Voluntary activation of the human diaphragm in health and disease

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Sinderby, Christer, Jennifer Beck, J adranka Spahija, Jan Weinberg, and Alex Grassino. Voluntary activation of the human diaphragm in health and disease. J. Appl. Physiol. 85(6): 2146–2158, 1998.—Intersubject comparison of the crural diaphragm electromyogram, as measured by an esophageal electrode, requires a reliable means for normalizing the signal. The present study set out 1) to evaluate which voluntary respiratory maneuvers provide high and reproducible diaphragm electromyogram root-mean-square (RMS) values and 2) to determine the relative diaphragm activation and mechanical and ventilatory outputs during breathing at rest in healthy subjects (n = 5), in patients with severe chronic obstructive pulmonary disease (COPD, n = 5), and in restrictive patients with prior polio infection (PPI, n = 6). In all groups, mean voluntary maximal RMS values were higher during inspiration to total lung capacity than during sniff inhalation through the nose (P = 0.035, ANOVA). The RMS (percentage of voluntary maximal RMS) during quiet breathing was 8% in healthy subjects, 43% in COPD patients, and 45% in PPI patients. Despite the large difference in relative RMS (P = 0.012), there were no differences in mean transdiaphragmatic pressure (P = 0.977) and tidal volumes (P = 0.426). We conclude that voluntary maximal RMS is reliably obtained during an inspiration to total lung capacity but a sniff inhalation could be a useful complementary maneuver. Severe COPD and PPI patients breathing at rest are characterized by increased diaphragm activation with no change in diaphragm pressure generation.

The aims of the present study were 1) to obtain the peak RMS values in healthy subjects during four voluntary diaphragm EMG to evaluate neural drive to the diaphragm.

One of the issues in using the diaphragm EMG signal strength is, however, related to the anatomic variations between subjects that cause the amount of crural diaphragm-to-electrode (radial) distance filtering effects to vary, making it difficult to reliably compare the data obtained from different subjects unless it is normalized. To overcome this problem, some authors have used the EMG signal strength obtained at total lung capacity (TLC) for normalization (8, 19, 21, 22), whereas others have used the EMG signal strength obtained during a maximal transdiaphragmatic pressure (Pdi) maneuver (38) or have simply normalized their data to the highest EMG signal strength obtained at any time (9). “Fold increases” or “percent increases” from resting levels have also been used for normalization. Of the normalization procedures described above, no rationale was provided by any of the investigators concerning the normalization values selected. To our knowledge, there is no documentation of an appropriate and standard method for normalization of the diaphragm EMG signal strength. For the purpose of clarity, the term EMG signal strength is used to describe any technique that calculates the sum or power of the rectified EMG, independent of the time base used for the integration.

The most preferred value for normalization of the EMG signal strength would be an involuntarily induced maximal EMG signal strength, which would eliminate the influence of such factors as motivation and comprehension. For reasons that are clarified in the Discussion, it is difficult, if not impossible, to obtain an involuntarily induced maximal EMG signal strength that would represent maximal motor unit recruitment and motor unit firing rate. The second-best method would be to normalize to a maximal voluntary EMG signal strength, which is the highest EMG signal strength obtained during a voluntary effort and increases with motor unit recruitment and firing rate. To be successful, such a maximal voluntary maneuver should be easy to teach to a subject or patient and easy to perform. In the present study and in previous studies (5, 6) we have opted to use the root-mean-square (RMS) values of the diaphragm EMG to describe the strength of the signal.

The aims of the present study were 1) to obtain the peak RMS values in healthy subjects during four voluntary...
different maximal voluntary respiratory maneuvers to determine which maneuver provides the highest and most reproducible RMS value and 2) to determine the habitual level of relative diaphragm activation by evaluating the diaphragm RMS during resting breathing expressed as a fraction of the maximal voluntary diaphragm RMS value in healthy subjects, in patients with severe chronic obstructive pulmonary disease (COPD), and in patients with severe chronic restrictive ventilatory impairment after prior polio infection (PPI). We also evaluated the mechanical and ventilatory outputs of the respiratory system, e.g., mean inspiratory esophageal pressure (Pes), gastric pressure (Pga), Pdi, inspiratory flow, and tidal volumes (VT), in the same groups.

**METHODS**

**Subjects**

Five healthy men, all very familiar with respiratory maneuvers, as well as five patients (2 men, 3 women) with moderate-to-severe COPD (mean percent predicted forced expired volume in 1 s = 28%, mean forced expired volume in 1 s-to-forced vital capacity ratio = 41%) and six patients (5 men, 1 woman) with severe chronic restrictive ventilatory impairment due to respiratory muscle paralysis and kyphoscoliosis after PPI agreed to participate in the study. Nocturnal intermittent positive-pressure ventilation had been prescribed for all the PPI patients as a treatment for latent respiratory insufficiency. At the time of the study the COPD and PPI patients were outpatients, alert, and not prescribed sedative medication. One PPI patient was prescribed β-blockers for cardiac arrhythmia. Three other PPI patients were treated for high blood pressure: two with diuretics and one with angiotensin-converting enzyme inhibitors. All COPD patients were prescribed bronchodilators (salbutamol, Atrovent) and corticosteroids (prednisolone for inhalation use). One COPD patient had received oral corticosteroids 1 wk before the test. The study was approved by the Ethics Committees of Notre Dame Hospital for healthy subjects and COPD patients and the Söder Hospital (Stockholm, Sweden) for PPI patients, and informed consent was obtained from all healthy subjects and COPD and PPI patients. Anthropometric and spirometric data for healthy subjects and COPD and PPI patients are presented in Table 1.

**Experimental Setup**

Crural diaphragm EMG signals were obtained via a multiple-array esophageal electrode consisting of nine stainless steel rings (2 mm wide, 2 mm diameter), placed 10 mm apart, creating an array of eight sequential differential bipolar electrode pairs, mounted on silicone tubing (2 mm diameter). The most caudal pair of rings was referred to as electrode pair 1 and the most cephalad pair of rings as electrode pair 8. Two Teflon tubes were placed inside the silicone tubing (0.75 mm diameter), and two latex balloons (5 cm long, 1.5 cm diameter) were mounted ~10 cm below the most distal EMG ring and 2 cm above the most cephalad ring to allow for measurements of Pga and Pes, respectively. The two balloon catheters were connected to two differential pressure transducers (±350 cmH₂O). Mouth pressure (Pm) was measured via a side port in the mouthpiece and connected to a third differential transducer (±350 cmH₂O). Inspiratory flow was measured with a pneumotachograph (no. 2, Fleisch). Rib cage and abdominal displacements were measured throughout the protocol using respiratory inductive plethysmography (Respirac; Ambulatory Monitoring). In the COPD patients we also recorded costal diaphragm EMG with bipolar surface electrodes (Graphics Control, Meditrace).

Diaphragm EMG signals from esophageal electrode pairs 1–8 (crural diaphragm) and from the electrode pair on the rib cage (costal diaphragm) were amplified (model INA102, Burr-Brown) and high-pass filtered at 10 Hz with an anti-aliasing filter at 1,000 Hz (model D70L8L, Frequency Devices, 8-pole Bessel filter). Diaphragm EMG signals were acquired and digitized using an analog-to-digital converter (model 2821, Data Translation), with 12-bit resolution, at a sampling frequency of 2,000 Hz and stored on hard disk for off-line analysis. Flow, Pm, Pes, Pga, and rib cage and abdominal displacements were acquired simultaneously with the EMG data (model DT 2811-PGH, Data Translation) at a sampling frequency of 100 Hz. All signals related to the diaphragm

| Table 1. Description and statistical comparison of anthropometric, spirometric, and related data obtained in different groups |
|--------------|-------------|-----------|-----------|-----------|-----------|-----------|
|               | Healthy Subjects (1) | COPD Patients (2) | PPI Patients (3) | Difference of Means |
|               | Age, yr | 36.6 ± 5.5 | 60.0 ± 7.2 | 62.3 ± 8.8 | 23.4* | 25.7* | 2.3 |
|               | Height, cm | 172.8 ± 5.4 | 163.4 ± 9.6 | 175.3 ± 6.4 | 9.4 | 2.5 | 11.9* |
|               | Weight, kg | 70.6 ± 10.7 | 58.3 ± 9.7 | 71.7 ± 9.5 | 12.3 | 1.1 | 13.4 |
|               | BMI, kg/m² | 23.5 ± 2.2 | 22.1 ± 4.9 | 23.3 ± 2.9 | 1.4 | 0.2 | 1.2 |
|               | VC, liters | 4.9 ± 0.87 | 1.90 ± 0.50 | 2.26 ± 0.63 | 2.92* | 2.66* | 0.26 |
|               | FEV₁, liters | 0.69 ± 0.19 | 1.15 ± 0.44 | NA | NA | 0.89* | NA |
|               | TLC, liters | NA ± NA | 7.12 ± 1.73 | 3.80 ± 0.95 | NA | NA | 3.3* |
|               | RV, liters | NA ± NA | 5.22 ± 1.46 | 1.64 ± 0.70 | NA | NA | 3.58* |
|               | FRC, liters | NA ± NA | 5.90 ± 1.60 | NA ± NA | NA | NA |
|               | PCO₂, Torr | NA ± NA | 50.9 ± 4.9 | 48.5 ± 4.8 | NA | NA | 2.4 |
|               | Peak Pdi, cmH₂O | 66.0 ± 14.6 | 40.2 ± 16.3 | 46.5 ± 24.5 | 25.8 | 19.5 | 6.3 |
|               | Insp TLC | 188.6 ± 24.7 | 97.6 ± 34.4 | 67.3 ± 31.7 | 91.2* | 121.5* | 30.3 |
|               | Sniff | 221.0 ± 44.1 | NA ± NA | NA ± NA | NA | NA |
|               | Combined | 208.2 ± 30.1 | NA ± NA | NA ± NA | NA | NA |

Values are means ± SD. COPD, chronic obstructive pulmonary disease; PPI, prior polio infection; NA, not available; BMI, body mass index; VC, vital capacity; FEV₁, forced expiratory volume in 1 s; TLC, total lung capacity; RV, residual volume; FRC, functional residual capacity; Pco₂, Pco₂ estimated from capillary blood; Pdi, transdiaphragmatic pressure; combined, combined Müller and expulsive maneuver; Sniff, sniff inhalation maneuver; Insp TLC, inspiration to TLC maneuver; MVV, maximal voluntary ventilation maneuver. *P < 0.05.
EMG and respiratory mechanics could be observed on-line during the experiment.

Instrumentation

All healthy subjects and patients were studied while seated in an upright chair, facing a computer monitor, which provided visual feedback for the various maneuvers. For example, subjects would have a flow-volume loop displayed to them if an inspiration to TLC was the maneuver required. Feedback could also be provided about peak Pdi, where Pes, Pga, and Pdi were displayed as a function of time and a horizontal line would indicate the peak Pdi value achieved; the subject would then be encouraged to surpass the line on the following attempt. In the COPD patients the surface EMG electrodes were placed over the lowest rib interspace (in the direction of the ribs) in the midclavicular line on the right side. The interelectrode distance was \( \sim 25 \) mm. Respiratory bands were positioned on the subjects and secured in place with tubular surgical dressing (no. 7, Surgifix) placed over the thorax. The esophageal catheter with the EMG electrodes and pressure balloons was then passed through the nose and swallowed, and the EMG electrodes were positioned at the level of the gastroesophageal junction with feedback from an on-line display of the diaphragm EMG signals from all eight electrode pairs on the computer monitor. With this position of the catheter, the esophageal balloon is located in the lower third of the esophagus and the gastric balloon in the stomach.

Experimental Protocol

All healthy subjects and patients were asked to perform the following maneuvers: 1) a maximal sniff inhalation maneuver performed from functional residual capacity (FRC) \((27)\) and 2) an inspiration to TLC followed by a slow expiration to residual volume (RV).

These maneuvers were determined to be suitable, because they have the potential to provide the highest RMS values and are easy to explain to the subject. Patients could understand the instructions and could perform the maneuvers without discomfort. During the sniff maneuver, one nostril was occluded.

In healthy subjects only we also added the following maneuvers to the protocol: 1) a combined Müller and expulsive maximal static Pdi maneuver performed at FRC, as described by Laporta and Grassino (23), and 2) a maximal voluntary ventilation (MVV) maneuver sustained for 10 s.

A rest period of \( > 15 \) s was allowed between attempts for a given maneuver. The combined (healthy subjects) and sniff (all groups) maneuvers were repeated until three reproducible “maximal” Pdi values were obtained. The inspiration to TLC, followed by an expiration to RV, was repeated until three reproducible maximal vital capacity (VC) values were achieved. The MVV maneuver was performed only once in each healthy subject. All attempts were recorded and used in the analysis. Subjects rested 10–15 min between the different types of maneuvers. To evaluate the reproducibility of the inspiration to the TLC maneuver, the healthy subjects repeated the test on a second occasion 1–6 wk later.

EMG Signal Processing

Timedomain. Diaphragm EMG and respiratory mechanics analysis was performed off-line. EMG signals were automatically processed with computer algorithms that eliminate the influence of electrocardiogram (ECG), motion artifacts, background noise, and disturbances from the mains and continuously calculate the RMS value for nonoverlapping sequential EMG segments of 50-ms duration.

The influence of the ECG on the EMG signal was eliminated by an optimized filter developed to separate the ECG and the EMG from a compound signal that also is disturbed by background noise and motion artifacts. Wiener filtering enabled us to find filters that give the highest possible signal-to-disturbance ratio for the EMG. The optimal filters were determined from experimental data, implemented with individual filter links of low-pass, band-pass, high-pass, and notch filter characteristics. They were then transformed into recursive time domain filters. Included in the total filter was also a suppression of disturbances from the mains. Eventual residuals of the ECG were detected by relating the EMG and ECG signals that were separated from the compound signal. Residual ECG artifacts in the signal segment used to calculate the RMS value were eliminated by replacement with the latest undisturbed RMS value.

In humans the crural diaphragm forms a muscular tunnel around the esophagus (a few centimeters thick), and the muscle fibers are mostly perpendicular to the esophageal catheter. During voluntary contractions the crural diaphragm can be considered an electrically active region (referred to as EAR\(_{\text{dcenter}}\)), and the center of this activity, where the majority of the signals originate, is referred to as the EAR\(_{\text{dcenter}}\). The relative position of the EAR\(_{\text{dcenter}}\) with respect to the electrode array is important for correct physiological interpretation of the diaphragm EMG. With a perpendicularly oriented electrode arrangement, signals that are obtained on opposite sides of the EAR\(_{\text{dcenter}}\) or on the same side of the EAR\(_{\text{dcenter}}\) correlate with extreme values (i.e., the correlation coefficient is expected to be close to \(-1\) or \(+1\)) at a 0-ms time shift. Cross-correlation analysis was performed between signals from, e.g., electrode pairs 1 vs. 3, 2 vs. 4, and 3 vs. 5 for each of the 50-ms signal segments. The most negative correlation coefficient between any two pairs of electrodes indicates that the respective signals are the most reversed in polarity. The electrode pair that is located between these two most negatively correlated pairs is the electrode pair closest to EAR\(_{\text{dcenter}}\). After the EAR\(_{\text{dcenter}}\) position was determined, the 50-ms signal segments obtained from the two electrode pairs that were located next to the EAR\(_{\text{dcenter}}\), i.e., 10 mm caudal and 10 mm cephalad, were subtracted from each other. This algorithm yields a new signal, the “double-subtracted signal,” which is less influenced by electrode filtering and enhanced in signal-to-noise (SN) ratio (33). The double-subtraction technique is described in detail elsewhere (4, 33).

From the double-subtracted signal, RMS was calculated as

\[
\text{RMS} = \left( \frac{\sum_{i=1}^{n} s_i^2}{l_{\text{max}}} \right)^{1/2}
\]

where \(s_i\) is the index over which the signal (s) is summed, \(i = 1\) is the index for the first signal data point used in the summation, and \(l_{\text{max}}\) is the index associated with the last signal data point used in the summation.

A graphic description of the time domain analysis is provided in Fig. 1. Figure 1A shows the trajectory of Pdi and the EMG representative of different phases of the analysis during an inspiration toward TLC. The raw EMG signal, i.e., as the signal appears after amplification and initial bandpass filtering, is illustrated for all eight channels in Fig. 1B. Figure 1C is a presentation of the eight channels of raw EMG after processing with an optimized filter. The arrows in Fig. 1C indicate the channels detected by the cross-correlation technique that are on opposite sides of the EAR\(_{\text{dcenter}}\) and are used in the double-subtraction technique. Note how the
EAR_{di}_{center} (located between the arrows) moves five channels (inter-electrode distance = 1 cm) in the caudal direction as the inspiration proceeds, suggesting that the diaphragm slides ~5 cm caudally along the electrode during the inspiration. The double-subtracted signal is depicted in Fig. 1D, and the RMS calculated from each 50-ms segment of the double-subtracted signal is presented in Fig. 1E.

The time domain analysis of the costal diaphragm EMG obtained with bipolar electrodes on the rib cage in the COPD patients was performed as described above, except for the double-subtraction technique, which could not be implemented for those signals.

Frequency domain. For calculation of the diaphragm EMG center frequency (CF) values, the analysis was performed in the frequency domain. Diaphragm EMG signals were analyzed with computer software that, on the basis of predetermined criteria, evaluates signal contamination by such factors as the ECG, noise, motion artifacts, and esophageal peristalsis (34). The raw diaphragm EMG signals were automatically selected between the QRS complexes of the ECG (~50–75% of the R-R interval) from all eight electrode pairs. From the eight raw diaphragm EMG signals, the direct-current levels and trends were removed by linear regression analysis; the tails of the raw signals were zero padded from the first and last zero crossings of the EMG signal to fit the segments for a fast Fourier transform of 1,024 points.

The exact position of the array of electrode pairs with respect to the EAR_{di} was determined by cross-correlation analysis, as described above (4, 33). The two pairs of electrodes with the most negative correlation coefficient were included in the analysis only if the correlation coefficient (for the 2 most negatively correlated signal segments) was less than or equal to −0.50. The double-subtraction technique was applied for every EMG segment selected between the ECG QRS complexes (33).

The time domain segments of the double-subtracted signal were then converted to the frequency domain by fast Fourier transform, and the power spectrums were calculated. CF was calculated from the diaphragm EMG power spectrum as the spectral moment of order 1 (M_1) divided by that of order 0 (M_0)

\[
CF = \frac{M_1}{M_0}
\]

where spectral moments (M) of order n are obtained by

\[
M_n = \sum_{i=0}^{i_{\text{max}}} \text{power density}_i \times \text{frequency}_i^n
\]

where \(i\) is the index over which the power density frequency product is summed, \(i = 0\) is the direct-current component, and \(i_{\text{max}}\) is the index associated with the highest frequency in the spectrum.
In each subject, signal contamination was evaluated for each electrode pair’s power spectrum by contamination-sensitive indexes. The four indexes used to evaluate signal contamination were the SN ratio, the signal-to-motion artifact (SM) ratio, the drop in power density of the spectrum (DP) ratio, and a spectral deformation (t) index. The indexes are described in more detail in the recent work by Sinderby et al. (34).

It has been determined that the following combination of the above-described indexes allows for an error of CF values in the range of -5 to +10 Hz: SM $\geq$ 12 dB, SN $\geq$ 15 dB, DP $\geq$ 30 dB, and $t$ $\leq$ 1.4 (34); these acceptance levels were used in the present study.

Statistical Analysis

Mean Pes, Pga, and Pdi are calculated as the mean area during each inspiration. The peak RMS value obtained during quiet breathing, expressed as percentage of the highest RMS value obtained during any of the maneuvers performed (subsequently referred to as the diaphragm “relative RMS”), was used to determine the resting level of diaphragm activation in the three groups. Values are means $\pm$ SD. Statistical comparison of two groups was performed with Student’s t-test for independent groups. Statistical comparison of single variables between the three groups was performed with one-way ANOVA. Comparison of multiple variables (e.g., different maneuvers to obtain maximal voluntary RMS) between the three groups was performed with two-way ANOVA. Post hoc pairwise multiple comparison was performed with the Tukey test. The calculation of mean values for the coefficient of variation of each maneuver included all attempts.

RESULTS

Comparison of Anthropometric Data, Spirometric Data, and Diaphragm Pressure-Generating Capacity

Statistical comparison (one-way ANOVA) of anthropometric data, spirometric data, and diaphragm strength between the three groups discriminated differences in age ($P < 0.001$), height ($P = 0.046$), VC ($P < 0.001$), and sniff maneuver Pdi values ($P < 0.001$). As shown in Table 1, the normal subjects were younger than patients and PPI patients were taller than COPD patients. VC values and peak Pdi obtained during a sniff maneuver in the COPD patients were $\sim$ 39 and 52% of the healthy subjects’ respective values. In the PPI patients the VC and peak sniff Pdi values were 45 and 37%, respectively, of the values observed in the healthy subjects. No differences between the three groups were found for body weight ($P = 0.092$), body mass index ($P = 0.787$), and peak Pdi during inspiration to TLC ($P = 0.129$). Also in Table 1, spirometric data describing the different obstructive and restrictive components are compared in COPD and PPI patients.

Maneuvers for Determination of Maximal Voluntary Activation of the Diaphragm

In the healthy subjects the combined expulsive and Müller, sniff inhalation, and inspiration to TLC maneuvers were repeated on average 3.2, 4.2, and 3.8 times, respectively. In the COPD patients the sniff and inspiration to TLC maneuvers were repeated 4.6 and 3.6 times, respectively. In the PPI patients both maneuvers were repeated on average 3.7 times.

The time course of the RMS, pressures, and abdominal displacement during an inspiration to TLC and a sniff maneuver in a COPD patient is illustrated in Fig. 2. In all groups the general pattern for the sniff maneuver was that the highest RMS values occurred when the Pdi values were highest and diaphragm shortening (inferred from abdominal displacement) was relatively small. During the inspiration to TLC in healthy subjects and both groups of patients and during the MVV maneuver in healthy subjects, the highest RMS values coincided with relatively low Pdi values and large amounts of diaphragm shortening (high lung volumes). During the combined maneuver in the healthy subjects the highest RMS values coincided with the highest Pdi values, as could be expected from a static maneuver.

To evaluate whether the costal and crural regions of the diaphragm are similarly activated, we compared the RMS values obtained with the esophageal and chest wall surface electrodes in the COPD patients by means of cross-correlation of RMS values obtained during the inspiration to TLC and the sniff maneuvers. The mean correlation coefficients obtained were 0.85 (range 0.76-0.91) and 0.91 (0.83-0.97) during the inspiration to TLC and sniff maneuvers, respectively. An example of the similarities between the costal and crural regions of the diaphragm RMS values during the inspiration to TLC and sniff maneuvers is presented in Fig. 2. The RMS is expressed as percentage of the highest RMS value obtained during either of the maneuvers.

Table 2 shows how the highest RMS values were distributed in terms of the different maneuvers performed for the different groups of subjects. For example, in 60% of the healthy subjects the MVV maneuver yielded the highest RMS value. It was evident that the inspiration to TLC and MVV maneuvers (which are associated with large inspiratory volumes) produced the highest RMS values more frequently than the high pressure-generating maneuvers (sniff maneuver and combined maneuver).

Figure 3 illustrates the RMS values obtained during a given maneuver normalized to the highest RMS value obtained during any of the maneuvers performed in a given subject. Comparison by two-way ANOVA did not discriminate between groups ($P = 0.486$) but did reveal a difference between maneuvers ($P = 0.035$). Post hoc pairwise multiple comparisons showed that group mean RMS values obtained during the inspiration to TLC were higher ($P < 0.05$) than the group mean values for the peak RMS obtained during the sniff maneuver (Fig. 3).

To determine whether the COPD patients could voluntarily activate their diaphragm to the same level as the healthy subjects, the absolute peak RMS values were compared between the two groups. Also, to evaluate whether there were differences in diaphragm-to-electrode distance between the healthy subjects and the COPD patients (which would also influence the absolute peak RMS values), CF values were calculated.
In the COPD patients the CF was \(102.6 \pm 5.5\) (SD) Hz and was not different \((P = 0.394)\) from that obtained in the healthy subjects \((99.2 \pm 6.4\) Hz). Comparison (Student's t-test for independent groups) between the COPD patients and healthy subjects revealed no statistical differences for the absolute peak RMS values obtained during the inspiration to TLC \(7\%\), \(P = 0.815\), the sniff maneuver \(18\%\), \(P = 0.574\), or the highest obtained value during any of these maneuvers \(10\%\), \(P = 0.705\).

Two-way ANOVA comparing the coefficient of variation for the peak RMS for the three groups and different maneuvers showed no significant differences between groups \((P = 0.854)\) or maneuvers \((P = 0.226)\). The coefficients of variation are presented in Table 3.

Comparison of the highest RMS values obtained in each healthy subject during an inspiration to TLC maneuver on two separate occasions showed an insignificant difference \([2 \pm 7.34\%\) (SD), \(P = 0.487\), 1-way ANOVA for repeated measures].

Relative Activation During Resting Breathing

There was a significant difference (1-way ANOVA) between the three groups during quiet breathing for RMS expressed as percentage of the highest value obtained during any maneuver \((P = 0.012)\), for mean inspiratory flow \((P = 0.021)\), and for mean inspiratory Pes \((P = 0.009)\) and Pga \((P = 0.018)\). The RMS during quiet breathing was more than five times higher in the patient groups than in the healthy subjects (Fig. 4). No differences were found between groups for VT or mean

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Table 2. Relative distribution of maneuvers that produced highest diaphragm RMS values in each of the subjects across the three groups

<table>
<thead>
<tr>
<th>Maneuver</th>
<th>Healthy Subjects</th>
<th>COPD Patients</th>
<th>PPI Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Insp TLC</td>
<td>1 (20)</td>
<td>4 (80)</td>
<td>3 (50)</td>
</tr>
<tr>
<td>Sniff</td>
<td>0 (0)</td>
<td>1 (20)</td>
<td>3 (50)</td>
</tr>
<tr>
<td>Combined</td>
<td>1 (20)</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>MVV</td>
<td>3 (60)</td>
<td>NA</td>
<td>NA</td>
</tr>
</tbody>
</table>

Values represent number of subjects/patients, with percentage in parentheses. RMS, root mean square.
inspiratory Pdi (P = 0.426). Means ± SD and differences between groups (post hoc pairwise multiple comparison) are presented in Table 4. Breath-by-breath variability in RMS was estimated by calculating the coefficient of variation for RMS during quiet breathing and is presented in Table 3. One-way ANOVA showed that the coefficients of variation for RMS during quiet breathing were not different between groups (P = 0.130). Examples of breath-by-breath variability in RMS (expressed as percentage of highest RMS value obtained during any maneuver) and VT during 60 s of resting breathing in one healthy subject, one patient with COPD, and one PPI patient are depicted in Fig. 5.

To evaluate whether the relative activation of the diaphragm is associated with the loss of pressure-generating capacity, linear regression analysis was performed on the RMS expressed as percentage of the highest value obtained during any maneuver and peak Pdi obtained during the sniff maneuver. All subjects were included in the analysis (n = 16). The regression slope described that resting breathing relative RMS equal to 70.9 – (0.329 × sniff Pdi), with a correlation coefficient of 0.81 (P < 0.001) and a determination coefficient of 0.65, suggesting that 65% of the changes in relative activation can be explained by a reduction in pressure-generating capacity.

### DISCUSSION

#### Techniques to Quantify Diaphragm Activation in Humans

Besides the EMG, several other techniques have been used to evaluate the level of diaphragm or global inspiratory muscle activation. Diaphragm activation...
has been evaluated by the twitch interpolation technique, where an electrical (7) or magnetic (32) stimulus is applied during maximal voluntary static efforts. It has been demonstrated that the superimposed twitch Pdi (Pditw) amplitude is inversely proportional to the Pdi generated by the subject and that the ratio of Pditw to Pdi can be used as an index of central diaphragm activation (7). The use of the twitch interpolation technique is likely to guarantee that all diaphragm motor units are recruited. Therefore, with this technique the relative level of motor unit recruitment can be determined, but because the technique involves stimulation of the phrenic nerves at a fixed frequency (usually a single pulse because the tetanic stimulation is painful), it probably does not provide Pdi values that represent maximal motor unit firing rates. In order for the twitch interpolation technique to reflect a maximally evoked diaphragm activation, the Pditw amplitude should presumably be obtained by a tetanic supramaximal bilateral stimulation of the phrenic nerves at a frequency that resembles the maximal motor unit firing rates. Because it is questionable whether the twitch interpolation technique can provide a true measure of diaphragm activation (in terms of recruitment and firing rate), it is suggested that the technique be referred to as a “diaphragm motor unit recruitment index.”

De Troyer et al. (11) measured single motor unit firing rates of diaphragm motor units in COPD patients with needles inserted into the costal diaphragm. This technique of counting frequency of identical single motor unit action potentials is limited to low levels of contraction, e.g., quiet breathing at rest, and does not provide information about motor unit recruitment. In accordance with the results of the present study, their findings showed that motor unit firing rate during resting breathing was clearly higher in COPD patients than in healthy subjects.

The pressure measured at the mouth, which is obtained during the first 100 ms of occlusion of an occluded breath, referred to as “P0.1,” has frequently been used to determine global inspiratory muscle activation. The use of P0.1 in determining respiratory drive is based on “mechanical” measurements, which are the outcome of respiratory muscle activation. The P0.1 is therefore influenced by the electromechanical coupling of the respiratory muscles. It has been proposed that “brief occlusions [pressure at 0.1 s (P0.1)] are useful in measuring the output in the very first part of inspiration in conscious subjects but must be treated with a great deal of caution. They are most reliable when end-expiratory volume remains constant and when there are no important phase lags between flow and pressure” (39). This suggests that factors such as hyperinflation and intrinsic positive end-expiratory pressure affect the accuracy of occlusion pressure measurements. Also, factors such as fatigue (defined as a reduction in maximal force-generating capacity) can alter the electromechanical coupling of the respiratory muscles, such that a given combination of motor unit recruitment and motor unit firing rate may produce

### Table 4. Description and statistical comparison of RMS, flow, volume, and pressure variables obtained in different groups during breathing at rest

<table>
<thead>
<tr>
<th></th>
<th>Healthy Subjects (1)</th>
<th>COPD Patients (2)</th>
<th>PPI Patients (3)</th>
<th>1 vs. 2</th>
<th>1 vs. 3</th>
<th>2 vs. 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>RMS, %</td>
<td>8.4 ± 2.5</td>
<td>43.4 ± 22.1</td>
<td>45.1 ± 22.8</td>
<td>-35.0*</td>
<td>-36.7*</td>
<td>-1.7</td>
</tr>
<tr>
<td>Vt, liters</td>
<td>0.50 ± 0.15</td>
<td>0.49 ± 0.04</td>
<td>0.48 ± 0.08</td>
<td>0.01</td>
<td>0.02</td>
<td>0.01</td>
</tr>
<tr>
<td>Vt/Ti, l/s</td>
<td>0.36 ± 0.07</td>
<td>0.48 ± 0.08</td>
<td>0.36 ± 0.05</td>
<td>-0.12*</td>
<td>0.00</td>
<td>0.12*</td>
</tr>
<tr>
<td>Mean Pdi, cmH2O</td>
<td>4.96 ± 0.92</td>
<td>8.08 ± 4.04</td>
<td>7.68 ± 5.31</td>
<td>-3.12*</td>
<td>-2.72</td>
<td>0.40</td>
</tr>
<tr>
<td>Mean Pes, cmH2O</td>
<td>-2.65 ± 0.35</td>
<td>-8.42 ± 2.87</td>
<td>-3.71 ± 3.40</td>
<td>5.77*</td>
<td>1.06</td>
<td>4.71*</td>
</tr>
<tr>
<td>Mean Pga, cmH2O</td>
<td>2.31 ± 0.57</td>
<td>-0.34 ± 2.55</td>
<td>3.97 ± 2.55</td>
<td>2.65</td>
<td>-1.66</td>
<td>-4.31*</td>
</tr>
</tbody>
</table>

Values are means ± SD. RMS, root mean square of diaphragm EMG (expressed as percentage of highest value obtained during any maneuver); Vt, tidal volume; Vt/Ti, mean inspiratory flow; Pes, esophageal pressure; Pga, gastric pressure. *P < 0.05.

![Figure 5](https://example.com/figure5.png)  
Fig. 5. RMS and tidal volume (Vt) obtained during 60 s of breathing at rest in 1 healthy subject, 1 COPD patient, and 1 PPI patient.
different occlusion pressures before and after the onset of fatigue; the evaluation of respiratory drive by $P_{0.1}$ will therefore be incorrectly estimated. It should also be noted that, for adequate determination of $P_{0.1}$, at least six repeated measures are required because of large variability (10).

When tidal Pdi and maximal Pdi values are known for all instantaneous values of $V_T$, then the relative Pdi (Pdi/maximal Pdi, when maximal Pdi is obtained at any given lung volume) and the RMS are uniquely related, independent of muscle length. This implies that the relative Pdi and the RMS can be used to measure diaphragm activation. The relationship between RMS and relative Pdi has been described in detail by Beck et al. (5), who demonstrated that the RMS is a more convenient measurement of diaphragm activation.

The tidal and maximal RMS values of the diaphragm EMG signal represent the temporal and spatial summation of action potentials obtained at the level of the sarcolemma and are therefore not affected by changes in the diaphragm’s electromechanical or electroventilatory couplings. The use of pressure or ventilatory parameters to assess respiratory drive is always influenced by 1) the transfer function for neural drive to tension (influenced by, e.g., muscle length), 2) the transfer of tension to pressure (influenced by, e.g., chest wall configuration), and 3) the transfer of pressure to flow and volume (influenced by elastance and resistance). Hence, only the interference pattern EMG (which represents the summated electrical activity generated by asynchronously firing diaphragm motor units) is directly linked to both motor unit recruitment and motor unit firing rate. Furthermore, the use of relative RMS appears to provide easy and reliable intersubject comparison of diaphragm activation. A critique of the use of RMS to infer crural diaphragm activation has been presented by Beck et al. (5).

Is the Crural Diaphragm EMG a Representation of Global Diaphragm Activation?

On the basis of findings that the action of the costal and crural portions of the diaphragm on the rib cage are different, De Troyer et al. (12) introduced the concept that the diaphragm actually consists of two muscles.

During nonbreathing maneuvers such as vomiting, regurgitation, swallowing, or eructation, the EMG activity is inhibited in the crural diaphragm fibers surrounding the esophagus (2, 28). It has also been demonstrated that inflation of a balloon in the lower esophagus inhibits the EMG activity in the crural portion but not in the costal portion of the diaphragm (13).

During breathing the differences between costal and crural diaphragm activation are less prominent. Van Lunteren et al. (36, 37) demonstrated that the crural diaphragm in cats and dogs is activated before the costal diaphragm, and the increase in crural diaphragm EMG from baseline is larger during increased ventilation. Mechanical evidence from measurements of muscle shortening and velocity suggests a proportionally greater increase in neural activation for the crural than for the costal diaphragm (14, 17, 31). One should, however, keep in mind that these differences in activation between the costal and crural portions of the diaphragm, although significant, are not of major magnitude.

Other studies indicate that activation of the crural and costal portions of the diaphragm are similar. Lourenco et al. (26) demonstrated that the EMG measured in dogs with bipolar electrodes implanted directly in the diaphragm (costal and crural) and the EMG measured with bipolar esophageal electrodes is proportional to the activity of the phrenic nerve. Oyer et al. (35) found in the decerebrate cat that the central neural input to the costal and crural portions of the diaphragm is similar in eupnea and in response to chemical and mechanical stimuli. Pollard et al. (30) studied the EMG activity in the costal and crural diaphragm in chronically instrumented rats and concluded that “the diaphragm acts as a single functional unit when under the respiratory control system.” We previously provided evidence that crural diaphragm EMG signal strength is related to global diaphragm activation (5), and in the present study the high correlation between the RMS values of the costal and crural diaphragm EMG in the COPD patients supports the notion that the diaphragm works as a single entity during breathing in humans.

On the basis of the above discussion, we argue that during breathing the assumption that the diaphragm acts as a single unit is fairly reasonable. Hence, the diaphragm EMG signal obtained with an esophageal electrode (in the crural region) may well be used as an indicator of global diaphragm activation.

Does the Diaphragm EMG Relate to Global Inspiratory Muscle Activation?

When evaluating how changes in the diaphragm activation relate to changes in global inspiratory muscle activation, most investigators have related the phrenic nerve activity or the diaphragm EMG signal strength to occlusion pressures (e.g., $P_{0.1}$). A linear relationship between mouth occlusion pressure and phrenic nerve activity was described in animal preparations (15, 16, 26). In humans, linear relationships between mouth occlusion pressure and mean inspiratory diaphragm EMG activity were described during conditions of progressive increase in respiratory drive (1, 24) and inspiratory flow-resistant loading (20, 25). In conclusion, changes in the crural diaphragm EMG signal strength appear to be related to changes in global inspiratory muscle activation during breathing.

Determination of Maximal Voluntary Diaphragm Activation

The major problem associated with obtaining a voluntary maximal RMS value is in finding maneuvers that ensure that the patient really activates the diaphragm. The combined maneuver has been described to generate the highest peak Pdi values that can be voluntarily generated at FRC (23) and has been described to
produce maximal motor unit recruitment in healthy subjects (7). The sniff maneuver generates a high Pdi value but is associated with some amount of muscle shortening, and the peak Pdi value obtained during the sniff maneuver is therefore not necessarily obtained at an optimal position for the length-tension relationship. Although Pdi values obtained during a sniff maneuver may not be as high as those obtained during the combined maneuver, the RMS value obtained may still demand maximal diaphragm activation because of a shorter muscle length and provide a voluntary maximal RMS. The inspiration to TLC maneuver does not generate much Pdi as indicated in Table 1, but at TLC it is reasonable to assume that the recoil forces generated by the lungs, chest wall, and abdomen equal the maximal Pdi that can be generated with a maximally shortened diaphragm, and therefore the diaphragm would still be maximally activated. Our choice of testing the MVV maneuver was based on the expectation that at some point during this maneuver (which involves breathing with the largest possible Vr and flow rates) the diaphragm should be maximally activated and should hence generate a peak RMS value representing a voluntary maximum.

With respect to diaphragm activation during a sniff inhalation maneuver, Nava et al. (29) reported higher peak RMS values during the sniff maneuver than during a combined maneuver in healthy subjects with no previous experience in performing the maneuvers. Note that the experienced healthy subjects in the present study had higher RMS values during the combined maneuver than during the sniff maneuver. The somewhat unexpected findings of Nava et al. that inexperienced subjects show higher Pdi and RMS values during a sniff maneuver (than during an inspiratory effort against occluded airways at FRC) are most likely due to difficulties with respiratory muscle coordination, comprehension, and insufficient time to practice the static maneuver. This is not the case for the sniff maneuver, which is simple to teach and more natural to perform and does not require practice.

The MVV maneuver is also relatively easy to teach and to perform, but the hyperventilation is demanding and often causes dizziness, which makes this maneuver less useful in the clinic. The finding that the RMS values during the MVV maneuver peaked at the end of inspiration at lung volumes equal to the inspiratory capacity, in combination with relatively low pressure generation, suggests that the peak RMS values obtained during the MVV maneuver are due to similar factors during the inspiration to TLC maneuver, i.e., relatively low Pdi generated at a short muscle length. This is also confirmed by the findings that the RMS values obtained during the MVV and the inspiration to TLC maneuvers in the healthy subjects showed almost identical group mean values. Because the inspiration to TLC maneuver is less demanding than the MVV maneuver and does not cause dizziness, the inspiration to TLC maneuver may be recommended over the MVV maneuver to obtain maximal voluntary RMS values.

Besides the fact that the inspiration to TLC maneuver provided high RMS values, it also seemed to be the easiest maneuver to teach, comprehend, and perform. In the present study the lowest coefficient of variation for the peak RMS values was found during the inspiration to TLC maneuver (11.1%). Other investigators (21, 22) also showed low intrasubject variability of 5–10% in the peak RMS values during repeated maximal inspiration to TLC maneuvers. To avoid bias in the present study, all attempts for a given maneuver (also failed ones) were included in the analysis for the coefficient of variation, which explain why our values were slightly higher than those of previous investigators. In the healthy subjects we demonstrated high reproducibility of the RMS values for the inspiration to TLC maneuver for repeated measurements on one testing day and between testing days on two separate occasions. This further supports the idea that an inspiration to TLC is a maneuver that is the least difficult to comprehend and perform. We also found that the coefficients of variation for the peak RMS values (obtained for the inspiration to TLC and sniff maneuvers) in the healthy subjects were similar to those obtained in COPD and PPI patients. These findings were somewhat surprising, since the healthy subjects were very familiar with all the maneuvers, and therefore a higher reproducibility of the RMS values was expected for the healthy subjects. The similarity in coefficients of variation for the experienced healthy subjects and the patients, who were assumed to be “naive,” could, however, be due to years of repeated pulmonary function tests in the chronically ill patients that could actually have trained them to become experts in the performance of the maximal inspiration to TLC maneuver. In fact, other investigators have demonstrated that an inspiratory capacity maneuver is reliable and reproducible in COPD patients (40).

In this context the large standard deviations of the coefficients of variation of RMS for the different maneuvers and during quiet breathing are worth noting. The large standard deviations of the coefficients of variation for RMS during the different maneuvers reflect interindividual differences in learning how to perform the maneuver; e.g., in some subjects/patients, three reproducible RMS values were obtained during the three first attempts (low coefficient of variation), whereas in other subjects/patients the first attempts varied a lot before the subject/patient could reproduce three maximal RMS values (high coefficient of variation). No failed attempts were excluded from this analysis. The large standard deviation for the coefficients of variation during quiet breathing represents the variability between different subjects’ breathing patterns; e.g., in some subjects/patients there were no interruptions of the breathing pattern, whereas others intermittently demonstrated sighs or deep inspirations after swallowing. Evidence for a normal distribution of the variability of the data is the fact that normality tests and equal variance tests passed.

To summarize, the inspiration to TLC maneuver seems to be the more reproducible maneuver that
provides the highest maximal voluntary RMS value. However, in individual patients the maximal voluntary RMS values obtained for the sniff maneuver sometimes exceeded the maximal values during an inspiration to TLC. A useful compromise to obtain a voluntary maximal RMS in patients would therefore be the combined use of the maximal inspiratory volume maneuver and the sniff maneuver.

Are Severely Ill Patients Able to Voluntarily Activate Their Diaphragm to the Same Levels as Healthy Subjects?

It is possible that the increased relative activation observed during quiet breathing in the COPD and PPI patients was due to the inability of these patients to perform a maximal activation. In other words, was the increased relative RMS observed during quiet breathing due to a lower maximal RMS and not to the increase in RMS during quiet breathing?

The diaphragm EMG power spectrum is strongly affected by changes in distance between the bipolar electrode and the diaphragm, such that the CF and RMS values decrease when the bipolar electrode moves away from the diaphragm. This diaphragm-to-electrode distance filtering is actually the major reason why the EMG signal strength requires normalization when data are compared between subjects. If diaphragm properties such as motor unit territory, innervation ratio, and diaphragm thickness are constant, CF should be similar if the muscle-to-electrode distance is similar. On the basis of this assumption, the finding of similar EMG CF values in the healthy subjects and the COPD patients supports the notion of similar influence of diaphragm-to-electrode distance filtering in both groups. Therefore, the similarity between group mean RMS absolute values suggests that patients with severe COPD are as able to maximally activate their diaphragm as the healthy subjects. It should be noted that all subjects and patients who participated in the present study were mentally alert and that the use of the voluntary maximal RMS (or any parameter) is difficult to apply in patients who are sedated or mentally incapacitated or who have comprehension and motivation disabilities.

The PPI patients were not included in the power spectrum analysis, since their EMG signals are affected by paralysis and sprouting (abnormal innervation ratio and motor unit territories), which make a direct comparison with the healthy subjects difficult.

Relative Diaphragm Activation During Quiet Breathing

As mentioned previously in the introduction, the use of the relative RMS instead of absolute values appears to be more reliable for comparing diaphragm activation between subjects. Three conditions can result in an increase in the relative RMS of the diaphragm EMG.

Condition 1. Maximal pressure-generating capacity of the diaphragm is normal, but the pressure that the diaphragm needs to generate for a given inspiratory volume is increased because of reduced respiratory system compliance or increased airway resistance. The maximal voluntary activation (absolute RMS) level remains unaltered, but the diaphragm must generate relatively more pressure to achieve a given volume. Hence, diaphragm relative activation (relative RMS) will increase, because more motor units need to be recruited and/or must fire at a higher discharge rate.

Condition 2. The pressure that the diaphragm must generate for a given inspiratory volume is normal, but the maximal pressure-generating capacity is reduced because of a mechanical disadvantage, e.g., hyperinflation. On the basis of three-dimensional reconstruction of the in vivo diaphragm shape at different lung volumes in humans, Gauthier et al. (18) suggested that hyperinflation reduces the pressure-generating capacity of the diaphragm by altering the following factors: “1) its in vivo three-dimensional shape, radius of curvature, and tension according to the Laplace law, 2) the relative degree to which it is apposed to the rib cage (i.e., the zone of apposition) and lungs (i.e., diaphragm dome), and 3) its length-force properties.” The maximal voluntary activation (absolute RMS) level remains unaltered, but because of impaired maximal pressure-generating capacity, the relative diaphragm activation (relative RMS) increases to generate the pressure required to maintain VT.

Condition 3. The pressure that the diaphragm generates for a given inspiratory volume is normal, but the maximal force-generating capacity of the diaphragm is decreased because of a reduced number of motor units available for contraction (e.g., paralysis). The maximal activation level (absolute RMS) is reduced, but the level of activation (absolute RMS) required to maintain a given VT is unchanged, and hence the relative activation (relative RMS) of the diaphragm must increase.

Usually, none of the three conditions described above occurs in isolation. With respect to the present study, the COPD patients are mainly affected by conditions 1 and 2 because of their increased airway resistance and hyperinflation. The PPI patients are, in fact, influenced by all three conditions, because they are faced with an increased load because of rib cage stiffness, they are scoliotic and, therefore, have some degree of mechanical impairment, and they have muscular impairment due to PPI. Increased velocity of diaphragm shortening was not included in the above discussion, since mean inspiratory flow rates up to 1.4 l/s do not seem to impair diaphragm function (6).

With the combined knowledge about 1) the maximal pressure-generating capacity of the diaphragm, 2) the pressure generated during quiet breathing, 3) the maximal RMS, and 4) the relative RMS, one can gain useful information about the different functional aspects of a ventilatory disorder. It is, however, important to notice that the relative RMS is the only common parameter that describes the degree of functional impairment for conditions 1–3. This suggests that, regardless of which combination of conditions 1–3 causes the diaphragm to be incapacitated, the relative RMS offers...
a clinically useful tool to quantify the progress of diaphragm function in patients.

Conclusion

A voluntary maximal RMS value can be obtained during voluntary inspiration to TLC and sniff inhalation maneuvers, which are easy to teach and comprehend and are perceived as natural to perform. To best ensure that a maximal voluntary RMS value is obtained, subjects should perform both the inspiration to TLC and sniff inhalation maneuvers. Relative diaphragm activation in healthy subjects is 8%, whereas in severe COPD and PPI patients with developed or latent hypercapnia the relative diaphragm activation is 43 and 45%, respectively, during quiet breathing. Despite large differences in diaphragm activation, the VT and pressures developed were similar in all groups.

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