A mathematical model to detect inspiratory flow limitation during sleep

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Mansour, Khaled F., James A. Rowley, A. A. Meshenish, Mahdi A. Shkoukani, and M. Safwan Badr. A mathematical model to detect inspiratory flow limitation during sleep. J Appl Physiol 93: 1084–1092, 2002.—The physiological significance of inspiratory flow limitation (IFL) has recently been recognized, but methods of detecting IFL can be subjective. We sought to develop a mathematical model of the upper airway pressure-flow relationship that would objectively detect flow limitation. We present a theoretical discussion that predicts that a polynomial function \( F(P) = aP^3 + bP^2 + cP + d \), where \( F(P) \) is flow and \( P \) is supraglottic pressure, best characterizes the pressure-flow relationship and allows for the objective detection of IFL. In protocol 1, step 1, we performed curve-fitting of the pressure-flow relationship of 20 breaths to 5 mathematical functions and found that highest correlation coefficients \( R^2 \) for quadratic \((0.88 \pm 0.10)\) and polynomial \((0.91 \pm 0.05)\; (P < 0.05) \) for both compared with the other functions (functions). In step 2, we performed error-fit calculations on 50 breaths by comparing the quadratic and polynomial functions and found that the error fit was lowest for the polynomial function \((3.3 \pm 0.06 \text{ vs. } 21.1 \pm 19.0\%; P < 0.001)\). In protocol 2, we performed sensitivity/specificity analysis on two sets of breaths (50 and 544 breaths) by comparing the mathematical determination of IFL to manual determination. Mathematical determination of IFL had high sensitivity and specificity and a positive predictive value \( (>99\%) \) for each. We conclude that a polynomial function can be used to predict the relationship between pressure and flow in the upper airway and objectively determine the presence of IFL.

A steady flow-limitation events have been associated with excessive daytime sleepiness (5) and changes in blood pressure (6), which are clinical and physiological responses that have also been noted with apneas and hypopneas. In addition, our research laboratory has shown that the presence of IFL in otherwise apparently normal subjects can predict different responses to mechanical and chemical interventions during sleep (2, 4).

The increasing clinical and physiological significance of the presence of IFL necessitates that there be an objective and reproducible method to detect IFL. Investigators have shown that flow-limitation events can be detected without esophageal manometry (1, 7), but the detection of flow-limitation in these studies is based on visual inspection of the flow contour only, increasing the potential for a subjective interpretation of the data. In studies from our laboratory, we have determined whether a breath demonstrates IFL by either visual analysis (2) or manual analysis of the pressure-flow loop (Fig. 1; see METHODS for definitions) (4, 17). Manual analysis of the pressure-flow loop is a time-consuming task, and, despite a clear definition of IFL, we have found there to be frequent interscorer differences in determining whether a breath demonstrates IFL and that some breaths are not easily characterized as either IFL or noninspiratory flow limited (NIFL). We hypothesized that a mathematical model may provide a method for the objective detection of IFL. Previous investigators have shown that the pressure-flow relationship of the upper airway can be modeled mathematically (9, 16, 20), but these investigators did not specifically develop a model to detect flow limitation. Therefore, the objective of the work presented in this paper was to develop a mathematical model of the pressure-flow relationship in the upper airway that would detect flow limitation with precision, objectivity, and reproducibility.

Theory and Hypothetical Considerations

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 that 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

$$F = \rho_1 A_1 V_1 = \rho_2 A_2 V_2$$

(1)

Solving for $V_1$

$$V_1 = \frac{\rho_2 A_2}{\rho_1 A_1} V_2 = \Omega V_2$$

(2)

where

$$\Omega = \frac{\rho_2 A_2}{\rho_1 A_1} = \frac{A_2}{A_1}$$

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

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

(3)

Because air is a compressible, we need to consider the heat kinematic ratio $\gamma/\gamma - 1$. If we set the kinematic heat ratio as $K = \gamma/\gamma - 1$, then we can rewrite Eq. 3 as

$$K \frac{P_1}{\rho_1} + \frac{1}{2} V_1^2 = K \frac{P_2}{\rho_2} + \frac{1}{2} V_2^2$$

(4)

Because the path of the upper airway is short, we may assume $\rho_1 \approx \rho_2 = \rho$. We can then rearrange Eq. 4 as

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

(5)

Substituting $V_1^2$ from Eq. 2

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

(6)

Solving for $V_2^2$

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

(7)

Squaring both sides of Eq. 1, we can obtain the flow squared at point $M_2$

$$F^2 = \rho^2 A_2^2 V_2^2$$

(8)

Substituting for $V_2^2$ from Eq. 7

$$F^2 = \frac{2\rho A_2^2 K}{(1 - \Omega^2)} \left( P_1 - \frac{P_2}{P_2} \right)$$

(9)

Rearranging

$$F^2 = \frac{2\rho A_2^2 K}{(1 - \Omega^2)} P_1 \left( 1 - \frac{P_2}{P_1} \right)$$

(10)

By taking the square root of both sides of Eq. 10, we obtain

$$F = \frac{(2\rho A_2^2 K P_1)^{\frac{1}{2}}}{(1 - \Omega^2)} \left( 1 - \frac{P_2}{P_1} \right)^{\frac{1}{2}}$$

(11)

Let

$$G = \frac{(2\rho A_2^2 K P_1)^{\frac{1}{2}}}{(1 - \Omega^2)^{\frac{1}{2}}}$$

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

$$F = G \left( 1 - \frac{P_2}{P_1} \right)^{\frac{1}{2}}$$

(12)

With the use of 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

$$F = G + \frac{G}{2P_1} P_2 + \frac{G}{8P_1^2} P_2^2 + \frac{3G}{48P_1^3} P_2^3 + \ldots$$

(13)

If we let

$$A = \frac{3G}{48P_1^3}, \quad B = \frac{G}{8P_1^2}, \quad C = \frac{G}{2P_1}, \quad D = G$$
functions to mathematically model the upper airway pressure in IFL breaths. This is because, for IFL breaths, the polynomial function is characterized by two deflections (Max and Min), whereas the quadratic function is characterized by one deflection (Max).

Per Newton’s expansion law, the relationship between pressure and flow could also be predicted by a quadratic equation

\[ F(P) = AP^2 + BP + C \]  

(15)

However, the nature of a polynomial function predicts that a polynomial function would be expected to better estimate the pressure-flow relationship than the quadratic function for flow-limited breaths. This is because, for IFL breaths, the polynomial function is characterized by two deflections, as illustrated in Fig. 2. A two-deflection relationship will better approximate the measured pressure-flow relationship of IFL breaths, which are characterized by a point of maximum flow, followed by a decrease and plateau in flow (Fig. 1). The quadratic function, however, is characterized by only one deflection (see Fig. 2) and, therefore, is not as closely approximate the measured pressure-flow relationship of IFL breaths.

While performing the initial curve-fitting analysis (see METHODS), we noted that the nature of the polynomial function, in contrast to the quadratic function, would allow for the objective differentiation of IFL and NIFL breaths. In particular, we noted that for the polynomial function, the maximal flow of the predicted relationship usually was at the same pressure as the measured maximal flow. In contrast, the predicted maximal flow for the quadratic function would be at a more negative pressure. To objectify these observations, we hypothesized that we could determine the presence of flow limitation by examining a derivative of the polynomial function, which is represented by the slope of the pressure-flow relationship. The derivative of the polynomial function is

\[ \frac{dF}{dP} = 3AP^2 + 2BP + C \]  

(16)

Theoretically, for NIFL breaths, flow would continue to increase beyond the point of maximal flow if there were further decreases in supraglottic pressure. Therefore, the derivative of the polynomial function (or the slope of the pressure-flow curve) at the actual maximal flow is negative. This is illustrated in Fig. 3A, which shows a NIFL breath (solid line) and the theoretical relationship by using the polynomial function (dashed line). At the measured maximal flow, the slope of the theoretical pressure-flow relationship is negative, as illustrated in Fig. 3B. However, for breaths that demonstrate IFL, there are no further increases in flow despite decreases in supraglottic pressure (Fig. 3C). Therefore, the slope or derivative of the polynomial function at the measured maximal flow is either zero or positive for flow-limited breaths (Fig. 3D). Therefore, at maximal flow, two cases can be determined from Eq. 15. If 1) \( \frac{dF}{dP} < 0 \), the breath is NIFL; and 2) \( \frac{dF}{dP} < 0 \) or \( \frac{dF}{dP} = 0 \), the breath is IFL.

By a similar analysis, we hypothesized that the derivative of the quadratic function cannot be used to determine whether the pressure-flow relationship demonstrates flow limitation. The derivative of the quadratic function is given as

\[ \frac{dF}{dP} = 2AP + B \]  

(17)

However, if the quadratic function is used to characterize the pressure-flow relationship (dashed lines in Fig. 3, A and C), the derivative of the quadratic function cannot be used to distinguish between nonflow-limited and flow-limited breaths. This is illustrated in Fig. 3, B and D, which shows that the derivative of the quadratic equation will be negative for both types of breaths. In other words, \( \frac{dF}{dP} < 0 \) for all breaths.

In summary, theoretical considerations indicate that the relationship between flow and supraglottic pressure in the upper airway can be characterized by either a quadratic or polynomial function. However, on the basis of theoretical considerations, we hypothesized that the polynomial function was the better of the two functions to mathematically model the upper airway.
because it would provide the best fit compared with the actual pressure-flow relationship, and use of its derivative would provide an objective and accurate method for the detection of IFL.

**METHODS**

**Measurements and Manual Determination of Flow Limitation**

For each breath, airflow was measured by a pneumotachometer (model 3700A, Hans Rudolph) attached to a nasal mask. Supraglottic air pressures were measured by using 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.

The sequence of analysis is illustrated in Fig. 4. During the studies, airflow and supraglottic pressure were recorded simultaneously with Biobench data acquisition software (National Instruments, Austin, TX) on a separate computer (Fig. 4A). 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 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. A pressure-flow loop was generated (Fig. 4B), and the loop was analyzed for the presence of IFL (Fig. 1). A breath was labeled IFL if there was a ≥1 cmH2O 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.

All analyzed breaths in the following protocols were obtained during stage 2 non-rapid eye movement sleep. Breaths from wakefulness were not analyzed as IFL is not observed during wakefulness. As 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. All breaths were obtained from healthy adults with no sleep-related complaints who had volunteered for research studies in the laboratory. All subjects were free of SDB, as measured by apneas and hypopneas, on baseline polysomnography. Demographics of the subjects are presented within each protocol.

**Protocol 1: Does the Polynomial Function Best Predict the Relationship Between Pressure and Flow in the Upper Airway?**

**Step 1: curve fitting.** To model the upper airway mathematically, we performed a curve-fitting analysis with Sigma Stat 2.0 software (Figs. 4C and 5A). The purpose of this analysis was to determine which of five regression equations (Table 1) best estimated inspiratory flow (the dependent variable) as a function of supraglottic pressure (the independent variable). This process is similar to performing a linear regression, in which the predicted relationship can be given by the equation: \( F(P) = AP + B \). However, because the pressure-flow relationship is not linear, we used five nonlinear regression functions. The first two are derived from the theoretical considerations above: quadratic and polynomial. The third, a single-term hyperbolic, has previously been proposed as an accurate predictor of the pressure-flow relationship (9). In addition, we analyzed two additional functions: double-term hyperbolic and exponential (13). Neither pressure nor flow values were transformed before the curve fitting (14). This analysis was performed on 20 breaths (10 NIFL, 10 IFL) derived from four subjects (1 man, 3 women, mean age 22 ± 3 yr, mean body mass index (BMI) 23.0 ± 3.0 kg/m²). For each calculated function, we determined the coefficient of determination \( R^2 \), which indicates how much of the variability in one variable (flow) is explained by knowing the value of the other (supraglottic pressure) (12). \( R^2 \) for
IFL and NIFL breaths were compared between the five functions by using one-way repeated-measures ANOVA, with breath number as the repeated measure and the function as the factor for comparison. If there was a significant difference between the groups, a Student-Newman-Keuls test was performed to detect between-group differences, with $P < 0.05$ set as the level for a significant test. The same test was performed on the combined groups of breaths.

**Step 2: error fit.** To determine the degree of approximation between the pressure-flow relationship derived from either the quadratic or polynomial function to the actual pressure-flow relationship, we determined the error fit for 50 breaths, 25 each NIFL and IFL derived from 8 subjects (5 men, 3 women, mean age 25 ± 4 yr, mean BMI 26.2 ± 4.8 kg/m²). Only the quadratic and polynomial functions were studied on the basis of the results of the curve-fitting analysis (see results). An illustration of the concept of error fit is given in Fig. 5. The right shows the actual pressure-flow relationship for an IFL breath (solid line) and the predicted pressure-flow relationship by using the quadratic function (dashed line).
Table 1. Functions used for curve fitting

<table>
<thead>
<tr>
<th>Function</th>
<th>Equation</th>
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<tbody>
<tr>
<td>One-term hyperbolic</td>
<td>$F(P) = A\frac{P}{(B + P)}$</td>
</tr>
<tr>
<td>Two-term hyperbolic</td>
<td>$F(P) = A\frac{P}{(B + P)} + CP/ (D + P + FP)$</td>
</tr>
<tr>
<td>Exponential</td>
<td>$F(P) = Ae^{-BP} + Ce^{-DP}$</td>
</tr>
<tr>
<td>Quadratic</td>
<td>$F(P) = Ap^2 + Bp + C$</td>
</tr>
<tr>
<td>Polynomial</td>
<td>$F(P) = Ap^3 + Bp^2 + Cp + D$</td>
</tr>
</tbody>
</table>

$F(P)$, flow as a function of pressure; $A, B, C, D,$ and $F$, coefficients; $e$, exponential mathematical constant ($e = 2.78$).

The gray areas show the difference between the two relationships. The smaller the gray area, the smaller the error fit and the more closely the predicted relationship approximates the actual pressure-flow relationship. The error fit is a mathematical representation of this gray area. Mathematically, error fit is defined as

$$100\left(\sum_{i=1}^{k} 1 - \frac{y_i}{y} \right)$$

where $\sum^k_{i=1}$ is the summation of a series of points, $y_i$ represents the points in the original function, and $y$ represents the points in the fitted function (14). By using this formula, as the predicted pressure-flow relationship more closely approximates the actual relationship, the error fit or difference between the two relationships decreases. The error fit for IFL and NIFL breaths were compared between the two functions by using one-way repeated-measures ANOVA, with breath number as the repeated measure and the function as the factor for comparison. If there was a significant difference between the groups, a Student-Newman-Keuls test was performed to detect between-group differences with $P < 0.05$ set as the level for a significant test. The same test was performed on the combined groups of breaths.

Protocol 2: Does the Polynomial Function Objectively Detect Flow Limitation?

Step 1. By using the same 50 breaths with which we determined the error fit, we determined the slope of the polynomial function at the measured maximal flow for the polynomial equation (Fig. 4D). Per the hypothesis, if the slope at the measured maximal flow was < 0, we labeled the breath NIFL; if the slope at the measured maximal flow was ≥0, we labeled the breath IFL. We calculated the sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) for the detection of IFL breaths by the polynomial model compared with the standard method (described at the beginning of METHODS) with the use of standard formulas (18).

To confirm the hypothesis that the slope at the measured maximal flow for the quadratic equation would be negative for both IFL and NIFL breaths, we determined the slope at the measured maximal flow for the same 50 breaths. We report the proportion of NIFL and IFL breaths with a negative slope.

Step 2. To validate the results, we then determined the slope of the polynomial function at the measured maximal flow by using the polynomial equation for 544 randomly selected breaths from 20 subjects without SDB as measured by apneas and hypopneas (10 men, 10 women, mean age 30 ± 8 yr, mean BMI 25.2 ± 4.3 kg/m²). Applying the hypothesis, we labeled each breath as NIFL or IFL. We calculated the sensitivity, specificity, PPV, and NPV for the detection of IFL breaths by the polynomial model compared with the standard method using standard formulas (18).

RESULTS

Protocol 1

Step 1: curve fitting. The results of the curve fitting are presented in Table 2. There was a significant difference between the $R^2$ values when all the breaths are combined and for the NIFL and IFL breaths when analyzed separately ($P < 0.001$ for all three comparisons). For NIFL breaths, post hoc testing showed that $R^2$ was significantly larger for the polynomial function compared with all other functions and that the quadratic function had a larger mean $R^2$ compared with the other three functions. For IFL breaths, there was no difference in the mean $R^2$ values between the quadratic, polynomial, and double-hyperbolic functions. All three functions had larger mean $R^2$ values compared with the single-hyperbolic and exponential functions. For all breaths combined, mean $R^2$ was highest for the polynomial function; in addition, $R^2$ values were higher for the quadratic equation compared with the other three functions. In summary, the polynomial and quadratic functions had better fits to the data than the single- and double-term hyperbolic and exponential functions. Therefore, further analysis was performed only on the quadratic and polynomial functions.

Step 2: error fit. Representative graphs depicting the relationship between the actual pressure-flow curve and the curve as predicted by either the quadratic or polynomial equations for one IFL and one NIFL breath are illustrated in Fig. 3. As can be seen, there is more overlap (less error) between the actual and predicted curves for the polynomial function than for the quadratic function. For the total group of 50 breaths, the error fits for the polynomial function were smaller on average than the quadratic function for the IFL breaths (2.0 ± 2.7 vs. 25.0 ± 22.2%; $P < 0.001$), NIFL breaths (4.0 ± 7.7 vs. 16.0 ± 14.0%; $P = 0.003$), and all breaths combined (3.3 ± 0.6 vs. 21.1 ± 19.0%; $P < 0.001$).

Table 2. $R^2$ values for the various functions

<table>
<thead>
<tr>
<th></th>
<th>Quadratic</th>
<th>Polynomial</th>
<th>Single-Hyperbolic</th>
<th>Double-Hyperbolic</th>
<th>Exponential</th>
</tr>
</thead>
<tbody>
<tr>
<td>IFL breaths</td>
<td>0.85 ± 0.10</td>
<td>0.90 ± 0.06</td>
<td>0.61 ± 0.14</td>
<td>0.79 ± 0.13</td>
<td>0.55 ± 0.32</td>
</tr>
<tr>
<td>NIFL breaths</td>
<td>0.89 ± 0.06</td>
<td>0.92 ± 0.04</td>
<td>0.54 ± 0.20</td>
<td>0.79 ± 0.24</td>
<td>0.24 ± 0.24</td>
</tr>
<tr>
<td>All breaths</td>
<td>0.88 ± 0.08</td>
<td>0.91 ± 0.05</td>
<td>0.57 ± 0.17</td>
<td>0.78 ± 0.19</td>
<td>0.67 ± 0.30</td>
</tr>
</tbody>
</table>

Values are means ± SE. IFL, inspiratory flow limited; NIFL, noninspiratory flow limited. See text for statistical analysis.
In summary, in protocol 1, we showed that curve fitting the pressure-flow relationship in the upper airway will result in a tight fit (high $R^2$) of the data only for the quadratic and polynomial functions. However, when a test that determines the degree of correlation between the actual and experimental relationships (error fit) was used, only the polynomial function accurately predicts the pressure-flow relationship.

**Protocol 2**

**Step 1.** The sensitivity, specificity, PPV, and NPV for the detection of flow limitation in the initial 50 breaths by using the polynomial function is summarized in Table 3. As the table illustrates, use of the slope at maximal flow of the polynomial equation results in both high sensitivity and specificity for determination of IFL breaths. PPV and NPV were also high. For the quadratic function, we confirmed that the majority of breaths of both NIFL (24 of 25; 96%) and IFL (22 of 25; 88%) breaths had a negative slope, indicating that the quadratic function would be unhelpful in detecting IFL breaths.

**Step 2.** In the larger group of breaths, sensitivity and specificity remained high (Table 3, right column), as did PPV and NPV.

In summary, in protocol 2, we performed a sensitivity/speciﬁcity analysis of the use of polynomial function to detect IFL breaths compared with the standard method using a pressure-flow loop. This analysis indicates that the polynomial function has an excellent ability to predict the presence of flow limitation in the pressure-flow relationship. In contrast, the quadratic function cannot be used to distinguish between IFL and NIFL breaths.

**DISCUSSION**

There are two major findings of this study. First, a polynomial equation, $F(P) = AP^3 + BP^2 + CP + D$, provides an estimation of the upper airway pressure-flow relationship with relative precision compared with other mathematical equations. Second, the derivative of this equation can be used to objectively and precisely determine the presence of IFL. The main requirement for the accurate determination of IFL with the use of the polynomial function is a continuous and simultaneous measurement of flow and supraglottic pressure.

The relationship between flow and pressure in the upper airway during wakefulness was first described by Rohrer using the equation: $P = K_1V + K_2V^2$, where $V$ is flow and $K_1$ and $K_2$ are constants (16). Hudgel et al. (9) noted that the pressure-flow relationship during sleep was curvilinear and therefore less likely to be adequately described by the Rohrer equation. Instead, they determined that a hyperbolic function (see Table 1) better characterized the upper airway pressure-flow relationship during sleep, as indicated by a correlation coefficient of 0.89 compared with 0.55 for the Rohrer equation. They hypothesized that the characterization was better because the hyperbolic equation approximated the pressure-flow relationship for both NIFL and IFL breaths. Similarly, Tamisier and colleagues (20) recently found that the hyperbolic equation better characterized the pressure-flow relationship, as evidenced by larger Pearson’s square correlations for all breaths analyzed as well as for the subset of IFL breaths. In contrast, we found that a three-term polynomial function best characterized the pressure-flow relationship during sleep. In addition, we found that a hyperbolic function provided a poor characterization of the pressure-flow relationship.

There are possible explanations for the different findings. First, although the Rohrer equation is a polynomial function, it is only a two-term quadratic func-

![Graphical representation of an IFL breath (solid line) and the fitted hyperbolic function (dashed line) when flow is fit to raw pressure data.](image-url)

**Table 3. Sensitivity/speciﬁcity analysis**

<table>
<thead>
<tr>
<th></th>
<th>Development Breaths ($n = 50$)</th>
<th>Validation Breaths ($n = 544$)</th>
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</thead>
<tbody>
<tr>
<td>Sensitivity</td>
<td>100</td>
<td>99</td>
</tr>
<tr>
<td>Specificity</td>
<td>100</td>
<td>99</td>
</tr>
<tr>
<td>PPV</td>
<td>100</td>
<td>97</td>
</tr>
<tr>
<td>NPV</td>
<td>100</td>
<td>99</td>
</tr>
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PPV, positive predictive value; NPV, negative predictive value.

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tion. Our data indicate that a three-term function provides a better fit of the pressure-flow relationship than a two-term function. Neither of the previous groups tested a three-term polynomial function. Second, it should be noted that we performed our curve fitting on the raw pressure-flow data. Therefore, our pressure points were negative in value at the time of the curve fitting. The other groups used pressure values that had been transformed to positive pressures before curve fitting. The importance of this difference is illustrated in Fig. 6. As can be seen, if positive values are used for pressure values, a hyperbolic curve does closely approximate the actual pressure-flow relationship (Fig. 6B). However, if negative values are used, a hyperbolic curve does not approximate the relationship (Fig. 6A). We believe that our use of the negative values for pressure is proper because the mathematical equations for curve fitting were derived to determine the relationship between predicted and observed (or actual), not transformed, variables (14).

Limitation of Methods

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 any given breath. Nevertheless, the percentage of IFL are not known. Conversely, mathematical methods and visual methods were remarkably reproducible, indicating that our choice of parameter was valid for the recognition of the phenomenon. Our study provides an objective operational definition, which can be used in future studies to ascertain physiological relevance.

IFL in our study was evaluated as a dichotomous variable. However, deviation from linearity between flow and pressure is a continuous variable. Our method detects flow limitation as defined by a plateau in flow only; any other a linear flow profile is classified as nonflow limitation. One could argue that changes in the slope of the pressure-flow relationship indicate pharyngeal narrowing and turbulent flow. In fact, these were the breaths missed by the mathematical equation. However, we doubt the physiological significance of deviation from linearity without true flow limitation.

Finally, detection of IFL in our study required the use of supraglottic pressure measurement via a pharyngeal catheter and quantitative flow measurement with the use of a sealed mask and a pneumotachometer. This combination is rather intrusive and may not be feasible for routine clinical use. Whether IFL can be detected from the flow vs. time profile is yet to be determined.

Implications

The ability to detect IFL objectively may have significant relevance to the diagnosis of SDB. The description of UARS expanded the spectrum of SDB by including patients without episodes of apnea or identifiable hypopnea (5). The main features of UARS are the recurrent arousal due to repetitive episodes of IFL and decreases in esophageal pressure. Recent studies have shown a moderate correlation between the number of respiratory events, including periods of IFL, and daytime sleepiness (7). Unfortunately, detection of IFL was based on subjective visual detection of a square flow profile without pressure measurements. Conversely, manual analysis of the pressure-flow loop is laborious and fraught with subjective pitfalls. We have shown that the polynomial function is both highly sensitive and specific for the determination of the presence of flow limitation. Thus our method can be used on a large number of breaths in an automated fashion and may be useful in future studies that assess the relationship between SDB and other variables. For instance, we have recently shown that the percentage of breaths that are IFL is related to BMI and upper airway resistance (17) and to the presence of long-term facilitation (3). Therefore, we hypothesize 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.

REFERENCES


