiratory muscle fatigue or central fatigue). Similowski and colleagues have shown that by examining changes in TwPes, TwPga, and the TwPes/TwPga ratio, CMS can be used to detect both rib cage and diaphragmatic fatigue. As predicted by Similowski and colleagues for the patients with predominant diaphragmatic fatigue, TwPdi fell after hyperpnea to a greater extent during TES than during CMS, although the difference did not reach statistical significance. In the patients with predominant rib cage fatigue, TwPdi fell after hyperpnea to a greater extent during CMS than during TES, although again the difference did not reach statistical significance. With BAMPS, in patients with predominant diaphragmatic fatigue, TwPdi fell after hyperpnea to a similar extent as during TES, while in patients with predominant rib cage fatigue, TwPdi fell after hyperpnea to a similar extent as during CMS. It would be worthwhile to repeat the experiments of Similowski and colleagues in which isolated rib cage fatigue was produced to better delineate the manner in which rib cage fatigue affects the twitch responses during BAMPS.

In conclusion, BAMPS is an easy and reproducible technique that can effectively detect diaphragmatic fatigue in human subjects.

**REFERENCES**