Noninvasive determination of upper airway resistance and flow limitation

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Noninvasive determination of upper airway resistance and flow limitation. J Appl Physiol 97: 1840–1848, 2004. First published May 28, 2004; doi:10.1152/japplphysiol.01319.2003.—We have shown that a polynomial equation, \( F(P) = A P^3 + B P^2 + C P + D \), where \( F \) is flow and \( P \) is pressure, can accurately determine the presence of inspiratory flow limitation (IFL). This equation requires the invasive measurement of supraglottic pressure. We hypothesized that a modification of the equation that substitutes time for pressure would be accurate for the detection of IFL and allow for the noninvasive measurement of upper airway resistance. The modified equation is \( F(t) = A t^3 + B t^2 + C t + D \), where \( F \) is flow and \( t \) is time from the onset of inspiration. To test our hypotheses, data analysis was performed as follows on 440 randomly chosen breaths from 18 subjects. First, we performed linear regression and determined that there is a linear relationship between pressure and time in the upper airway (\( R^2 = 0.96 \pm 0.05 \), slope 0.96 \( \pm 0.06 \)), indicating that time can be a surrogate for pressure. Second, we performed curve fitting and found that polynomial equation accurately predicts the relationship between flow and time in the upper airway (\( R^2 = 0.93 \pm 0.12 \), error fit 0.02 \( \pm 0.08 \)). Third, we performed a sensitivity-specificity analysis comparing the mathematical determination of IFL to manual determination using a pressure-flow loop. Mathematical determination had both high sensitivity (96%) and specificity (99%). Fourth, we calculated the upper airway resistance using the polynomial equation and compared the measurement to the manually determined upper airway resistance (also from a pressure-flow loop) using Bland-Altman analysis. Mean difference between calculated and measured upper airway resistance was 0.0 cmH\(_2\)O \( \cdot \) \( \text{cm}^2 \cdot \text{s}^{-1} \cdot \text{atm}^{-1} \) (95% confidence interval \(-0.2 \pm 0.2\)) with upper and lower limits of agreement of 2.8 cmH\(_2\)O \( \cdot \) \( \text{cm}^2 \cdot \text{s}^{-1} \cdot \text{atm}^{-1} \) and \(-2.8\) cmH\(_2\)O \( \cdot \) \( \text{cm}^2 \cdot \text{s}^{-1} \cdot \text{atm}^{-1} \). We conclude that a polynomial equation can be used to model the flow-time relationship, allowing for the objective and accurate determination of upper airway resistance and the presence of IFL.

THEORY AND HYPOTHETICAL CONSIDERATIONS

The theoretical considerations on which the relationship between pressure and flow can be characterized by a polynomial equation have been previously presented (20). A modification of these theoretical considerations that relates flow and time is presented in full detail in the Appendix. These theoretical considerations result in the following polynomial equation that characterizes the relationship between flow (F) and time (t):

\[
F(t) = A t^3 + B t^2 + C t + D
\]

In our previous work on the pressure-flow polynomial (20), we had shown that the derivative of the polynomial equation could be used to determine flow limitation. In particular, we showed that the derivative of the polynomial function (or slope of the pressure-flow curve) at the actual maximal flow was negative for non-flow-limited breaths and positive or zero for IFL breaths. We believed that a similar relationship could be determined for the flow-time relationship. The derivative of the flow-time equation is

\[
\frac{dF}{dt} = 3 A t^2 + 2 B t + C
\]

However, as time is increasing during inspiration, as opposed to pressure, which is decreasing, the slope or derivative of the polynomial function at the measured maximal flow is either zero or negative for flow-limited breaths and positive for non-flow-limited breaths. Therefore, at maximal flow, we hypothesized that if \( dF/dt > 0 \), the breath is non-flow-limited, and if \( dF/dt < 0 \) or \( dF/dt = 0 \) (where \( P \) is pressure), the breath is flow limited.

These hypothetical considerations are illustrated in Fig. 1. Figure 1A illustrates the concepts for a non-IFL (NIFL) breath, whereas Fig. 1B illustrates the concepts for an IFL breath. For

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both breaths, the pressure-flow relationship (with pressure treated as a positive value only for consistency in the x-axes of the graphs) is illustrated in the top panels. The middle panels show both the measured flow-time relationship (solid lines) and the polynomial curve-fitted flow-time relationship (dashed line). The bottom panels illustrate the derivative (or slope) as a function of time. For the NIFL breath, the slope of the flow-time curve at the maximal measured flow (vertical dashed line) is >0, whereas for the IFL breath the slope of the flow-time curve is <0.

We have also recently shown that the pressure-flow polynomial equation could be used to accurately measure the Rua during the linear portion of the inspiration (19). Therefore, we hypothesized that Rua could also be determined from the flow-time polynomial equation. In particular, the theoretical considerations (see APPENDIX) lead to the following equation:

\[ R = \frac{C_o}{F^2 t} \]

where \( F \) is the flow at the end of the linear portion of the inspiratory pressure-flow curve (see Fig. 2), \( t \) is the time at that point in inspiration, \( R \) is Run, and \( C_o \) is a constant.

The theoretical approach above does not allow us to solve for resistance unless we also know the value of \( C_o \). As is noted in METHODS below, we solved for \( C_o \) for several breaths using the manually measured value for resistance. This approach allowed us to determine that \( C_o \) was the same value as the coefficient \( C \) in Eq. 1. This result is congruent with the theoretical considerations for the following reasons. On the basis of the Bernoulli principle, as flow proceeds from an area of high pressure to an area of low pressure, the velocity of the

Fig. 1. Graphical representation of the theoretic considerations regarding the ability of the polynomial function to distinguish between non-inspiratory flow-limited (NIFL; A) and inspiratory flow-limited (IFL) breaths (B). Top, measured pressure (Psg)-flow (V) relationship; middle, measured flow-time relationship (black solid line) and the derived flow-time relationship using the polynomial equation (black dashed line); bottom, change in the slope of the flow-vs.-time relationship graphed vs. time. The vertical dashed line in the lower graphs is at the measured maximal flow. The slope at the measured maximal flow for NIFL breaths remains positive, whereas the slope becomes negative for IFL breaths. The vertical dotted line indicates where the slope of the flow-vs.-time relationship is either a maximum or a minimum; measured flow and time at this point were used to calculate upper airway resistance (Rua).

Fig. 2. Measurement of manual linear resistance. Measured Rua (mRua) was determined by drawing a line through the first linear portion of the ascending limb. mRua was determined as the inverse of the slope of the drawn line.

\[ mR_{m} = \frac{1}{\text{slope}} \]
air increases. As the velocity of air increases, flow can change from laminar to turbulent, as it does in the upper airways (13, 23, 27). The relationship between pressure and flow is linear when flow is laminar, whereas it is nonlinear when flow is turbulent (27, 28, 38). Mathematically, this can be represented as \( F \propto P^N \), where \( F \) is the flow, \( P \) is the pressure, and \( N \) is an exponent. If \( N = 1 \), flow is laminar, whereas if \( N > 1 \) or \( N < 1 \), the flow is turbulent (28, 38). Using the polynomial equation, \( F(P) = A t^3 + B t^2 + C t + D \), we can hypothesize that turbulent flow is mathematically represented by the term \( A t^3 + B t^2 \), whereas laminar flow is represented by the term \( C t + D \). Because the Rua is best determined on the linear portion of the pressure-flow relationship, when upper airway area is a constant, the measurement of resistance must occur while the flow is laminar. Therefore, the coefficient \( C \) should be related to the linear characteristics of the inspiratory pressure-flow relationship. We recently proved this hypothesis when determining Rua from the pressure-flow polynomial equation (19).

METHODS

Measurements. A total of 440 breaths were chosen for the analysis outlined below. The breaths were randomly chosen from 18 subjects (11 women, 7 men, age 39.3 \( \pm \) 10.4 yr, BMI 26.8 \( \pm \) 5.7 kg/m\(^2\)). All breaths were obtained from healthy adults with no sleep-related complaints who had volunteered for research studies in the laboratory; studies were approved by the local institutional review board and subjects provided written, informed consent. All subjects were free of sleep-disordered breathing, as measured by apneas and hypopneas, on polysomnography. However, to ensure that we had a significant number of flow-limited breaths in the data set, we included breaths from several subjects with a significant degree of flow-limited breaths (>50% of breaths were flow limited). All analyzed breaths in the following protocols were obtained during stage 2 non-rapid eye movement sleep. In addition to the above breaths, 75 breaths from wakefulness from four subjects were analyzed only in question 3 below as negative controls (based on the observation that IFL is generally not observed during wakefulness). Because slow-wave and rapid eye movement sleep are uncommonly observed in the heavily instrumented subjects, breaths from these stages could not be analyzed. In addition, only breaths free from artifact were included in the analysis.

For each breath, airflow was measured by a pneumotachometer (model 3700A, Hans Rudolph) attached to a nasal mask. Supraglottic airway pressures were measured with a pressure-tipped catheter (model TC-500XG, Millar) threaded though the mask and positioned in the oropharynx just below the base of the tongue. Correct placement in the hypopharynx was confirmed by advancing the catheter tip for 2 cm after it disappeared behind the tongue. During the studies, airflow and supraglottic pressure were recorded simultaneously with PowerLab data-acquisition software (ADI Instruments, Colorado Springs, CO) on a separate computer.

Data analysis. For each breath, the onset of inspiration was defined as the sampling point at which inspiratory flow \( = 0 \). On the rare occurrence in which there was a shift in baseline, the nadir flow was determined and the flow values were shifted appropriately. Because the Millar catheter provides relative pressures, supraglottic pressure was set to zero for the inspiration onset sampling point and the remaining values for the breath were calculated. The determination of the presence of IFL was performed manually for each breath as follows. A pressure-flow loop was generated (Fig. 1, top), and the loop was analyzed for the presence of IFL. A breath was labeled IFL if there was a 1 cmH\(_2\)O or greater decrease in supraglottic pressure without any corresponding increase in flow during inspiration. If the flow-pressure relationship did not meet this criterion, the breath was labeled as NIFL. On the basis of the manual determination of IFL, there were 197 IFL breaths and 243 NIFL breaths in the sample.

The manual measurement of linear resistance is illustrated in Fig. 2 and was performed as previously described (19). On the pressure-flow loop, a straight line was drawn from the origin of the axis through the first linear portion of the inspiratory cycle. Measured Rua (mRua) was defined as the inverse of the slope of the drawn line.

Additional data analysis was performed to answer the following four questions.

**Question 1: Is the relationship between pressure and time linear?** We hypothesized that the rate of change in pressure over time would be similar between breaths and different subjects. If the rate of change was similar between breaths and subjects, time could be a surrogate for pressure. To test this hypothesis, the following analysis was performed. Because both the time and pressure axes could vary significantly between breaths, and time and pressure have different units, we first normalized the pressure and time data before performing linear regression analysis. To normalize the data, we took each point of time and pressure as a percentage of the total time or pressure, respectively. Total time for this analysis was the total time to the end of the linear portion of the ascending inspiratory pressure-flow curve. We then used these normalized values to perform linear regression analysis to determine the slope of the pressure-time relationship and the coefficient of determination \( R^2 \). We hypothesized that if the time could be substituted for pressure there would have to be a near one-to-one relationship between the two variables during the linear portion of the pressure-flow curve. In other words, the slope of a pressure-time curve was hypothesized to have a value of one. We determined the \( R^2 \) as an indication of how much of the variability in one variable (pressure) is explained by knowing the value of the other (time) (17). A large \( R^2 \) indicates that the variability in flow is largely explained by the variability in time, indicating a tight relationship between the two variables.

**Question 2: Does the polynomial function predict the relationship between time and flow in the upper airway?** To model the upper airway mathematically, we performed a curve-fitting analysis using SigmaStat 2.0 software (Fig. 1, bottom). This process is similar to performing a linear regression, in which the predicted relationship can be given by the equation \( F(t) = At + B \), except in this case we used a three-term polynomial equation. Neither the time nor flow values were transformed before the curve fitting (24). For each calculated function, we determined the \( R^2 \) (17).

To determine the degree of approximation between the flow-time relationship derived from the polynomial function to the actual flow-time relationship, we determined the error fit (20). The error fit measures the degree of error between the actual flow-time relationship and the fitted relationship. The smaller the error fit, the more closely the predicted relationship approximates the actual pressure-flow relationship. The error fit is a mathematical representation of this gray-shaded area. Mathematically, error fit is defined as

\[
100 \left( \frac{1}{k} \sum_{i=1}^{k} \left( y_i - \tilde{y}_i \right) \right)
\]

where \( \sum_k \) is the summation of a series of points, \( y_i \) represents the points in the original function, and \( \tilde{y}_i \) represents the points in the fitted function (24). Using this formula, as the predicted flow-time relationship more closely approximates the actual relationship, the error fit or difference between the two relationships decreases.

**Question 3: Does the polynomial function objectively detect flow limitation?** For each of the breaths, we determined the slope of the flow-time polynomial function at the measured maximal flow for the predicted polynomial equation (24). For any breath for which there may be multiple data points with the same flow, the first data point with the maximal flow was chosen for the subsequent analysis. Per the hypothesis, if the slope of the flow-time curve at the measured
maximal flow was $>0$, we labeled the breath NiFL; if the slope of the flow-time curve at the measured maximal flow was $\leq 0$, we labeled the breath IFL. We calculated the sensitivity, specificity, positive predictive value, and negative predictive value for the detection of IFL breaths by the polynomial model compared with the manual method of determination (described at the beginning of METHODS) using standard formulas (30).

**Question 4: Can the Rua be accurately calculated by using the polynomial equation?** We first tested our hypothesis that the constant, $C_\infty$, in Eq. 3 was the same value as the coefficient $C$ in Eq. 1. To test this hypothesis, we calculated $C_\infty$ for 22 randomly chosen breaths (11 NiFL, 11 IFL) from 7 subjects, using the Rua manually measured from the pressure-flow loop and the flow and time at the end of the linear portion of the inspiratory curve. To determine the end of the linear portion of the inspiratory curve, we calculated the slope of the flow-time curve at each time point; by definition, when the slope of the flow-time curve was either a maximum or a minimum (dotted vertical line, Fig. 1), the pressure-flow relationship is no longer linear. Thus, to measure resistance, we chose the flow and time when the slope of the relationship of flow-time was either a maximum or minimum. We then compared the calculated $C_\infty$ with the coefficient $C$ determined on the basis of curve fitting (question 1 above) using a Wilcoxon’s signed-rank test (because the data were nonparametric).

The results (shown below), confirmed our hypothesis and we proceeded to measure the Rua on the remaining breaths.

For each of the breaths, we calculated the Rua ($cR_{UA}$) using Eq. 3 under THEORY AND HYPOTHETICAL CONSIDERATIONS, using the value of coefficient $C$ derived from the curve fitting for the value of constant $C_\infty$. To determine the degree of agreement between $mR_{UA}$ and $cR_{UA}$ measurements, the two analyses were performed. First, $mR_{UA}$ and $cR_{UA}$ were compared by using a Wilcoxon’s signed-rank test because the data were nonparametric. The results showed no significant difference between the values.

We believed it important to determine whether differences in $mR_{UA}$ and $cR_{UA}$ were clinically significant. In other words, we wished to determine whether the mean data for each subject would have changed if the $cR_{UA}$ values were used instead of the $mR_{UA}$ values. We believed this to be important because most research studies would likely report the mean Rua for each subject rather than the Rua on a breath-by-breath basis. Therefore, we performed an analysis based on subject as opposed to breath. For each of the 18 subjects, we determined the mean $mR_{UA}$ and $cR_{UA}$ of the analyzed breaths. We then compared the mean $mR_{UA}$ and $cR_{UA}$ breaths in two ways. First, we performed a Wilcoxon’s signed-rank test. Second, we performed a Bland-Altman analysis to determine the upper and lower limits of agreements between the two variables.

**RESULTS**

**Question 1: Is the relationship between pressure and time linear?** For the group of breaths overall, the slope was 0.96 ± 0.06 and the $R^2$ was 0.96 ± 0.05, indicating that there was a predictable, linear relationship between pressure and time.

**Question 2: Does the polynomial function predict the relationship between time and flow in the upper airway?** For the group of breaths overall, the polynomial equation was an accurate representation of the upper airway flow-vs.-time relationship as indicated by the $R^2$ of 0.93 ± 0.12 and the error fit of 0.02 ± 0.08.

**Question 3: Does the polynomial function objectively detect flow limitation?** Using the slope at maximal flow of the flow-time polynomial equation results in both high sensitivity, 96%, and high specificity, 99%, for the determination of IFL breaths. The positive predictive value, 99%, and negative predictive value, 97%, were also high. For the group of 75 wakefulness breaths, all of which were non-flow limited, all the breaths were characterized as NiFL by the polynomial equation (accuracy 100%).

These results indicate that a polynomial equation that relates flow to time can be used to accurately determine the presence of IFL.

**Question 4: Can the Rua be accurately calculated by using the polynomial equation?** For the 22 breaths used to test the hypothesis that coefficient $C$ and constant $C_\infty$ were the same value, there was no significant difference between coefficient $C$ (median, 0.65, interquartile range 0.50, 1.20) and the constant $C_\infty$ (median, 0.64, interquartile range 0.50, 1.24).

The box plot of $mR_{UA}$ and $cR_{UA}$ for the whole group of 440 breaths is shown in Fig. 3A. The median $mR_{UA}$ (7.1 cmH$_2$O·l$^{-1}·s^{-1}$, interquartile range 4.3 to 10.2 cmH$_2$O·l$^{-1}·s^{-1}$) was not significantly different from the median $cR_{UA}$ (7.1 cmH$_2$O·l$^{-1}·s^{-1}$, interquartile range 4.2 to 10.3 cmH$_2$O·l$^{-1}·s^{-1}$, $P = NS$). The Bland-Altman analysis for the whole group of points is depicted in Fig. 4A. The Bland-Altman analysis showed...
excellent agreement between cRua and mRua with a mean difference between cRua and mRua of 0.0 cmH₂O (95% confidence interval (CI) −0.2 to 0.2 cmH₂O·l⁻¹·s⁻¹). The upper limit of agreement was 2.8 (95% CI, 2.6 to 3.0 cmH₂O·l⁻¹·s⁻¹) whereas the lower limit was −2.8 cmH₂O·l⁻¹·s⁻¹ (95% CI, −3.0 to −2.6 cmH₂O·l⁻¹·s⁻¹).

When analyzed by individual subject, there was no difference between the group median mRua (median 7.4 cmH₂O·l⁻¹·s⁻¹, interquartile range 4.5, 11.0 cmH₂O·l⁻¹·s⁻¹) and cRua (median 7.5 cmH₂O·l⁻¹·s⁻¹, interquartile range 4.2, 11.2 cmH₂O·l⁻¹·s⁻¹; P = NS; see Fig. 3B). The Bland-Altman analysis showed excellent agreement between cRua and mRua with a mean difference between cRua and mRua of 0.1 cmH₂O·l⁻¹·s⁻¹ (95% CI −0.6 to 0.4 cmH₂O·l⁻¹·s⁻¹; see Fig. 4B). The upper limit of agreement was 0.5 (95% CI, −0.3 to 1.3 cmH₂O·l⁻¹·s⁻¹), whereas the lower limit was −0.7 cmH₂O·l⁻¹·s⁻¹ (95% CI, −1.50 to 0.1 cmH₂O·l⁻¹·s⁻¹).

**DISCUSSION**

In this study, we have demonstrated that a polynomial equation, \( F(t) = A t^2 + B t + C t + D \), allows for the objective and precise determination of the measurement of Rua at the beginning of inspiration, a frequently used surrogate for upper airway patency, and the presence of inspiratory flow limitation, which is a descriptor of the behavior of the upper airway at peak flow. The main requirement for the accurate determination of IFL and Rua using the polynomial function is a continuous and simultaneous measurement of flow and time.

**Noninvasive measurement of Rua.** Resistance is defined as the change in pressure divided by the change in flow. Therefore, the measurement of Rua requires the simultaneous measurement of flow and supraglottic pressure. The primary finding of this study was that Rua could be measured accurately in a noninvasive fashion by using values derived from a polynomial flow-time equation. In other words, we were able to compute Rua without the measurement of supraglottic pressure. The accuracy of such determination is predicated on the validity of time as a surrogate for pressure. This requires that the time-pressure relationship is linear and constant and falls very close to the line of identity, i.e., slope of the pressure-time curve of 1; this work establishes such a relationship. We emphasize that this method is accurate only for the linear duration of inspiration. Our computation may not be accurate when there is dissociation between pressure and flow (non-laminar relationship, as occurs after the onset of flow limitation), in other biological systems or during expiration as the pressure-time relationship may be different.

Several previous studies have attempted to ascertain upper airway mechanics noninvasively. Surface inductive plethysmography is based on the observation that there is inward movement of the suprasternal fossa during inspiration (31, 36). This method has been used to measure pleural pressures and compliance in humans (36) and Rua in intubated dogs (31). In dogs, there was close agreement between Rua measured by surface inductive plethysmography and esophageal pressure under a variety of conditions, including spontaneous breathing, inspiratory resistive loading, and bronchoprovocation. The forced oscillation technique is based on superimposing a small-amplitude pressure oscillation on the nasal mask of a subject, allowing the calculation of Rua from the oscillatory pressure and flow signals recorded from the nasal mask. In one study, resistance using the forced oscillation technique showed an excellent correlation with resistance measured using pleural pressure while nasal continuous positive airway pressure was applied (22).

**Noninvasive detection of IFL.** The “gold-standard” method for the detection of IFL requires the measurement of supraglottic or esophageal pressure, which allows the breath-by-breath plotting of pressure-flow plots. The plots can then be analyzed for the presence of dissociation between flow and pressure that is characteristic of flow limitation. We have previously shown that the pressure-flow relationship can be characterized by a polynomial equation that relates pressure to flow and that this equation can be used to detect flow limitation (20). However, an accurate and sensitive noninvasive approach to the detection of flow limitation would be ideal. In this work, we present a unique method of analyzing the flow-time relationship to detect flow limitation in an accurate and objective fashion.

Previous investigators have presented methods in which flow limitation can be determined noninvasively. The first method is visual inspection of the flow-time curve, with flow limitation characterized by a plateau or squared-off appearance of the curve (2, 8, 12). By using this approach, it has been shown that there is a good correlation between the visually identified classification of breaths and Rua measured by an esophageal balloon (8) as well as with excessive daytime sleepiness (12). Although these results suggest that visual analysis can be objectively performed, in our experience there...
is large room for subjectivity, decreasing the accuracy of the method.

Inductive plethysmography is based on the detection of changes in the volume of the chest and abdomen over the breathing cycle, with the sum of these measurements providing an estimate of the tidal volume if calibration is maintained (6). Inductive plethysmography has been studied as a method to detect IFL (7, 15, 18). In particular, Kaplan et al. (15) studied whether parameters derived from the plethysmography signal, such as ratio of the fractional inspiratory time and peak tidal inspiration to mean tidal inspiratory flow, could be used to reliably detect IFL breaths. In general, these parameters had a reasonable discrimination function as measured by the area under of the curve of the receiver operator characteristic (range 0.7 to 0.9), corresponding to a best sensitivity and specificity of ~80%. Loube et al. (18) showed that inductive plethysmography could be used to identify patients with the upper airway resistance syndrome (UARS). Although inductive plethysmography has potential, its use is limited by two factors. First, the use of inductive plethysmography requires strict maintenance of calibration of the signals, which we have found difficult to achieve in both the research and clinical laboratory settings. Second, there is a continuous range of values from the parameters derived from the sum signal; this necessitates choosing a cutoff point that maximizes sensitivity and specificity. This contrasts to the dichotomous result (IFL vs. NIFL) obtained from the polynomial equation. Furthermore, the sensitivities and specificities do not approach that obtained in this study.

Other investigators have also examined the flow-time relationship and derived indexes from the relationship that can be used to determine the presence of IFL (7, 33). In particular, Clark et al. (7) calculated an “area index” to distinguish IFL and NIFL breaths. The area index measured the difference between a template NIFL breath obtained during wakefulness and the breath being analyzed where the area was the area under the curve of the Δflow rate-vs.-Δtime plot. Flow was measured with a conventional pneumotachometer and by nasal pressure transducer and inductive plethysmography. Sensitivities and specificities of the area index for all three flow methods were generally between 70 and 85%, all lower than achieved with the flow-time polynomial equation. Problems with the use of the area index include whether there is an appropriate cutoff (see discussion above). Also, the index is derived by using a “normal” breath as a template breath; selection of a poor template breath could clearly result in inaccurate identification of both NIFL and IFL breaths.

Finally, we note that the physiological basis of autotitrating continuous positive airway pressure devices is the noninvasive detection of flow limitation. In particular, there is one device that monitors the flow-time contour for the detection of flow limitation and has been used both for the automatic titration of positive pressure (10, 33, 34) and the diagnosis of sleep-disordered breathing (when set in a diagnostic mode) (9, 21, 26). In both modes, this device has been shown to be relatively accurate for the detection of IFL.

**Methodological considerations.** The theoretical approach presented at the beginning of the paper has one major potential limitation. In particular, to apply Newton’s expansion law, we had to create a constant, $G$, that contains multiple parameters including density, area, atmospheric pressure, and the kinematic heat ratio. Therefore, for $G$ to be a constant, these parameters must be assumed to be constant during flow between points $M_1$ and $M_2$. The assumption that density and the kinematic heat ratio are constants has been made by others (16) and is based on thermodynamic principles (32). Although area has also been assumed to be a constant by Rohrer (27), it has been shown that nasopharyngeal area will change during a flow-limited breath (14). However, in our model, the downstream area ($A_3$) is the area at the level of the supraglottic pressure catheter, and we do not know of a study that shows that area of the supraglottic space changes during inspiration in normal subjects. In contrast, oropharyngeal and hypopharyngeal area have been shown to change in patients with sleep apnea (25). Therefore, we cannot be certain that $G$ is a constant during any given breath. Nevertheless, the excellent agreement between the measured data and polynomial function data supports the validity of the assumptions, including that area is a constant, that we made while developing the theoretical background.

We chose to focus only on the ascending segment portion of the inspiratory-pressure-flow curve for several reasons. First, because there is no driving pressure during the descending segment of inspiratory-pressure-flow curve, one cannot describe a resistance. Second, it has been previously shown that the ascending limb to the point of maximal pressure is the majority of the inspiratory time and contains information of biological interest compared with the descending limb (3, 4).

To our knowledge, the determination of IFL is based only on a relationship between flow and driving pressure and therefore can only be made on this part of the inspiratory curve. Fourth, Rua has only been measured on the ascending segment regardless of whether the measurement is measured at a fixed flow, at peak flow, at peak supraglottic pressure, or on the first linear portion and determination of IFL (7, 29, 35, 37).

We used a research pneumotachometer to measure flow. It is unclear whether the flow signals obtained from a nasal pressure transducer (2, 7) can be utilized in as accurate a fashion. Alternatively, there are now continuous positive airway pressure devices that contain pneumotachometers that can be used in a diagnostic mode (9, 26). Further investigations studying the accuracy of our theoretical approach with these alternative methodologies are necessary.

To ascertain the accuracy of mathematical detection of IFL, we had to use a “benchmark” for detection of flow limitation. We chose a definition of IFL in which there is demonstrated dissociation between pressure and flow for a 1-cm decrement in supraglottic pressure, based mainly on our ability to identify such decrement in pressure. We have previously shown excellent reproducibility between the pressure-flow polynomial equation and visual analysis of flow limitation (20). However, the physiological consequences of such mild degree of inspiratory flow limitation are not known.

In this study, inspiratory flow limitation was evaluated as a dichotomous variable. However, deviation from linearity between flow and pressure is a continuous variable (7). Our method detects flow limitation as defined by a plateau in flow only; as such, any other alinear flow profile is classified as noninspiratory flow limitation. However, we doubt the physiological significance of deviation from linearity without true flow limitation.

**Implications.** The ability to detect inspiratory flow limitation and measure Rua noninvasively may have significant relevance.
to the diagnosis of sleep-disordered breathing (SDB). The
description of the UARS expanded the spectrum of SDB by
including patients without episodes of apnea or identifiable
hypopnea (11). The main features of UARS are the recurrent
arousal due to repetitive episodes of IFL and decreases in
eosophageal pressure. Recently, a consensus statement defined
the respiratory event-related arousal (RERA), which is be-
lieved to be the characteristic event of UARS. As defined, a
RERA is a pattern of progressively negative esophageal pres-
sure lasting 10 s and ending in an arousal (1). Therefore,
researchers and clinicians must measure either supraglottic or
eosophageal pressure to detect RERAs. Unfortunately, detection
of inspiratory flow limitation has often been based on subjec-
tive visual detection of a square flow profile without pressure
measurements because of the perception that pressure mon-
itoring will be uncomfortable for the patient (2, 12). This
perception has prevented many clinical laboratories from
adapting esophageal pressure monitoring for routine clinical
use. Furthermore, visual detection does not allow actual mea-
surement of resistance, which should be increasing during
RERAs and could assist in detecting these events. We have
shown that the polynomial function relating flow and time
allows for an objective detection of the events associated with
UARS by both determining the presence of IFL and measuring
Rua. Our method could be used on a large number of breaths
in an automated fashion and may be useful for research and
clinical studies, particularly future studies that assess the rela-
tionship between SDB and other variables, such as excessive
daytime sleepiness, that requires large numbers of subjects for
accurate interpretation. Finally, we support a previous sugges-
tion (12) that a determination of the presence of flow limitation
may provide an alternative metric to assess the relationship
between SDB and daytime consequences such as excessive
daytime sleepiness and cardiovascular morbidity, particularly
in nonapneic forms of the syndrome.

APPENDIX

We consider a steady homogenous flow in a circular cylinder (the
upper airway), with the assumption that the flow of air in the upper
airway will expand without the loss or gain of heat. Consider a
streamline of air which connects two points $M_1$, the upstream
pressure, which is atmospheric pressure in our model, and $M_2$, the
downstream pressure, which is equivalent to supraglottic pressure in
our model. For each point, there is a density ($\rho$), pressure ($P$), area ($A$),
velocity ($V$), and flow ($F$) that characterizes that point. In the modeling
that follows, it should be noted that the goal is determination of the
flow of the upper airway at the downstream pressure point, $M_2$. Flow,
which is constant throughout the upper airway, is given by

$$F = \rho A_1 V_1 = \rho A_2 V_2 \quad (A1)$$

Solving for $V_1$:

$$V_1 = \frac{\rho A_2}{\rho A_1} V_2 = \Omega V_2 \quad (A2)$$

where

$$\Omega = \frac{\rho A_2}{\rho A_1} = \frac{A_2}{A_1}$$

The Bernoulli or energy equation for homogenous fluid such as air,
on one streamline, through $M_1$ and $M_2$ and neglecting the effect of
gavity is

$$\frac{P_1}{\rho_1} + \frac{1}{2} V_1^2 = \frac{P_2}{\rho_2} + \frac{1}{2} V_2^2 \quad (A3)$$

Because air is compressible, we need to consider the heat kinematic
ratio $\gamma/\gamma - 1$. If we set the kinematic heat ratio $K$ as $K = \gamma/\gamma - 1$,
then we can rewrite $Eq. A3$ as

$$\frac{P_1}{\rho_1} + \frac{1}{2} V_1^2 = \frac{P_2}{\rho_2} + \frac{1}{2} V_2^2 \quad (A4)$$

Because the path of the upper airway is short, we may assume
$\rho_1 = \rho_2 = \rho$. We can then rearrange $Eq. A4$ as

$$P_1 - P_2 = \frac{P}{2K} (V_2^2 - V_1^2) \quad (A5)$$

Substituting $V_1^2$ from $Eq. A2$

$$P_1 - P_2 = \frac{P}{2K} (\Omega^2 V_2^2 - V_2^2) \quad (A6)$$

Solving for $V_2^2$:

$$V_2^2 = 2K \frac{(P_1 - P_2)}{\rho(1 - \Omega^2)} \quad (A7)$$

Squaring both sides of $Eq. A1$, we can obtain the flow squared at point
$M_2$:

$$F^2 = \rho^2 A_2^2 V_2^2 \quad (A8)$$

Substituting for $V_2^2$ from $Eq. A7$:

$$F^2 = \frac{2P A_2^2 K}{(1 - \Omega^2)} (P_1 - P_3) \quad (A9)$$

Rearranging:

$$F^2 = \frac{2P A_2^2 K}{(1 - \Omega^2)} \frac{P_1 - P_3}{P_3} \quad (A10)$$

Taking the square root of both sides of $Eq. A10$, we obtain

$$F = \left[ \frac{2P A_2^2 K}{(1 - \Omega^2)} \right]^{1/2} \frac{1}{P_3} \left[ \frac{P_1 - P_3}{P_3} \right]^{1/2} \quad (A11)$$

Let

$$G = \left[ \frac{2P A_2^2 K}{(1 - \Omega^2)} \right]^{1/2} \quad (A12)$$

Therefore, flow through a streamline between two points, $M_1$ and $M_2$,
is given by

$$F = G \left[ \frac{P_1 - P_3}{P_3} \right]^{1/2} \quad (A13)$$

Because the flow is adiabatic, the first law of ideal gas, pressure is
proportional to volume, can be applied ($V_0$ is volume)

$$\frac{P_1}{P_2} = \frac{V_0_1}{V_0_2} \quad (A14)$$
Volume is the integral of flow by time:

\[ V_0 = \int F \, dt = Ft \]  

(A15)

Substitute Eq. A15 into Eq. A14:

\[ F = G \left( 1 - \frac{F_{o2}}{F_{t1}} \right)^{1/2} \]  

(A16)

where \( t_1 \) is the reference time and \( t_2 \) is the time at which flow is measured. For a short path, we make the assumption that \( F_1 = F_2 \).

Therefore,

\[ F = G \left( 1 - \frac{t_1}{t_2} \right)^{1/2} \]  

(A17)

Using Newton’s expansion law

\[(1 + x)^n = 1 + nx + \frac{n(n-1)}{2!} x^2 + \frac{n(n-1)(n-2)}{3!} x^3 + \ldots \]

we obtain

\[ F = G + \frac{G}{2t_1} + \frac{G}{8t_1^2} + \frac{3G}{48t_1^3} + \ldots \]  

(A18)

If we let

\[ A = \frac{3G}{48t_1}, \quad B = \frac{G}{8t_1}, \quad C = \frac{G}{2t_1}, \quad D = G \]

we can then substitute these coefficients into Eq. A18 to get a polynomial function that approximates flow in terms of the inspiratory time. For this function, we assume that \( t_1 \) is reference time, which is a constant, and \( t_2 = t \). which now define as the time at which flow is measured:

\[ F(t) = A t^2 + B t^2 + C t + D \]  

(A19)

With regards to the measurement of resistance, consider the compressible flow polytrophic cycle with constant specific heat or air

\[ PV_{h} = C_o \]  

(A20)

where \( C_o \) is a constant. For an ideal gas, \( M = 1 \). Therefore, Eq. A20 can be arranged as follows:

\[ P = \frac{C_o}{V_o} \]  

(A21)

Substituting Eq. A15 into Eq. A21:

\[ P = \frac{C_o}{F_t} \]  

(A22)

Divide both sides of Eq. A22 by \( F \)

\[ P = \frac{C_o}{F_t} \frac{F}{F} \]  

(A23)

Because resistance is pressure divided by flow,

\[ R = \frac{C_o}{F_t} \]  

where \( F \) is the flow at the end of the linear portion of the inspiratory pressure-flow curve (see Fig. 2) and \( t \) is the time at that point in inspiration.

REFERENCES