Effect of Inspiratory Muscle Fatigue on Inspiratory Muscle Relaxation Rates in Healthy Subjects*

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Simple methods to diagnose inspiratory muscle fatigue in the clinical setting would be of considerable benefit. Inspiratory muscle relaxation rates are known to slow following induction of fatigue. Inspiratory muscle relaxation rates have been measured following a short sharp inspiratory effort against an occluded airway (sniff\textsubscript{\text{max}}) or through the unoccluded nostrils (sniff\textsubscript{\text{nostril}}). Relaxation rates in the absence of fatigue are faster when sniffs are performed through the unoccluded nostrils. While both methods have been shown to be capable of detecting inspiratory muscle fatigue, there may be quantitative or qualitative differences between the two techniques in their ability to detect fatigue similar to the differences observed in the fresh state. Accordingly, we measured relaxation rates with the two sniff techniques in five healthy naive male subjects before and after induction of fatigue. Inspiratory muscle fatigue was induced by threshold loading at 50 percent of P\textsubscript{\text{max}} until the subjects were unable to generate the target pressure. For those trials in which sniff\textsubscript{\text{nostril}} were performed, the maximum relaxation rate from the esophageal pressure curve (MRR\textsubscript{\text{nostril}}) was significantly decreased following induction of fatigue in nine of ten trials, while the exponential time constant (\tau\textsubscript{\text{nostril}}) was significantly increased in all ten trials. In contrast, for those trials in which sniff\textsubscript{\text{max}} were performed, the MRR\textsubscript{\text{max}} was significantly decreased following induction of fatigue in only six of ten trials. Similarly, \tau\textsubscript{\text{max}} was significantly increased following induction of fatigue in only six of ten trials. In addition, the magnitude of change in the MRR or \tau following induction of fatigue was quantitatively greater with sniff\textsubscript{\text{max}} compared with sniff\textsubscript{\text{nostril}}. Similar findings were obtained when relaxation rates were measured from the diaphragmatic pressure tracing. In conclusion, changes in relaxation rate following induction of fatigue were quantitatively greater and more consistently observed when sniffs were performed through the unoccluded nostrils rather than against an occluded airway.

Over the past decade, it has become apparent that the respiratory muscles can fatigue and that fatigue may precipitate or intensify ventilatory failure.\textsuperscript{1} Patients with chronic obstructive lung disease or neuromuscular disease are at particular risk for the development of fatigue.\textsuperscript{2} Fatigue may play an important pathophysiologic role in the development of both acute and chronic respiratory failure in such patients. Furthermore, fatigue may contribute to the exercise intolerance and dyspnea experienced by these patients. In addition, fatigue may be an important problem in patients experiencing difficulties weaning from mechanical ventilation. Unfortunately, clinical research in this area has been hampered by the lack of diagnostic tests that can be used to diagnose inspiratory muscle fatigue in patients. It is well known that the rate at which a skeletal muscle relaxes after contraction is characteristic for a given muscle under resting conditions.\textsuperscript{3} Furthermore, as skeletal muscle fatigues, the relaxation rate slows.\textsuperscript{4} The inspiratory muscles behave in a similar fashion. Thus, measurement of inspiratory muscle relaxation rates, which is technically relatively simple to perform, represents a method of diagnosing inspiratory muscle fatigue that could potentially be applied to patients. Esau et al\textsuperscript{6} have shown that two relaxation parameters, the maximal relaxation rate (MRR) and the time constant of the exponential portion of the pressure decay curve (\tau) are significantly altered by the development of inspiratory muscle fatigue. These authors measured inspiratory muscle relaxation following a short, sharp voluntary inspiratory effort against an occluded airway (sniff\textsubscript{\text{max}}). More recently, Koulouris et al\textsuperscript{6} have measured the MRR from the esophageal pressure decay curve during voluntary, natural sniffs through the unoccluded nostrils (sniff\textsubscript{\text{nostril}}). These investigators observed a significant fall in the MRR\textsubscript{\text{nostril}} following induction of inspiratory muscle fatigue in four experienced respiratory physiologists. In addition, control MRR measurements were faster than those previously reported suggesting that the method by which a sniff

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is performed can affect the resultant relaxation rate. While both methods have been shown to be capable of detecting inspiratory muscle fatigue, there may be quantitative or qualitative differences between the two methods in their ability to detect fatigue similar to the differences observed in the fresh state. Accordingly, we measured relaxation rates with the two sniff methods in the same subjects before and after induction of inspiratory muscle fatigue. We found that changes in relaxation rate following inspiratory muscle fatigue were quantitatively greater and more consistently observed when sniffs were performed through the unoccluded nostrils.

**Methods**

**Subjects**

Six healthy male subjects volunteered for this study. Their age was 29.6 ± 6.3 (SD) years (range, 23 to 37 years), their weight was 77 ± 10 kg (range, 66 to 93 kg), and their height was 176 ± 9 cm (range, 163 to 185 cm). All subjects had normal spirometry. The forced vital capacity was 5.3 ± 1.2 L (percent predicted 90 ± 7 percent), forced expiratory volume in 1 s was 4.1 ± 0.9 L (percent predicted 93 ± 6 percent), and the maximum voluntary ventilation was 186 ± 25 L/min (percent predicted 103 ± 5 percent). One subject was unable to perform the sniff maneuver adequately against an occluded airway and was excluded from the study. The study was approved by the Buffalo VAAMC Institutional Review Board, and written informed consent was obtained from all subjects. However, the subjects were blinded to the purpose of the study.

**Maximal Pressures**

Gastric (P_gastric) and esophageal (P_esophageal) pressure were measured by means of two thin-walled latex balloons, one positioned in the stomach and the other positioned in the middle third of the esophagus. All measurements were obtained with the subject seated. Optimal placement of the esophageal balloon catheter was determined by the occlusion test. The subject's maximal transdiaphragmatic pressure (P_{max}) was obtained during a combined Mueller expulsive maneuver (maximal inspiratory effort against an occluded airway with simultaneous contraction of the abdominal muscles) at functional residual capacity. To prevent glottic closure, a small leak was produced by insertion of an 18-gauge needle in the mouthpiece. P_gastric and P_esophageal were displayed on a recorder (Gould) to provide visual feedback to the subject. At least three reproducible measurements were obtained in each subject. The highest value obtained was used for analysis. The subject's maximum esophageal pressure (P_{esophageal max}) was then recorded during a maximal Mueller maneuver near residual volume.

**Analysis of Sniffs**

Sniffs were performed with the subject in the sitting position. The subjects performed the sniff maneuvers in two different ways: (1) a short, sharp inspiratory effort against an occluded airway (sniff mouth) and (2) a short sharp inspiratory effort through the unoccluded nostrils with the lips closed (sniff nostrils). Subjects were trained to perform sniffs during an initial trial period via a visual presentation of the P_gastric, P_esophageal, and P_{max} tracings. One potential subject was unable to produce adequate curves during sniffing despite more than 100 attempts and was excluded from the study.

Prior to performing the sniff maneuver, the response time of each balloon catheter-recorder system was measured by placing the balloon catheter in a pressurized larger balloon and bursting the latter with a hot needle to create a square-wave fall in pressure (pop test). The 10 to 90 percent rise time (t) was found to be 0.015 s. The pressure signals were digitized at 250 Hz and stored on disk.

The MRR was measured as the peak rate of pressure decay (dP/dt_{max}) during the sniff (Fig 1). Since the MRR is pressure dependent, it was normalized by dividing by dP/dt (peak pressure—baseline pressure) to permit comparison of curves of different peak pressure. The time constant (tau) was also calculated (Fig 1). A plot of the natural logarithm of pressure vs time yields a straight line over the lower 60 to 70 percent of the pressure decay curve indicating that this portion of the curve declines in a monoexponential fashion. Tau is equal to the reciprocal of the slope of this line. The correlation coefficient of the regression line (In P vs time) had to be greater than 0.98 for a measure of tau to be accepted.

The following criteria were used to select those sniffs suitable for analysis: (1) peak pressure maintained for less than 50 ms; (2) total sniff duration less than 500 ms; (3) sniff pressure wave had smooth decay curve; and (4) sniffs performed from same baseline P_{max}.

**Method of Fatigue Induction**

The subjects were instructed to breathe against an inspiratory threshold load. Threshold loading was performed using the techn-
technique of Nickerson and Keens and Mador and Acevedo. Weights were added to the plunger so that the subjects were required to generate 80 percent of their P, max in order to initiate airflow. Expiration was unloaded and the subjects were allowed to choose their own breathing pattern. When the subject was unable to generate the target pressure for five consecutive inspiratory efforts, all of the inspiratory muscles, including the diaphragm, were considered to be fatigued. During the fatigue run, the plateau of each square wave for P, and P, was measured breath-to-breath for 1 min at the beginning, during the middle, and during the penultimate min of the fatigue run. Duty cycle (T/Tot) for the diaphragm and for the rib cage muscles was measured directly from the P, and P, tracing, respectively. We then calculated a tension-time index for the diaphragm (P, max/T/Tot) and for the rib cage muscles (P, max/T/Tot).  

Experimental Procedure

All subjects participated in at least one preliminary session to allow the subjects to practice the maximal respiratory pressure and sniff maneuvers and to become familiar with breathing against the threshold load. Subjects performed four experimental trials each separated by at least two days’ rest. During two of the trials, sniff were performed against an occluded mouthpiece while during the other two trials, sniffs were performed through the unoccluded nostrils. The order in which the two different sniff maneuvers were performed was randomly allocated. For each experimental trial, at least 20 sniffs were obtained in the prefatigue (control) state. Control P, max and P, max were also obtained. The subjects then breathed against the threshold load until they were unable to generate the target pressure. The endurance time was calculated as the time from the start of the run until the subject was no longer able to generate the target pressure in a square wave fashion for five consecutive breaths. The subject then performed three P, max and P, max maneuvers, each effort separated by approximately 20 s of rest. The highest value was selected for comparison to baseline. Since some recovery from fatigue might have occurred during the period that the subjects were performing the maximal pressure maneuvers, the subjects were returned to breathing against the threshold load. When the subject could again no longer generate the target pressure (which always occurred in less than ten breaths), a series of 20 sniffs were performed over 5 min with the majority of sniffs performed in the first 2 min. Additional series of ten sniffs each were performed at 10, 15, 30, and 45 min following induction of fatigue. In addition, maximal pressures were obtained at 5 min and immediately following the series of sniffs at 10, 15, 30, and 45 min following induction of fatigue.

Data Analysis

The data were analyzed by one-way analysis of variance with a repeated measures design. If the F value was significant, the individual times following the induction of fatigue were compared with control using Tukey’s multiple comparison test. For each individual experimental trial, the sniffs immediately following induction of fatigue were compared to control by unpaired t test. Correlations between sniff parameters were determined by least squares linear regression.

Results

Fatigue Run

The fatigue thresholds for the diaphragm of 0.15 to 0.18 and for the rib cage of 0.26 to 0.30 were exceeded in every trial. There was no difference in the tension-time index for the diaphragm (TTd) or the rib cage (TTc) during the fatigue runs between those runs in which sniffnostris were measured compared with those runs in which sniffmouth were measured. For sniffmouth trials, the TTd was 0.29 ± 0.06 and the TTc was 0.36 ± 0.06. For sniffnostris trials, TTd was 0.31 ± 0.03 and TTc was 0.40 ± 0.04. Endurance times were also not significantly different, 10.9 ± 8.6 min for those runs in which sniffmouth were measured and 11.8 ± 4.5 min for those runs in which sniffnostris were measured. Similarly, breathing frequencies during the fatigue runs were not significantly different, 13.8 ± 3.7 breaths/min for sniffmouth trials and 13.6 ± 3.0 breaths/min for sniffnostris trials.

Maximal Pressures

Control P, max and P, max were not significantly different between trials in which sniffmouth were measured compared with trials in which sniffnostris were measured. Following the fatigue runs, P, max and P, max fell significantly from control values for both sniffmouth trials (p<0.0001 in each instance) and sniffnostris trials (p<0.0001 in each instance) (Fig 2). For sniffmouth trials, P, max and P, max were still significantly decreased 15 min following induction of fatigue but had returned to control values at 30 min following induction of fatigue. For sniffnostris trials, P, max returned to control values at 30 min following induction of fatigue, while P, max returned to control values at 15 min following induction of fatigue. There was no difference in the magnitude of the decrease in P, max following induction of fatigue for sniffmouth trials compared with sniffnostris trials. However, the magnitude of the decrease in P, max following the fatigue run was slightly greater for sniffmouth trials than for sniffnostris trials (p<0.05).

Control Sniff Measurements

Variability (expressed as the coefficient of variation)
Table 1—Variability (Coefficient of Variation) of Control Sniff Measurements*

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<tr>
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<th>MRR&lt;sub&gt;a&lt;/sub&gt;</th>
<th>MRR&lt;sub&gt;b&lt;/sub&gt;</th>
<th>Tau&lt;sub&gt;a&lt;/sub&gt;</th>
<th>Tau&lt;sub&gt;b&lt;/sub&gt;</th>
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<td></td>
<td>Within-trial variability</td>
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<td>Sniff&lt;sub&gt;a&lt;/sub&gt;</td>
<td>7.2 ± 2.2%*</td>
<td>6.2 ± 2.6%</td>
<td>11.1 ± 1.9%</td>
<td>10.5 ± 2.9%</td>
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<td>Sniff&lt;sub&gt;b&lt;/sub&gt;</td>
<td>6.7 ± 1.9%</td>
<td>4.8 ± 1.1%</td>
<td>10.7 ± 1.5%</td>
<td>13.6 ± 3.4%</td>
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<td>Within-subject day-to-day variability</td>
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<tr>
<td>Sniff&lt;sub&gt;a&lt;/sub&gt;</td>
<td>10.8 ± 3.8%</td>
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<tr>
<td>Sniff&lt;sub&gt;b&lt;/sub&gt;</td>
<td>9.4 ± 3.7%</td>
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<td>13.0 ± 8.1%</td>
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<td>Between-subject variability</td>
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<td>7.5%</td>
<td>10.4%</td>
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*Mean ± standard deviation for the coefficient of variation.
MRR<sub>a</sub> = maximal relaxation rate from esophageal pressure curve;
MRR<sub>b</sub> = maximal relaxation rate from diaphragmatic pressure curve;
Tau<sub>a</sub> = exponential time constant from esophageal pressure curve;
Tau<sub>b</sub> = exponential time constant from diaphragmatic pressure curve; Sniff<sub>a</sub> = sniffs performed against an occluded airway; Sniff<sub>b</sub> = sniffs performed through unoccluded nostrils.

There was no significant difference in within-trial, day-to-day, or between-subject variability between the two sniff techniques. Tau values were generally more variable than MRR values.

For Sniff<sub>b</sub>, MRR<sub>a</sub> was significantly correlated with MRR<sub>b</sub> (r = 0.71, p < 0.025) and Tau<sub>a</sub> (r = 0.78, p < 0.01). MRR<sub>b</sub> was not significantly correlated with Tau<sub>b</sub> (r = 0.58, p < 0.10) and Tau<sub>a</sub> was not significantly correlated with Tau<sub>b</sub> (r = 0.48, p = NS). An identical pattern was observed with Sniff<sub>b</sub>.

Effect of Fatigue on Sniff Measurements

For Sniff<sub>a</sub>, there was a significant decrease in MRR<sub>a</sub> (p < 0.004) but not MRR<sub>b</sub> following the fatigue run compared with control. MRR<sub>b</sub> was no longer significantly different from control at 2 to 5 min following induction of fatigue. Examining each individual trial, there was a significant decrease in MRR<sub>a</sub> immediately following induction of fatigue (0 to 2 min) compared with control in six of ten trials (unpaired t test) (Fig 3). MRR<sub>a</sub> fell significantly in five of ten trials. For Sniff<sub>b</sub>, there was a significant decrease in both MRR<sub>a</sub> (p < 0.0001) and MRR<sub>b</sub> (p < 0.0001) following the fatigue run compared with control. Both MRR<sub>a</sub> and MRR<sub>b</sub> were no longer significantly different from control at 10 min following induction of fatigue. Examining each individual trial, MRR<sub>a</sub> fell significantly following induction of fatigue in nine of ten trials (Fig 3), while MRR<sub>b</sub> fell significantly in all ten trials. The decrease in MRR following induction of fatigue was greater for Sniff<sub>a</sub> than for Sniff<sub>b</sub> for both MRR<sub>a</sub> (p < 0.04) and MRR<sub>b</sub> (p < 0.002).

For Sniff<sub>a</sub>, both Tau<sub>a</sub> and Tau<sub>b</sub> increased significantly following induction of fatigue compared with control (p < 0.004 and p < 0.0004, respectively). Both Tau<sub>a</sub> and Tau<sub>b</sub> were no longer significantly different from control at 2 to 5 min following induction of fatigue. Examining each individual trial, Tau<sub>a</sub> increased significantly following induction of fatigue in six of ten trials (Fig 4), while Tau<sub>b</sub> increased significantly in seven of ten trials. For Sniff<sub>b</sub>, both Tau<sub>a</sub> and Tau<sub>b</sub> increased significantly following induction of fatigue compared with control (p < 0.0001 in both instances). Both Tau<sub>a</sub> and Tau<sub>b</sub> were no longer significantly different from control at 10 min following induction of fatigue. Examining each individual trial, both Tau<sub>a</sub> and Tau<sub>b</sub> increased significantly following induction of fatigue in every trial (Fig 4). The increase in Tau following induction of fatigue was greater for Sniff<sub>a</sub> than for Sniff<sub>b</sub> for Tau<sub>a</sub> (p < 0.04) and approached statistical significance for Tau<sub>b</sub> (p = 0.07).

Following induction of fatigue, the fall in P<sub>a</sub>max or P<sub>e</sub>max was not significantly correlated to the changes in relaxation parameters whether expressed as an absolute or percentage change (for percent change;
P_d,max vs MRR_d, r = -0.02; P_d,max vs tau_d, r = 0.28; P_e,max vs MRR_e, r = 0.18; P_e,max vs tau_e, r = -0.05).

**Discussion**

The major findings of this study were as follows: (1) following induction of inspiratory muscle fatigue, the relaxation rate measured from either the diaphragmatic or esophageal pressure curve slowed resulting in measurable changes in MRR and tau; (2) the changes in MRR or tau were quantitatively greater and more consistently observed when sniffs were performed though the unoccluded nostrils rather than against an occluded airway; (3) there was no relationship between the magnitude of change in relaxation rate parameters following induction of fatigue and the degree of force loss elicited by inspiratory muscle fatigue.

**Comparison of Sniff_{mouth} vs Sniff_{nostrils}**

The rationale for measuring MRR or tau from pressure curves generated during a sniff maneuver is based on the assumption that the decay portion of the pressure curve corresponds to the relaxation phase of inspiratory muscle contraction. This means that there must be no postinspiratory muscle activity and expiration must be totally passive. In initial studies using the sniff technique, simultaneous EMG recordings were employed to ensure that these criteria were met. In later studies, criteria based on the shape of the pressure curve were developed to decide whether a sniff was adequately performed. We employed similar pressure criteria in this study. When sniffs were performed through the unoccluded nostrils, we were able to detect changes in MRR and/or tau following induction of fatigue in every trial. In contrast, when sniffs were performed against an occluded airway in the same subjects, changes in MRR and/or tau were not observed following induction of fatigue in some trials but not in others. For those trials in which changes in MRR and/or tau were not observed following induction of fatigue, the TT_d, TT_e, and endurance times were similar to the rest of the trials (TT_d = 0.35 ± 0.06, TT_e = 0.27 ± 0.04, endurance time = 12.9 ± 6.8 min). Thus, it is highly unlikely that the negative results achieved during these trials can be explained by differences in the degree of fatigue induced by threshold loading. It is noteworthy that the control MRR_e and MRR_d were higher for sniff_{nostrils} compared with sniff_{mouth}, although this difference did not quite reach statistical significance. Similar observations were made by Koulouris et al who compared their MRR_e with historic controls. The slower MRR for sniffs performed against an occluded airway could be due to a different pattern of muscle activation, differences in the degree of muscle shortening, postinspiratory muscle activity, or to other factors. Regardless of the mechanism, it is clear that sniffs performed against an occluded airway were not as reliable an indicator of inspiratory muscle fatigue as were sniffs performed through the unoccluded nostrils.

**Factors Influencing Inspiratory Muscle Relaxation**

A number of factors in addition to fatigue can potentially affect the relaxation rate. When the quadriceps contracts isometrically, the rate of relaxation increases as the peak tension increases due to a selective increase in fast fiber recruitment at higher peak tensions. In this study, there was no significant relationship between the normalized MRR and the pressure generated during the sniff maneuver. However, the majority of our sniff peak pressures exceeded 60 percent of P_max. At this level of activation, the effect of peak tension on relaxation is relatively minor even in the quadriceps.

During a sniff, both the diaphragm and the ribcage muscles contract. The relative contribution of each muscle group to the sniff varies between subjects and between sniffs in a single subject. In our study, the P_d/P_e ratio during the sniff (a crude index of the relative contribution of the diaphragm and intercostal muscles) had no discernable effect on any of the
relaxation parameters that we measured. The $P_a/P_i$ ratio was also not significantly different between sniff$_{mouth}$ and sniff$_{nasal}$.

Relaxation rates are also affected by changes in muscle length. In this study, sniffs were always performed at end-expiration and at the same baseline $P_c$. Thus, it is unlikely that lung volume changed substantially between sniffs.

In vitro studies show that hypcapnia and/or hypoxia can slow muscle relaxation directly. However, a recent preliminary study suggests that hypoxia and hypcapnia do not affect skeletal muscle or diaphragmatic MRR in vivo. A more detailed study by the same laboratory has demonstrated that hypcapnia has no effect on the MRR of the quadriceps and adductor pollicis muscles in man. We did not measure end-tidal $CO_2$ ($F_e CO_2$) or oxygen saturation in this study. In previous studies where we employed an identical threshold loading regimen to induce fatigue, $F_e CO_2$ was either unchanged or fell below baseline levels (due to a transient hyperventilation) immediately following threshold loading. Oxygen saturation was always greater than 95 percent immediately following threshold loading. Thus, we think it unlikely that changes in blood gases affected our results.

Clinical Implications

In this study, we have shown that inspiratory muscle relaxation rates measured while the subject made a short sharp inspiratory effort through the unoccluded nostrils were able to detect inspiratory muscle fatigue. Measurements of relaxation rates from the esophageal pressure curve were as efficacious as measurements from the diaphragmatic pressure curve. This is relevant since esophageal pressure measurements are potentially simpler requiring insertion of only one balloon catheter. We have also confirmed that when sniffs are performed through the unoccluded nostrils, simple pressure criteria can be employed to determine sniff acceptability.

Following induction of fatigue, the percentage increase in $tau$ was higher than the percentage decrease in MRR (38.3 ± 20.2 for $tau_{sniff}$ compared with 17.4 ± 8.0 percent for MRR$_{sniff}$, p < 0.01). However, within-subject variability was higher for $tau$ than for MRR (Table 1) so that neither measurement proved to be superior as an indicator of inspiratory muscle fatigue. As shown in Figures 3 and 4, normal values for MRR or $tau$ vary considerably between subjects and there can be considerable overlap between fresh and fatigued values. Accordingly, serial measurements of MRR and/or $tau$ are required to detect the onset of inspiratory muscle fatigue and its recovery.

We found no correlation between alterations in any relaxation parameter and the degree of force loss induced by threshold loading. Similar results have been obtained in skeletal muscle. This indicates that changes in inspiratory muscle relaxation rates cannot be used to estimate the degree of force reduction induced by fatigue.

While relaxation rates proved to be a useful method to detect inspiratory muscle fatigue under the circumstances of this experiment, several potential problems can be foreseen if this method was to be applied to patients. Relaxation rates recovered very quickly following induction of fatigue. In patients, this brief window of opportunity in which to make the appropriate measurements may not be sufficient. Furthermore, the rapid recovery rate suggests that relaxation rates during voluntary maneuvers may reflect high-frequency fatigue. Physiologic evidence suggests that low-frequency fatigue may be the more clinically relevant form of fatigue. It has also been suggested that slowing of the relaxation rate may reflect incipient rather than overt inspiratory muscle fatigue. However, even if slowing of the relaxation rate does not reflect low-frequency fatigue, it does appear to identify those respiratory loads that are of sufficient severity to be potentially fatiguing. Such information would be clinically useful.

In conclusion, relaxation rates measured from the esophageal pressure curve during a sniff performed through the unoccluded nostrils can be used to detect inspiratory muscle fatigue in healthy human subjects.

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