Frequency dependence of forced oscillatory respiratory mechanics in horses with heaves

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Young, S. S., D. Tesarowski, and L. Viel. Frequency dependence of forced oscillatory respiratory mechanics in horses with heaves. J. Appl. Physiol. 82(3): 983–987, 1997.—The effect of measurement frequency on respiratory mechanics was investigated in six horses with reversible allergic airway disease. Total respiratory impedance was measured at 1.5, 2.0, 3.0, and 5.0 Hz by using the forced oscillation technique with the horses in remission, after acute antigenic challenge producing clinical heaves, and with heaves but after the administration of 2 mg fenoterol by inhalation. The slopes of the magnitude (Zrs) and real part (R) of total respiratory impedance over the frequency range 1.5–3 Hz changed significantly after antigenic challenge and fenoterol. The ratio of R at 2 Hz to R at 3 Hz, however, discriminated better among the three conditions. Compliance and resonant frequency (calculated by using a three-element model) changed significantly after antigenic challenge and fenoterol, but inertance did not. We concluded that horses with heaves showed frequency dependence of R and Zrs at frequencies up to 3 Hz and that parameters derived from a three-element model were useful indicators of small airway obstruction in the horse.

Resistance; compliance; inertance; resonant frequency; airway obstruction

The mechanical properties of the respiratory system have been known for many years (15) to change with measurement frequency, an effect called frequency dependence. This phenomenon is much more marked in respiratory disease, particularly obstructive respiratory disease, and the subject was extensively reviewed by Cutillo and Renzetti (4). Frequency dependence of resistance has also been used to measure the response to bronchial challenge with histamine (19).

The forced oscillation technique is particularly suitable for measuring changes in respiratory mechanics with frequency because it measures total respiratory impedance over a range of frequencies in a rapid, noninvasive manner. The technique is well tolerated by conscious, unsedated animals including larger species, such as cattle (5, 6) and ponies (22). We have previously shown how the forced oscillation technique can be used to measure total respiratory impedance in normal Standardbred horses (23). The purpose of this study was to investigate the effect of measurement frequency on total respiratory impedance in horses with naturally occurring reversible allergic airway disease.

Materials and Methods

Six adult horses (three Standardbred, one Thoroughbred, one Arabian cross, and one Quarterhorse) affected by naturally occurring reversible allergic airway obstruction (heaves) and accustomed to being handled were used in the experiment. Their mean weight was 512 ± 28 (SD) kg, and their mean age was 12.7 ± 2.3 yr. The horses were housed and cared for in accordance with the recommendations of the Canadian Council on Animal Care, and the experimental protocol was approved by the Animal Care Committee of the University of Guelph. The horses were kept at pasture for several weeks before an experiment, and all were in clinical remission [defined as a pleural pressure swing (∆Ppl) of <20 cmH2O] at the start of the experiment. Each horse was gently restrained with a lead chain and halter in a 1 × 2-m stock without sedation while its respiratory impedance was measured.

Soon after the arrival of the horse in the clinic, its ∆Ppl was estimated by using a conventional esophageal balloon technique (23), and then the total respiratory mechanical impedance (Zrs) was measured. This was defined as Zrs in remission. The forced oscillation method that was used has been described previously (23). In brief, a sinusoidal airflow of the desired frequency was generated by a proportional pneumatic valve connected to a compressed air line. The oscillating airflow was applied to the horse’s respiratory system by using a plastic T-piece. A resistor of ~2 cmH2O·l−1·s−1 attached to the side arm directed most of the oscillating airflow into the horse while allowing it to breathe relatively normally. Mask pressure relative to atmospheric pressure was measured with a differential pressure transducer (DP-45, ±8 cmH2O range, Validyne Engineering, Northridge, CA), and airflow to the mask was measured with a heated Fleisch no. 4 pneumotachograph and differential pressure transducer (MP-45, ±2 cmH2O range, Validyne Engineering). Amplified pressure and flow signals were digitized at 25.6 Hz for 22 s by using a personal computer and a proprietary data-acquisition/analysis package (MacADIOS 8ain and Superscope, GW Instruments, Somerville, MA). The signals were band-pass filtered (12th order digital Butterworth filter with a 0.2-Hz-wide bandpass centered at the measurement frequency) and divided into consecutive 5-s epochs with 50% overlap from which Zrs was calculated (16). The coherence value was also calculated to provide an indication of the signal-to-noise ratio. Zrs was not corrected for the mechanical properties of the face mask.

Zrs was measured at 1.5, 2.0, 3.0, and 5.0 Hz. Coherence values of >0.9 were accepted for 2- to 5-Hz measurements and >0.8 for 1.5-Hz measurements. The forced oscillation data from each horse were also fitted to a series resistance-compliance-inertance (R-C-I) model. C and I were found by fitting the reactance (X) to the equation

\[ X = 2\pi f I - \frac{1}{2\pi f C} \]

where f is measurement frequency by using a proprietary program (DeltaGraph Professional, DeltaPoint, Monterey, CA). The resonant frequency (fres) of the respiratory system was calculated from

\[ f_{res} = \frac{1}{2\pi \sqrt{IC}} \]

An index of “dynamic compliance” (Cdyn) was also calculated at each frequency point. The inertive component of X was...
(2πf1) was subtracted from X (with the assumption that I was independent of f) to give Xc, X of C, from which Cdyn was calculated.

After Zrs (remission) had been measured, the horses were housed in a loose box that had a restricted air-exchange rate but with temperature and relative humidity kept within acceptable limits by an air-conditioning system. Moldy hay that was known to produce acute heaves in the horses was shaken up in the box twice a day. The horses were monitored frequently for signs of respiratory distress and removed from the box when they showed symptoms of acute heaves (tachypnea, flared nostrils, abdominal lift), and Zrs (exacerbation) was measured by forced oscillation. With the use of an equine Aeromask (Canadian Monaghan, London, ON), 2 mg fenoterol (Berotec, Boehringer Ingelheim) in a metered-dose inhaler were then given to the horse, and Zrs (bronchodilated) was measured 10 min later. ∆Ppl was also measured at the same time as Zrs.

The frequency dependence of the magnitude (Zrs) and real part (resistance or R) of Zrs was characterized by linear regression over the range 1.5–3 Hz and by the ratios of R and Zrs at low and high frequencies.

Significant differences in the measured and derived variables with condition (remission, exacerbation, bronchodilated) and frequency (where appropriate) were found by using analysis of variance followed by Scheffe’s F-test. P < 0.05 was considered significant.

RESULTS

C, fres, ∆Ppl, and respiratory rate all changed significantly with condition (Table 1), whereas I did not.

All the components of total respiratory impedance (Zrs, R, phase angle of Zrs, and X) changed significantly with condition (Fig. 1).

Cdyn in remission was significantly different from the values after challenge and bronchodilation but did not change significantly with frequency (Fig. 2).

The slope of Zrs and R against frequency over the range 1.5–3 Hz changed significantly with condition (Table 2) as did the ratio of R at 2 Hz to those of R at 3 and 5 Hz (R2Hz/R3Hz, R2Hz/R5Hz, respectively).

DISCUSSION

This study demonstrated negative frequency dependence of R and Zrs in horses with acute heaves, which was reversible with fenoterol and not present in remission. Furthermore, acute heaves produced an increase in fres and a decrease in C that were partially reversed by fenoterol. These changes were similar in nature to those of the respiratory rate and ∆Ppl, two conventional indicators of the severity of heaves (10,14,21).

Frequency dependence of R and Zrs. The changes in R and Zrs with condition were most pronounced at 1.5 Hz and had disappeared at 5 Hz. In humans, the larger change in R at low vs. high frequencies has been demonstrated after bronchial challenge (19), in asthmatic vs. normal humans (9, 13), and in asthmatic subjects after bronchodilation (20). The definitions of “high” and “low” frequencies depend on the size of the animal. We suggest that the fres is a useful guide in a comparison of data from mammals of different sizes. As a rough approximation, the division between low and high could be said to occur at about two times the normal fres. In humans, fres is ~7 Hz, and the differences in R and Zrs between normal and asthmatic subjects extend to ~15 Hz (9, 13). Horses have a normal fres of 2.4 Hz (23), and thus frequency-dependent effects would be expected up to 4.8 Hz, consistent with the results of this study.

We were interested in simple methods of quantifying the degree of frequency dependence of R and Zrs. Linear regression over the frequency range 1.5 Hz–3.0 Hz proved useful (Table 2). Extension of the range to 5.0 Hz produced less significant differences between conditions. Simple ratios of R and Zrs at low and high frequencies, however, produced more significant differences between the conditions than did linear regression (Table 2). Ratios of values at 1.5 Hz and 3 or 5 Hz were not useful because of the greater variance of the 1.5-Hz measurements. Hayes et al. (7) found that the ratio of total respiratory resistance at 5–9 Hz to that at 15–19 Hz was able to distinguish among normal human subjects, smokers, and subjects with obstructive pulmonary disease. When scaled for fres, the ratio used by Hayes et al. (7) is very similar to R2Hz/R5Hz in this study.

Compliance, Cdyn, and fres. In humans and animals with respiratory disease, fres increases. Clement et al. (2) measured X in normal human subjects and people with a range of respiratory diseases and demonstrated an increase in fres in patients with chronic obstructive pulmonary disease. Van Noord et al. (19) demonstrated an increase in fres after bronchial challenge with histamine and a fall in fres in asthmatic subjects after treatment with salbutamol (20). Fres only represents one point on the X-frequency curve (the zero crossing point) and thus may not be the best indicator of the changes in X with disease (2). Nevertheless, it is an easily measured variable that may have clinical application. In this study fres was a sensitive indicator of the condition of the horses, changing significantly after antigenic challenge and subsequent treatment with fenoterol (Table 1).

In a three-element (R-I-C) model, an increase in fres can be caused by either a decrease in C and/or I. Unlike in some studies (3), I was calculated in this experiment. It did not change significantly with condition, whereas C changed significantly and in a manner consistent with the changes in fres (Table 1). This is not surprising because acute heaves cause a fall in compliance as measured by conventional techniques (14). Thus the

<table>
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<tr>
<th>Table 1. Changes in C, fres, ∆Ppl, and respiratory rate during clinical remission, acute exacerbation of heaves, and after treatment with a bronchodilator</th>
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<tbody>
<tr>
<td>Remission</td>
</tr>
<tr>
<td>C, I/cmH2O</td>
</tr>
<tr>
<td>fres, Hz</td>
</tr>
<tr>
<td>∆Ppl, cmH2O</td>
</tr>
<tr>
<td>Respiratory rate, breaths/min</td>
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</tbody>
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Values are means ± SD; n = 6 horses. C, compliance; fres, resonant frequency; ∆Ppl, pleural pressure swing. Values with same superscript are significantly different from each other, P < 0.05.
increase in $f_{res}$ in acute heaves is due mainly to a decrease in $C$.

The change in compliance and resistance with frequency has been extensively studied (4). In the vast majority of these studies (especially earlier work), respiratory mechanics were calculated from simultaneous measurements of transpulmonary pressure and flow by using a technique (called the "conventional" technique) on the basis of the method of Mead and Whittenberger (12). This method calculates a value for $R$ and $C$ for each breath, and measurements can be made at different frequencies by changing the respiratory rate. Implicit in the technique is the assumption that the respiratory system is represented by an $R$-$C$ or $R$-$I$-$C$ model. This model cannot explain frequency dependence of either $R$ or $C$, and more complex models have been proposed to explain the frequency dependence of $R$ and/or $C$ that is seen during bronchoconstriction. The Otis et al. model (15) proposed that the peripheral airways consist of two parallel R-C units with different time constants, whereas the Mead model (11) brought in the concept of a central airway shunt compliance. The two ideas are frequently combined to yield models (8) that have a central airway compliance and inertance connected to two peripheral R-C units. These models typically have six or seven elements, and experimental data can be fitted to such models to yield best estimates of the values of the individual elements.

The forced oscillation technique assumes that the respiratory system can be modeled by an arbitrary combination of linear (i.e., time, frequency, and flow rate invariant) $R$, $I$, and $C$ elements but makes no assumption about the model details. Such a model has a unique value of impedance at each frequency, and data from forced oscillation experiments are often presented as graphs of resistance and reactance (or magnitude and phase) against frequency (20). A problem arises in a comparison of forced oscillation data with results obtained by the conventional method. The forced oscillation technique yields a value of "resistance" (the real part of the impedance) that can be compared with the resistance from conventional mea-
Changes in slope of $R$ and $|Z_{rs}|$ against frequency and $R_{2Hz}/R_{3Hz}$ and $R_{2Hz}/R_{5Hz}$ ratios during clinical remission, acute exacerbation of heaves, and after treatment with a bronchodilator.

<table>
<thead>
<tr>
<th></th>
<th>Remission</th>
<th>Exacerbation</th>
<th>Bronchodilated</th>
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<tbody>
<tr>
<td>$R$ slope, cmH$_2$O·l·s$^{-1}$</td>
<td>$0.00 \pm 0.28$</td>
<td>$-0.76 \pm 0.74$</td>
<td>$-0.03 \pm 0.37$</td>
</tr>
<tr>
<td>$</td>
<td>Z_{rs}</td>
<td>$ slope, cmH$_2$O·l·s$^{-1}$</td>
<td>$-0.03 \pm 0.28^*$</td>
</tr>
<tr>
<td>$R_{2Hz}/R_{3Hz}$</td>
<td>$1.00 \pm 0.30^*$</td>
<td>$1.60 \pm 0.50^*$†</td>
<td>$0.88 \pm 0.25^*$†</td>
</tr>
<tr>
<td>$R_{2Hz}/R_{5Hz}$</td>
<td>$0.93 \pm 0.21^*$</td>
<td>$2.06 \pm 0.81^*$</td>
<td>$1.22 \pm 0.84$</td>
</tr>
</tbody>
</table>

Values are means ± SD; $n = 6$ horses. $R$, real part of impedance (resistance); $|Z_{rs}|$, magnitude of impedance; $R_{2Hz}$, $R_{3Hz}$, and $R_{5Hz}$; $R$ at 2, 3, and 5 Hz, respectively. Values with same superscript are significantly different from each other, $P < 0.05$. There was an overall significant change in $R$ slope with condition, but individual values were not significantly different from each other.
REFERENCES


