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DETERMINING WHEN ENHANCED PAUSE (Penh) IS SENSITIVE TO CHANGES IN SPECIFIC AIRWAY RESISTANCE

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Penh is a dimensionless index normally used to evaluate changes in the shape of the airflow pattern entering and leaving a whole-body flow plethysmograph as an animal breathes. The index is sensitive to changes in the distribution of area under the waveform during exhalation and increases in a nonlinear fashion as the normalized area increases near the beginning of the curve. Enhanced pause (Penh) has been used to evaluate changes in pulmonary function and as a method to evaluate airway reactivity. However, the use of Penh to assess pulmonary function has been challenged (Bates et al., 2004; Lundblad et al., 2002; Mitzner et al., 2003; Mitzner & Tankersley, 1998; Petak et al., 2001; Sly et al., 2005). The objective of this study was to show how Penh of the thorax and plethysmograph flow patterns are related. That relationship is used to describe the conditions under which whole-body plethysmograph Penh measurements can be used to detect changes in sR_{aw}.

Penh was introduced as an index to describe the shape of the waveform of the flow patterns generated by an unrestrained animal spontaneously breathing in a whole-body plethysmograph (Hamelmann et al., 1997). As an animal breathes, air leaves the plethysmograph chamber when the pressure inside the chamber increases during inspiration and then enters the chamber as the pressure in the chamber decreases during exhalation. The interpretation of the airflow waveforms has spawned many discussions and has been the topic of a variety of published correspondence and comments. Those interests have been centered on the use of a waveform shape index, Penh, to evaluate changes in airway function. One of those communications (Bates et al., 2004) stated that there were no published papers that provided a link between Penh and airway resistance (R_{aw}), and many others argued that Penh should not be used as a measure of airway mechanics (Sly et al., 2005; Lundblad et al., 2002; Mitzner et al., 2003).

In the past, it may have been correct to insist that Penh was being overinterpreted in terms of its relationship to R_{aw}, but the overall relationship between Penh and airway mechanics has not been previously determined. The purpose of this study was to describe a link between Penh and $R_{aw}C_g$, where R_{aw} represents airway resistance and C_g accounts for gas compliance in the lung. The product, $R_{aw}C_g$, is proportional to specific airway resistance, sR_{aw}, according to the following definition: $sR_{aw} = [(R_{aw}C_g)(P_B - P_{LH2O})]$. In the preceding expression, P_B represents barometric pressure and P_{LH2O} represents the partial pressure of water vapor in the lung. Since sR_{aw} is proportional to $R_{aw}C_g$ when barometric pressure is constant, references to changes

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in $R_{aw}C_g$ in this study also apply to sR_{aw} and vice versa.

In this study, the link between $R_{aw}C_g$ and Penh was determined by considering a model whose input was the thoracic flow waveform and whose output was the plethysmograph box flow. As such, results showed that changes in Penh of the box airflow were produced by alterations in $R_{aw}C_g$ and/or changes in the shape of the thoracic airflow pattern. The relationship between Penh of the plethysmograph (box) flow, $R_{aw}C_g$, and Penh of the thoracic flow was established, and was then used to show how measuring Penh of the thorax flow in addition to Penh of the whole body plethysmograph flow may be used to determine when Penh of the plethysmograph flow related to changes in $R_{aw}C_g$.

The following definitions are used in this article:

C_g: compliance of the gas in the lungs
FRC: functional residual capacity
G: maximum fractional changes in volume and airflow due to changes in temperature and humidity
I_{box}: airflow into and out of a flow-type whole-body plethysmograph containing an unrestrained animal
I_{comp}: change in volume of the alveolar gas with respect to time
I_{cv}: change in volume of respired gases with respect to time due to heating, cooling, and changes in humidity
I_{nm}: flow of warm moist air under alveolar conditions into and out of the nose and mouth
I_{nmc}: airflow into and out of the nose and mouth after corrections made for changes in temperature and humidity
I_t: change in volume of the thorax with respect to time
L: difference between Penh(I_t) before and after an intervention when there is no change in $R_{aw}C_g$

Laplace transform: L(f(t)) = F(s) (Shearer et al., 1997)

P_{alv}: pressure (referenced to barometric pressure) in the alveolar region of the lung during a breath
P_B: barometric pressure
P_{CH2O}: partial pressure of water vapor in the plethysmograph chamber
P_{ef}: peak airflow during expiration
P_{if}: peak airflow during inspiration
P_{LH2O}: partial pressure of water vapor in the lung
Penh: airflow shape index (Hamelmann et al., 1997)
Φ: thermal time constant associated with heating/cooling and humidification/dehumidification of respiratory gases
R_{aw}: airway resistance
sR_{aw}: specific airway resistance = $R_{aw}C_g$ $(P_B - P_{LH2O})$
T_e: expiratory time
T_r: relaxation time, the time interval for 64% of the gas volume to enter the plethysmograph during expiration
V_{tg}: thoracic gas volume, the average volume of gas in the lung during a breath

MATERIALS AND METHODS

Whole-Body Plethysmograph Model

Consider an unrestrained animal breathing inside a whole-body flow-type plethysmograph. The relationship between $R_{aw}C_g$ of the animal, Penh of the airflow waveform entering and leaving the plethysmograph, and Penh of the thoracic flow pattern can be derived in a series of steps. During the first step, a model of the pulmonary system was developed that describes the relationship between the change in volume of the thorax with respect to time and the airflow waveform entering and leaving the plethysmograph. That relationship was defined in terms of airway resistance (R_{aw}) thoracic gas compliance (C_g), and the effects of differences in temperature and humidity between the lungs and plethysmograph.

In the second step, the plethysmograph airflow measurement and the range of possible $R_{aw}C_g$ values that could be assumed by the lung's airway system were combined with the model to generate a series of possible thoracic airflow waveforms capable of generating that plethysmograph airflow signal. Next, the Penh value of each of the possible thoracic airflow signals was calculated and plotted as a function of its corresponding value of $R_{aw}C_g$. Examples of these curves were compared before and after an intervention to determine the nature of the animal's pulmonary response.

Theoretical Analysis

A simple model of the lungs and thorax, similar to models previously described (DuBois et al., 1956; Pennock et al., 1979), is shown in Figure 1. The model can be used to determine the relationship between I_t, the change in volume with respect to time of the thorax, and I_{nm}, the flow of air entering and leaving the nose and mouth. I_{comp} is the change in volume of the gas in the thorax with respect to time that results from gas compression/decompression during a breath, so that:

$$I_t = I_{nm} + I_{comp} \tag{1}$$

The flow of gas into and out of the nose and mouth can be written as:

$$I_{nm} = \frac{P_{alv}}{R_{aw}} \tag{2}$$

In order to estimate I_{comp}, it is assumed that the product of alveolar pressure (P_{alv}) and the thoracic gas volume (V_{tg}) is essentially constant within the thoracic gas space. Under these conditions:

$$dV_{tg} = \left[\frac{V_{tg}}{P_{alv} + P_B - P_{LH_2O}}\right] dP_{alv} \tag{3}$$

Since $P_{alv} << P_B$, the compliance of the gas in the thorax can be defined as:

$$C_g = \frac{V_{tg}}{P_{alv} + P_B - P_{LH_2O}} \cong \frac{V_{tg}}{P_B - P_{LH_2O}} \tag{4}$$

As a result, I_{comp} can be written as:

$$I_{comp} = \frac{dV_{tg}}{dt} = C_g \cdot \frac{dP_{alv}}{dt} \tag{5}$$

Differentiating Eq. (2), it can be shown that

$$\frac{dP_{alv}}{dt} = R_{aw} \cdot \frac{dI_{nm}}{dt} \tag{6}$$

so that I_{comp} can be written in terms of $R_{aw}C_g$ as:

$$I_{comp} = R_{aw}C_g \cdot \frac{dI_{nm}}{dt} \tag{7}$$

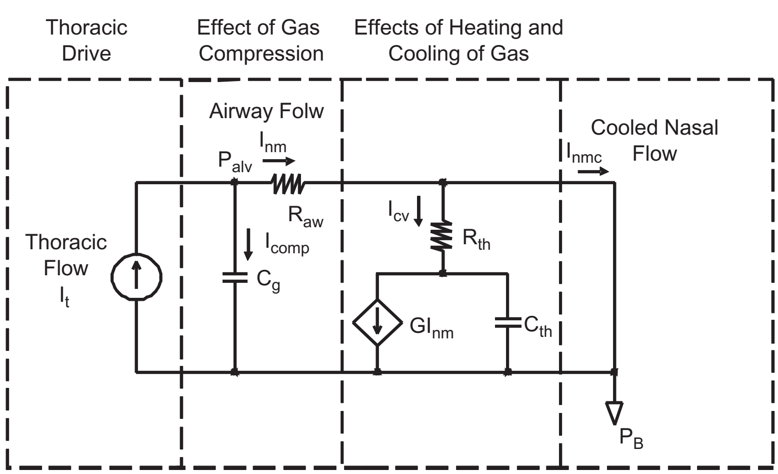

FIGURE 1. An electrical equivalent circuit that represents an animal's respiratory system. I_t represents a current source that generates the thoracic flow pattern. R_{aw} represents airway resistance, and C_g represents the compliance of the gas in the lung. The dependent current source is proportional to I_{nm} (G I_{nm}). R_{th} and C_{th} represent the thermal resistance and thermal capacitance.

Now Eq. (1) can be written in terms of a differential equation of the form:

$$I_t = R_{aw}C_g \cdot \frac{dI_{nm}}{dt} + I_{nm} \qquad (8)$$

Taking the Laplace transform of Eq. (8), it can be written as:

$$I_{nm} = \frac{I_t}{R_{aw}C_g s + 1} \qquad (9)$$

As gas enters and leaves the alveolar region of the lung it can change in volume due to variations in temperature and humidity of the gas. The time dependence of these transitions can be accounted for with a first-order differential equation similar to that described by Peslin et al. (1995). The change in volume of the gas due to heating and cooling and changes in humidity with respect to time are represented by I_{cv}, which can be written as:

$$\phi \frac{dI_{cv}}{dt} + I_{cv} = G\, I_{nm} \qquad (10)$$

In this expression Φ represents the time constant, $R_{th}C_{th}$, which is the product of an equivalent thermal resistance and thermal capacitance of the gas. The value of G in Eq. (10) can be calculated from the differences in temperature and humidity of the air in the alveoli, nose, and in the plethysmograph (Drorbaugh & Fenn, 1955). The value of G is a function of the absolute temperature in the plethysmograph (T_P), the absolute temperature in the alveoli (T_A), barometric pressure (P_B), the partial pressure of water vapor within the chamber (P_{CH20}), and the water vapor pressure in the alveolar gas (P_{LH20}). G is defined as

$$G = 1 - \frac{T_P}{T_A}\frac{(P_B - P_{LH_2O})}{(P_B - P_{CH_2O})} \qquad (11)$$

and can have a different value during inhalation and exhalation. The flow of gas leaving the lungs during expiration, corrected to include the effects of cooling (I_{nmc}), is equal to the difference between the flow of warm moist air leaving the alveoli and the decrease in volume of the air as it cools. This relationship is described by Eq. (12):

$$I_{nmc} = I_{nm} - I_{cv} \qquad (12)$$

A similar analysis of the events occurring in the plethysmograph can be formulated during lung inflation to describe the warming and humidification of air entering the lung. Writing Eqs. (1)–(5) in terms of the Laplace transforms of those equations and solving for the relationship between I_{nmc} and I_t (Frazer et al., 1997) gives

$$\frac{I_{nmc}}{I_t} = \frac{\phi s + (1 - G)}{(R_{aw}\, C_g s + 1)(\phi s + 1)} \qquad (13)$$

The electrical equivalent circuit in Figure 1 has the same transfer function described by Eq. (13). In this configuration, I_t is represented by a current source, and the heating and cooling process is described by a dependent current source and equivalent thermal resistance and capacitance. If it is assumed that the air cools prior to exiting the nose of small laboratory animals (Schmid, 1976) or nearly instantaneously in the plethysmograph chamber, Eq. (13) reduces to

$$\frac{I_{nmc}}{I_t} = \frac{1 - G}{R_{aw}C_g s + 1} \qquad (14)$$

The flow of air into a whole-body plethysmograph containing an animal is $I_{box} = I_t - I_{nmc}$. This expression can be written as:

$$I_{box} = I_t \frac{R_{aw}C_g s + G}{R_{aw}C_g s + 1} \qquad (15)$$

Equation (15) can be rearranged to represent an inverse filter so that a series of I_t waveforms can be calculated over a range of $R_{aw}C_g$ values for a given I_{box} measurement. In other words, each calculated I_t waveform combined with the appropriate value of $R_{aw}C_g$ would be capable of generating the measured I_{box} waveform.

It should be pointed out that Eq. (15) assumes that the resistance of the pneumotach used to detect I_{box} is sufficiently low so that the plethysmograph does not alter the I_{box} measurement. If the plethysmograph does not meet this requirement, the appropriate corrections can be easily applied.

The method for calculating Penh from an I_{box} waveform is illustrated in Figure 2. Penh is defined in terms of T_e (expiratory time), T_r (time interval for 64% of the gas volume to enter the plethysmograph during expiration), P_{ef} (peak airflow during expiration), and P_{if} (peak airflow during inspiration) as Penh $= [(T_e - T_r)/T_r](P_{ef}/P_{if})$. Values of Penh can be calculated and plotted for an entire series of I_t waveforms as a function of $R_{aw}C_g$, for a single I_{box} waveform using Eq. (16).

$$Penh(I_t) = Penh\left(I_{box}\frac{R_{aw}C_g s + 1}{R_{aw}C_g s + G}\right) \qquad (16)$$

It can be shown that Penh measurements are independent of scale. In other words, two signals with different amplitudes and frequencies can have the same Penh value if they have a similar shape. This is illustrated in Figure 4, where two signals of different amplitudes and time scales are shown that have the same Penh value. It also should be noted that if Penh(I_t) remains constant following an intervention, it does not require that tidal volume and breathing frequency remain unchanged. It only requires that the relative shape of I_t remains constant.

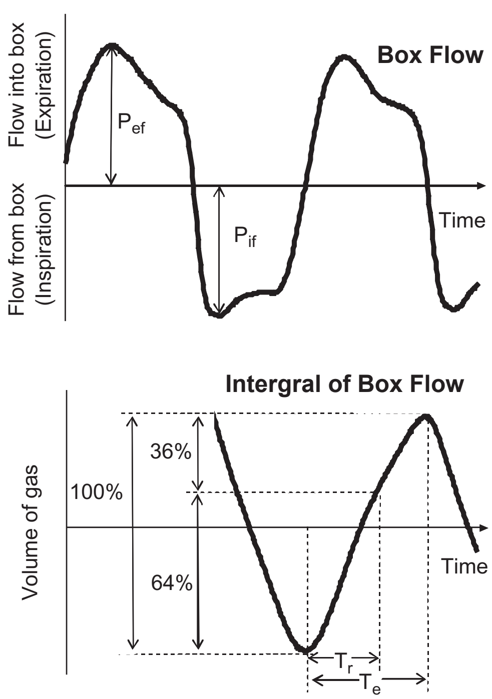

FIGURE 2. The variables used in the measurement of Penh based on the shape of the airflow pattern entering and leaving a whole-body flow plethysmograph during a breathing cycle. The airflow pattern and the volume of gas entering and leaving the plethysmograph are illustrated.

Plotting Penh(I_t) values as a function of $R_{aw}C_g$ results in a curve that represents all possible combinations of Penh(I_t) and $R_{aw}C_g$ that could produce a given Penh(I_{box}) measurement. When I_{box} measurements are made before and after an intervention, changes in the Penh(I_t) versus $R_{aw}C_g$ relationship can be evaluated in terms of alterations in either Penh(I_t), $R_{aw}C_g$, or both.

RESULTS AND DISCUSSION

One goal of this study was to establish the link between Penh(I_{box}) and $R_{aw}C_g$. That link determines the possible combinations of $R_{aw}C_g$ and thoracic airflow patterns that can generate a measured I_{box} waveform. Based on an I_{box} measurement of a normal rat as shown in Figure 2, it is possible to calculate a family of I_t curves as a function of $R_{aw}C_g$ using Eq. (15). The results of the calculations are shown in Figure 3. Applying Eq. (16), Penh(I_t) can be found for each of the I_t waveforms and plotted versus $R_{aw}C_g$ as demonstrated by the lower solid curve in Figure 5. That curve represents all the combinations of Penh(I_t) and $R_{aw}C_g$ that are capable of generating the measured I_{box} waveform. Unfortunately, additional information is usually needed to identify the unique point on the curve that represents the specific operating point. When there is a change in I_{box} due to an intervention, a different Penh(I_t) versus $R_{aw}C_g$ relationship is obtained. As Penh(I_{box}) increases, the (Penh (I_t) – $R_{aw}C_g$) curve is shifted upward and to the right, as illustrated by the upper solid curve in Figure 4. In this example, Penh(I_{box}) increased from 0.7 to 4.25. Note that Penh(I_t) is equal to Penh(I_{box}) when $R_{aw}C_g$

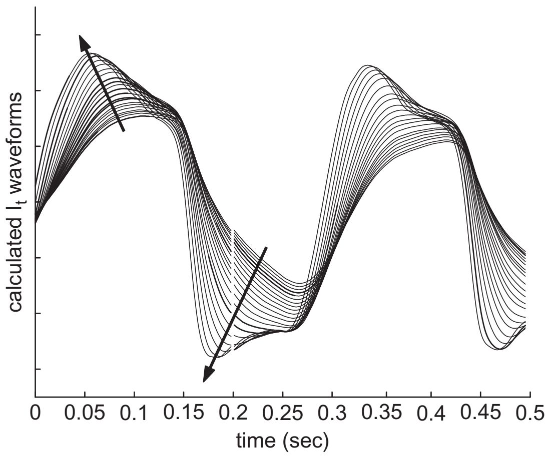

FIGURE 3. A family of thorax airflow patterns (I_t) that could generate the measured I_{box} waveform as a function as a function of $R_{aw}C_g$ using Eq. (15). Note that the I_{box} waveform is proportional to I_t, (G I_t), when $R_{aw}C_g$ is equal to zero. Arrows show the effect of decreasing values of $R_{aw}C_g$ on the I_t waveform.

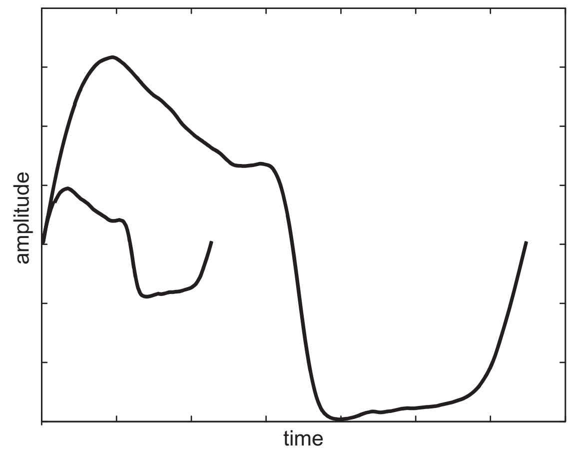

FIGURE 4. The Penh measurement itself is independent of frequency and amplitude. This is demonstrated by the two waveforms here, which have identical Penh values but different amplitudes and time scales.

approaches zero for both curves, due to the reduction in the effects of gas compression. Under these conditions, I_t and I_{box} have similar shapes, and equal Penh values, but very different scales.

In Figure 5, the three paths represented by the dashed lines A –B, A–C, and A–D between the operating points on the two Penh(I_{box}) curves illustrate how changes in Penh(I_{box}) after an intervention can result from a change in either Penh(I_t), $R_{aw}C_g$, or a combination of the two variables. Path A–B represents a situation where there was only a modest change in Penh(I_t), and the change in Penh(I_{box}) was

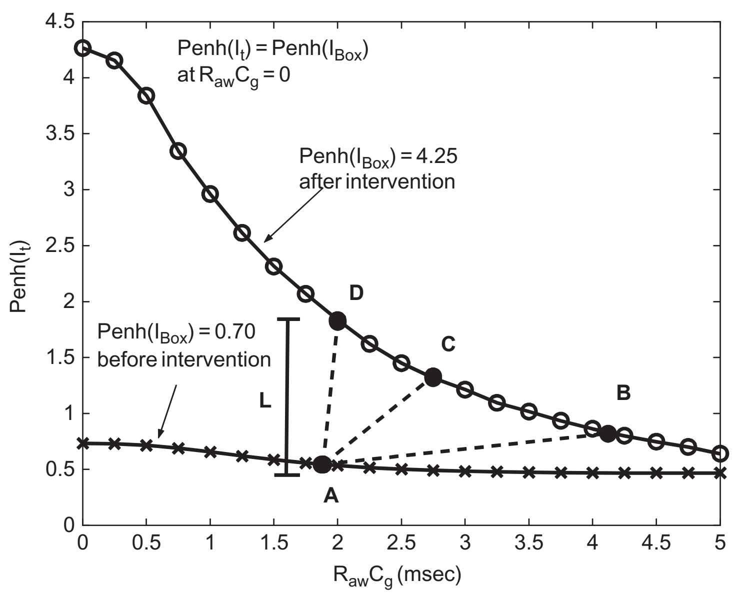

FIGURE 5. Penh(I_t) plotted as a function of $R_{aw}C_g$ before and after the animal was exposed to an intervention. The intercept of a Penh(I_t) curve with the axis, when $R_{aw}C_g$ is equal to zero, has a value equal to Penh(I_{box}). In this example Penh(I_{box}) increased from 0.7 to 4.25 following the intervention. Path A–B represents a path in which there was a significant change in $R_{aw}C_g$ with only a small change in Penh(I_t). Path A–C shows a path in which an intervention caused a large increase in Penh(I_t) and a modest decrease in $R_{aw}C_g$. Path A–D represents a change in I_{box} without a change in $R_{aw}C_g$. If ΔPenh(I_t) is less than L, ΔPenh(I_{box}) reflects changes in $R_{aw}C_g$.

primarily related to an increase in $R_{aw}C_g$. Path A–C represents a response where there was an identical increase in Penh(I_{box}) but a smaller increase in $R_{aw}C_g$ because of a greater change in Penh(I_t). Path A–D illustrates the situation when there was a large change in both Penh(I_{box}) and Penh(I_t) with little or no change in $R_{aw}C_g$.

Now, assume that the changes in Penh(I_t) and Penh(I_{box}) before and after an intervention are equal to ΔPenh(I_t) and ΔPenh(I_{box}), respectively. In Figure 5, L represents the vertical distance between possible operating points on the constant Penh(I_{box}) curves before and after an intervention. It can be seen that if ΔPenh(I_t) is negative or much less than L, then the path between operating points must travel in the direction of increasing values of $R_{aw}C_g$, and ΔPenh(I_{box}) becomes a sensitive indicator of increases in $R_{aw}C_g$. As ΔPenh(I_t) approaches L, however, ΔPenh(I_{box}) becomes less sensitive to changes in $R_{aw}C_g$. It should also be noted that if ΔPenh(I_t) is greater than or equal to L, then ΔPenh(I_{box}) is not related to an increase in $R_{aw}C_g$ and Penh(I_{box}) is a very poor indicator of a change in $R_{aw}C_g$.

This study suggests that one method that could be used to validate that an increase in ΔPenh(I_{box}) is related primarily to an increase in sR_{aw} (rather than an increase in Penh(I_t)) following any particular intervention would be to measure both Penh(I_t) and Penh(I_{box}) for a subset of animals. It can be seen from Figure 5 that the operating point on each curve before and after an intervention can be determined from the known (i.e. measured) value of Penh(I_t). It should also be noted that the range of $R_{aw}C_g$ values for control animals is often known so that point A in Figure 5 can be estimated. As previously indicated, if ΔPenh(I_t) is less than the vertical distance between the pre and post Penh(I_{box}) curves, which is equal to L in Figure 5, then changes in ΔPenh(I_{box}) reflect changes in $R_{aw}C_g$. The greater the difference between ΔPenh(I_t) and L (ΔPenh(I_t) $<$ L), the more sensitive ΔPenh(I_{box}) becomes as an indicator of changes in $R_{aw}C_g$.

It was previously shown that Penh(I_{box}) reflects changes in ($R_{aw}C_g$) following exposure to methacholine (Hammelman et al., 1997). The following illustrates how Penh responds to changes in sRaw under these experimental conditions. Values of $R_{aw}C_g$ were measured for five rats pre and post exposure to methacholine using a two-chamber plethysmograph. Both I_t and I_{nmc} were measured before and after exposure and I_{box} was computed assuming $I_{box} = I_t - I_{nmc}$. Penh(I_{box}) and Penh(I_t) were calculated based on these two sets of measurements. Table 1 shows how ΔPenh(I_{box}), ΔPenh(I_t), $\Delta R_{aw}C_g$, and L changed as a result of the exposure. Since, under these circumstances, ΔPenh(I_t) $<<$ L, changes in Penh(I_{box}) reflect changes in sR_{aw} ($\Delta R_{aw}C_g$). It should be noted, however, that ΔPenh(I_{box}) is not necessarily directly proportional to $\Delta R_{aw}C_g$.

Some investigators explored using Penh(I_t) or the shape of the thoracic flow pattern to detect pulmonary responses to an intervention instead of Penh(I_{box}) (Flandre et al., 2003). Flandre et al. (2003) suggested that Penh(I_t) measurements may even be superior to Penh(I_{box}) measurement as an index of pulmonary function because they are independent

TABLE 1. Changes in Penh(I_{box}), Penh(I_t), and $R_{aw}C_g$ Following Exposure to Methacholine

Animal number	ΔPenh(I_{box})	ΔPenh(I_t)	L	$\Delta R_{aw}C_g$ (ms)
1	4.81	–0.094	1.35	4.75
2	3.53	–0.041	1.24	3.44
3	3.17	0.103	1.74	2.40
4	1.52	0.089	0.68	2.13
5	2.63	0.227	0.69	3.37
Mean (SD)	3.13 (1.21)	0.057 (0.127)	1.14 (0.455)	3.22 (1.03)

Note. L, illustrated in Figure 5, represents the maximum change that can occur in Penh(I_t) if changes in Penh(I_{box}) reflect changes in $R_{aw}C_g$. In this case, ΔPenh(I_t) $<$ L, so changes in Penh(I_{box}) indicate changes in $R_{aw}C_g$.

of thermal effects, tidal volume, and changes in FRC. This study shows, however, that the interpretation of Penh(I_t) measurements can be easily misunderstood. Flandre et al. (2003) noted that Penh(I_t) did not appear to respond to interventions in the same way as Penh(I_{box}) under some experimental conditions and concluded that the Penh measurement was a poor indicator of increases in $R_{aw}C_g$. The theoretical analysis in this study shows that Penh(I_{box}) and Penh(I_t) are not equivalent and that Penh(I_t) should not be expected to respond in the same manner as Penh(I_{box}) to an intervention. This is because an elevation in Penh(I_{box}) can result from either an increase in Penh(I_t), or a rise in $R_{aw}C_g$, or both. In fact, when Penh(I_t) increases it is usually negatively correlated with an elevation in $R_{aw}C_g$. A measurement of a rise in Penh(I_t), therefore, would appear to be a very poor predictor of an increase in specific airway resistance.

At the present time, all the parameters that contribute to specific alterations in the thoracic breathing pattern as described by the Penh(I_t) index are not well understood. It is known that the breathing pattern is created by muscles under control of the central nervous system. That system is capable of incorporating information from many types of receptors that are continuously supplying information concerning airway function. That multifaceted body of information is integrated and used to modify the animal's breathing pattern to optimize the overall performance of the pulmonary system. Determining the complex relationship between airway function based solely on the thoracic breathing pattern may prove to be a difficult task.

In summary, this study describes the relationships between Penh of thoracic airflow patterns, Penh of airflow measurements from the whole-body plethysmograph, and specific airway resistance. These relationships were used to show that Penh of thoracic airflow and Penh of plethysmographic airflow should not be interpreted in the same manner to predict changes in specific airway resistance. Furthermore, if Penh of thoracic airflow decreases following an intervention, an elevation in Penh of plethysmographic airflow would be a very sensitive indicator of an increase in specific airway resistance. Conversely, if Penh of thoracic airflow shows a substantial increase, then Penh of plethysmographic airflow is not a useful indicator of changes in sR_{aw}. Finally, this study suggests how quantifying changes in Penh of thoracic flow in a subset of animals can be used to interpret changes in Penh of whole-body plethysmograph measurements in terms of specific airway resistance in larger groups of animals.

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