A Simplified Method for Measuring Critical Pressures during Sleep in the Clinical Setting

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ABSTRACT

Upper airway critical pressure measurements correlate with the degree of upper airway obstruction during sleep, and may have a role in the diagnosis and treatment of obstructive sleep apnea. Nevertheless, the utility of the critical pressure has not yet been realized in the clinical setting because significant technical expertise is still required for the acquisition and analysis of pressure-flow data. Using segmented regression, we developed and validated a simplified approach to analyze the pressure-flow relationship and to determine the effects of protocol-related factors in forty-four subjects with sleep apnea. When compared to expert visual analysis, segmented regression methodology was found to accurately determine the critical pressure (-0.98 ± 2.47 cm H₂O vs. –1.07 ± 2.47 cm H₂O respectively; p=0.46). Furthermore, it was found that two series of measurements acquired at varying nasal pressure levels with two or more breaths per level were sufficient to determine the critical pressure with a minimum of variability. Therefore, this analytical approach has the potential for standardizing and simplifying the ascertainment of the critical pressure for studies examining the effect of therapeutic devices and agents on upper airway collapsibility during sleep.

WORD COUNT = 186

KEY WORDS: sleep apnea; critical pressure; pathophysiology; upper airway
INTRODUCTION

Obstructive sleep apnea is a common disorder characterized by repetitive collapse of the upper airway during sleep. Obstruction of the upper airway has been attributed to increased pharyngeal collapsibility that may be related to alterations in either structural and/or neuromuscular properties of the upper airway (1,2). Measurements of upper airway collapsibility (i.e. critical pressure; \( P_{\text{CRIT}} \)) have been shown to correspond with the degree of airflow obstruction in individuals who have complete, partial, or no airflow obstruction during sleep (3). These measurements may help elucidate the pathophysiology of obstructive sleep apnea, identify individuals at risk for sleep apnea, and guide therapy for the disorder (4-9).

Despite the potential, measurements of upper airway collapsibility have not yet been incorporated into clinical practice, in part because significant technical expertise is required to implement protocols for determining \( P_{\text{CRIT}} \) during sleep. The critical pressure is determined by altering nasal pressure systematically during sleep (1,2,10-14), and is defined by the nasal pressure below which the upper airway occludes and airflow ceases. Nevertheless, studies to date differ substantially in the protocol used to alter nasal pressure, and in the methods for analyzing pressure-flow data generated (see below). Thus, a lack of standards for data collection and analysis has impeded the development of uniform methods for determining critical pressures, and may introduce variability in results between study populations and sleep centers.

We have previously developed an abbreviated protocol for delineating the upper airway pressure-flow relationship in a small sample of subjects with obstructive sleep apnea (15). The protocol standardized the exposure to nasal pressure, but still required substantial expertise in the collection and analysis of pressure-flow signals for accurate determinations of \( P_{\text{CRIT}} \). Specifically, esophageal manometry and pressure-flow waveform analysis were required to
identify the subset of “flow-limited” breaths to be included in the analysis. Thus, despite standardization of the data acquisition protocol, significant expertise was still required to perform esophageal manometry and to analyze pressure-flow data.

The purpose of the present study was to develop and validate a simplified, non-invasive method to identify the flow-limited segment of the pressure-flow relationship during sleep. The flow-limited segment is characterized by a positive slope of the pressure-flow relationship, as distinguished from segments with either an indeterminate or zero slope (non-flow limited or occluded segments) (1,12). Analytic methods were developed to identify the sloped portion of the pressure-flow relationship over which the airway collapses and flow limits. It was hypothesized that the flow-limited (sloped) portion of the pressure-flow relationship can be accurately identified with the method of segmented regression (16-22), which is well suited for modeling changes in slope that correspond to distinct states of upper airway patency (occluded, flow-limited and non-flow-limited). It was further hypothesized that simplifying and standardizing methods for data acquisition and analysis would allow us to account for protocol related factors, such as the number and duration of nasal pressure levels that could increase variability in the determination of \( P_{\text{CRIT}} \).

**CONCEPTUAL BACKGROUND**

**Theoretical Approach**

The Starling resistor model has been previously utilized to describe upper airway pressure-flow relationships (1,12). As predicted by the model, the upper airway flow-limits when downstream pressure (\( P_{\text{DS}} \)) falls below the critical pressure (\( P_{\text{CRIT}} \)). Under flow-limited conditions, pressure downstream to the site of collapse no longer influences maximal inspiratory airflow. Rather, maximal inspiratory airflow varies solely with changes in the upstream nasal
pressure (23), and increases proportionately with elevations in nasal pressure, leading to a sloped pressure-flow relationship. The lower end of the flow-limited (sloped) segment is bound by $P_{\text{CRIT}}$, the nasal pressure ($P_N$) below which airflow ceases (Fig. 1, segment A). The upper end of the pressure-flow relationship is bound by the minimally effective therapeutic pressure ($P_{\text{eff}}$), the nasal pressure above which airflow limitation is abolished (Fig. 1, segment C). As nasal pressure continues to rise above the minimally effective therapeutic pressure, the downstream pressure at peak inspiration no longer falls below $P_{\text{CRIT}}$, and a flow-limited condition no longer obtains. Under these circumstances, maximal inspiratory airflow is determined by the gradient, $P_N - P_{DS}$, which remains relatively constant during stable non-rapid eye movement (NREM) sleep, over a wide range of nasal pressures (24, 25).

The flow-limited segment of the pressure-flow relationship is utilized to define the critical pressure as the nasal pressure at which airflow ceases. The critical pressure is derived from linear regression of the data comprising the flow-limited segment (Fig 1, segment B).

Using previously described methods for data acquisition (15), we assessed maximal inspiratory airflow through the upper airway during sleep over a range of nasal pressures. Discrete levels of nasal pressure were set (bins) and maximal airflows were measured for several breaths at each nasal pressure level.

**Analytical Approach**

*Segmented Regression Analyses:* Previous investigators have analyzed pressure-flow waveforms on a breath-by-breath basis to isolate the subset of flow-limited breaths. Rather than relying on visual inspection, we isolated the flow-limited segment by detecting the range of nasal pressures over which inspiratory airflow amplitudes markedly varied. Relationships that demonstrated
sudden changes in slope on either side of an inflection point were modeled using segmented regression (16-22). We therefore employed segmented regression to model the discrete changes in upper airway patency produced by changes in nasal pressure between the upper and lower inflection points of the sloped (flow-limited) segment. The following approach was employed to define the upper and lower inflection points of the flow-limited segment:

1) The median maximal inspiratory airflow ($V_{I\text{max}}$) and $P_N$ of each established nasal pressure bin were determined and the slope between adjacent pressure bins was calculated using linear regression. Median values of $V_{I\text{max}}$ and $P_N$ were chosen for regression analyses in order to minimize influence from outliers.

2) The lower inflection point (near $P_{\text{CRIT}}$) of the pressure-flow relationship was established by determining the nasal pressure at which airflow and the slope approached zero (see Methods below). The lower inflection point was determined by examining pressure bins sequentially (from left to right) until the following criteria were met:
   a. The slope of the segment above the pressure bin was greater than a parameter defined as the “required minimal slope”,
   b. The slope of the segment below the pressure bin was less than the required minimal slope, and
   c. The median airflow for the pressure bin was below a parameter defined as “the no-flow threshold”.

3) The upper inflection point (minimally effective therapeutic pressure; $P_{\text{eff}}$) of the pressure-flow relationship was established by analyzing sequential slopes of segments from left to right. The upper inflection point was determined as the nasal pressure bin at which the slope became minimal using the following criteria:
a. The slope of the segment above the pressure bin was less than the required minimal slope, and

b. The slope of the segment below the pressure bin was more than the required minimal slope.

4) Once the upper and lower boundaries of the flow-limited (sloped) segment were identified, median pressure and airflow measurements from each intervening bin were used to obtain the upstream resistance ($R_{US}$) and $P_{CRIT}$.

*Modeling the flow-limited segment* (see Online Supplement for details): Measurements of pressure and flow within the flow-limited region were modeled with the following linear regression equation:

$$\left( V_{I \text{ max}} \right)_j = \beta_0 + \beta_1 (P_N)_j + \varepsilon_j \text{ (equation 2).}$$

In this equation, $V_{I \text{ max}}$ and $P_N$ measurements at nasal pressure level $j$ are represented, while $\varepsilon_j$ represents the standard error around the mean airflow for a given nasal pressure level $j$. $P_{CRIT}$ was determined by the ratio, $-\beta_0/\beta_1$ (where $\beta_0$ represents $V_{I \text{ max}}$ when $P_j$ is zero and $\beta_1$ is the mean change in $V_{I \text{ max}}$ for a 1 cm H$_2$O increase in $P_j$), and $R_{US}$ was determined by $1/\beta_1$. This relationship was used to determine $P_{CRIT}$ and $R_{US}$ for each subject. In the data collection protocol, repeated measurements of maximal inspiratory airflow were obtained for several breaths at each pressure level. To account for the correlation between repeated measurements within an individual, model fitting was performed using the techniques of regression analysis for repeated measures (26).
METHODS (WORD COUNT = 706)

Patient Recruitment

Forty-four subjects with obstructive sleep apnea (apnea-hypopnea index ≥ 20
events/hour) presenting for continuous positive airway pressure (CPAP) titration were studied.
Sleep apnea severity was determined by overnight polysomnography as previously described
(27). Subjects were divided consecutively between a development sample (Sample A; n=30) and
a validation sample (Sample B; n=14). The study was approved by the institutional review board
on human research.

Experimental Protocol

Patients underwent polysomnography with pressure and airflow measurements monitored
via a tight-fitting nasal mask and respiratory effort monitored through the use of piezoelectrode
abdominal and thoracic strain gauges (14). Patients slept in the supine position with one pillow
under their head.

During sleep, nasal pressure ($P_N$) was maintained at a holding pressure that eliminated
flow limitation (15). Nasal pressure was abruptly lowered for five breaths (a run) through a
remote control device attached to a CPAP unit designed to apply pressures between –20cm to
+ 20cmH2O. Three series of stepwise reductions in nasal pressure that encompassed zero
airflow ($P_{CRIT}$) were collected (Fig. 2). If an arousal occurred, the protocol was resumed after
patients reinitiated stage II – IV NREM sleep. Breaths associated with micro-arousals from sleep
were excluded from analyses.
A recording example of pressure-flow measurements is shown in Fig 3a for one series of runs at several nasal pressure levels during stable NREM sleep, with corresponding median \( V_{\text{max}} \) vs. \( P_N \) plot (Fig 3b). Maximal inspiratory airflow was measured as the difference in inspiratory flow maximum and the zero or mean airflow level (average airflow between the peak expiratory flow of breaths) during a run. A \( V_{\text{max}} \) vs. \( P_N \) plot was generated for each subject.

**Sensitivity Analyses**

Results of the segmented regression analyses for each individual were compared against the visual identification approach of identifying the flow-limited segment. Two experts (HS and AS) independently examined each pressure-flow curve, and identified the flow-limited segment. Separate analyses were undertaken to compare values of \( P_{CRIT} \) and \( R_{US} \) obtained from an analysis of: (a) only flow-limited breaths, based on established criteria (28,29), and from an analysis of: (b) all flow-limited and non-flow limited breaths. If significant differences in \( P_{CRIT} \) or \( R_{US} \) were not detected between these analytic methods, we concluded that flow-limited breaths need not have been identified visually, and that the detection and analysis of the flow-limited segment could be automated.

Sensitivity analyses were performed to optimize thresholds for the minimal slope and no-flow criteria by testing specific combinations of different thresholds on Sample A only. Comparison of segmented regression to expert visual identification demonstrated that a minimal slope criterion of 20 ml/s/cm H\(_2\)O and a no-flow threshold of 50 ml/s had the greatest levels of agreement (see Online Supplement, section B). The selected criteria were used to determine \( P_{CRIT} \) and \( R_{US} \) in both samples using segmented regression and prospectively validated in Sample B only.
Effects of Protocol-Related Factors on the Upper Airway Pressure-Flow Relationship

In order to standardize methods for data acquisition and analysis, analyses were performed to account for protocol-related factors, including the number of runs and duration of nasal pressure levels (number of breaths) that could increase variability in the determination of the critical pressure. Differences in the pressure-flow relationship among the five breaths during each run were examined. The PROC MIXED procedure (SAS Software, Inc.; Version 8.2) was used to estimate the parameters of interest in equation 3 (see Online Supplement, section A), while accounting for autocorrelation in the data (25). The minimum number of series of pressure-flow measurements necessary to accurately determine $P_{CRIT}$ was investigated. Segmented regression analysis was performed repeatedly after adding series of pressure-flow data sequentially (i.e. series 1, series 1 and 2, series 1 – 3). Results of the segmented regression analysis were then compared to the expert visual analysis of all 3 series with Bland-Altman plots of $P_{CRIT}$.

Statistical Analyses

Values are reported as mean ± standard deviation (SD). Paired t-test was performed to identify significant differences, between a) segmented regression analyses and expert visual analyses and between b) results obtained from the visual analysis of only flow-limited breaths compared to the automated analysis of all flow-limited and non-flow limited breaths. Bland Altman analyses (30) were performed to determine whether systematic differences existed between measurements of $P_{CRIT}$ from the expert visual and segmented regression analyses.
RESULTS

Forty-four subjects with obstructive sleep apnea were studied and divided between a development (sample A) and validation sample (sample B). The first 30 patients (sample A) were used to determine the minimal slope criteria and no-flow threshold criteria, while the final 14 patients (sample B) were used to validate the selected criteria. Patient characteristics of the development and validation samples were comparable in age (48.3 ± 9.8 vs. 47.4 ± 8.9 years); body-mass index (BMI) (36.6 ± 6.7 vs. 35.9 ± 9.1 kg/m²), non-rapid eye movement (NREM) apnea-hypopnea index (AHI) (68.3 ± 27 vs. 75.1 ± 31.6 events/hour), and gender (73.3 vs. 85.7% male). There were no significant differences in characteristics between the two groups. The median duration of time required to acquire pressure-flow data on each individual was 43.5 minutes (inter-quartile range: 30.0 – 68.8 minutes). The median number of runs required to obtain the three series of pressure-flow data was 17 runs (inter-quartile range: 14 – 23 runs). The median number of arousals during acquisition of data was 3 (inter-quartile range: 1 – 7).

For each patient, individual pressure-flow relationships were constructed. In the segmented regression analyses of patients in sample A, a minimal slope criterion of 20 ml/s/cm H₂O and a no-flow criterion of 50 ml/s demonstrated the greatest agreement in \( P_{CRIT} \) and \( P_{eff} \) with the expert visual analysis (see Online Supplement, Table E1 and E2). Using the identified criteria, we compared the expert visual analysis to the segmented regression analyses, and found no significant difference in \( P_{CRIT} \) (-0.98 ± 2.47 cm H₂O vs. -1.07 ± 2.47 cm H₂O; \( p=0.46 \)), \( P_{eff} \) (6.60 ± 3.49 cm H₂O vs. 6.92 ± 3.37 cm H₂O; \( p=0.40 \)) and \( R_{US} \) (17.28 ± 9.65 cm H₂O/ml/s vs. 17.25 ± 8.28 cm H₂O/ml/s; \( p=0.97 \)) respectively, between the two methods within Sample A. Bland-Altman plot is illustrated for Sample A in figure 4A. The plot demonstrates that the \( P_{CRIT} \) derived by the segmented regression analyses did not differ systematically from that derived by
the expert visual analysis (mean difference 0.09 cm H$_2$O; 95% confidence intervals [CI]: -0.15 to 0.32 cm H$_2$O) and that the limits of agreement were narrow (lower limit of agreement –1.18 cmH$_2$O [95% CI: -1.59 to –0.77 cm H$_2$O] and upper limit of agreement 1.35 cm H$_2$O [95% CI: 0.94 to 1.76 cm H$_2$O]). Outliers generated from the segmented regression were minimal.

The selected minimal slope and no flow criteria were then validated in Sample B. Comparison of the expert visual with the segmented regression analyses revealed no significant difference in $P_{CRIT}$ (-0.70 ± 3.07 cm H$_2$O vs. –0.76 ± 3.12 cm H$_2$O; $p=0.78$), $P_{eff}$ (7.56 ± 4.65 cm H$_2$O vs. 7.91 ± 4.21 cm H$_2$O; $p=0.17$) and $R_{US}$ (16.32 ± 10.07 cm H$_2$O/ml/s vs. 16.73 ± 9.90 cm H$_2$O/ml/s; $p=0.52$) respectively. Comparison of $P_{CRIT}$ determinations in sample B between the segmented regression method and expert visual analysis also demonstrated no significant systematic difference exists between the two methods (mean difference 0.06 cm H$_2$O; 95% CI: -0.40 to 0.52 cm H$_2$O), and that the limits of agreement were narrow (lower limit of agreement –1.54 cmH$_2$O [95% CI: -2.35 to –0.74 cm H$_2$O] and upper limit of agreement 1.66 cm H$_2$O [95% CI: 0.86 to 2.47 cm H$_2$O]) with only one outlier detected in the Bland-Altman analysis (figure 4B). Analyses were also performed in both samples to compare differences in $P_{CRIT}$ and $R_{US}$ obtained when using all breaths (flow-limited and non-flow limited) against flow-limited breaths only. No significant differences in $P_{CRIT}$ (difference of –0.2 cm H$_2$O; $p = 0.12$) or $R_{US}$ (difference of -0.03; $p = 0.97$) were found in these analyses.

The influence of protocol-related factors on the upper airway pressure-flow relationship for the entire group was then examined. In Table 1, inter-breath differences in airflow across the five breaths after abruptly lowering nasal pressure are presented. For example, the change in $V_{Imax}$ between breaths one and five was 36.7 ml/s, while the change in $V_{Imax}$ between breaths two and five was 16.5 ml/s. For the entire study sample, Table 1 shows that for a given level of
nasal pressure, maximal inspiratory airflow progressively decreased from the first to fifth breath, following a step-wise reduction in nasal pressure. However, no statistically significant differences in $V_{t,\text{max}}$ were detected after the first breath following a drop in nasal pressure, suggesting that on average, a quasi-steady state level of airflow had occurred by the second breath.

Subsequently, the minimum number of series of pressure-flow data necessary to accurately determine $P_{\text{CRIT}}$ was determined in the subset of subjects with at least three series of measurements ($n=34$). Bland-Altman plots did not reveal any significant systematic differences between the two measurement methods for one series, two series, or three series of pressure-flow measurements. Qualitative inspection of Bland-Altman analyses, however, demonstrated a narrower reference range ($\pm 2 \text{ SD}$) for between-paired measurements (3.9 cm H$_2$O vs. 5.8 cm H$_2$O) for two series compared to one series of pressure-flow measurements, respectively. In addition, a lower mean difference in between-paired measurements (-0.03 cm H$_2$O vs. –0.3 cm H$_2$O) was determined for two series compared to one series of pressure-flow measurements, respectively. No additional improvement in the determination of $P_{\text{CRIT}}$ with three series was evident based on visual inspection (see Figure 5A-C), suggesting that a minimum of two series of pressure-flow measurements, which include inspiratory flows below 50 ml/s were necessary to accurately determine $P_{\text{CRIT}}$. 
DISCUSSION

The objective of the current study was to develop a systematic approach for the acquisition and analysis of pressure-flow data used for determining critical closing pressures during sleep. A simplified non-invasive approach to the assessment of upper airway pressure-flow relationship was presented and provides a valid analytic method to identify the subset of measurements that describe the functional properties of the upper airway. A major finding of the present study was that segmented regression techniques could accurately identify the flow-limited segment, and that $P_{CRIT}$ values based on automated analysis did not differ from those determined by expert visual observations. The results of this study also illustrate that a quasi-steady state in the pressure-flow relationship was established within two breaths following changes in nasal pressure. Finally, the analyses demonstrate that at least two series of pressure-flow data were required to accurately assess $P_{CRIT}$. Collectively, our results of this study provide a systematic approach for the acquisition and analysis of pressure-flow data used in determining critical pressures during sleep.

Our approach to analyzing the pressure-flow relationship was chosen based on fundamental concepts regarding the pathophysiology of airflow obstruction in obstructive sleep apnea. As the nasal pressure is raised progressively in a patient with an occluded upper airway, three distinct states of upper airway patency have been observed (1,12,23,25). Airflow ceases (the airway occludes) when nasal pressure is less than $P_{CRIT}$, increases linearly during flow-limited breathing as pressure is raised above $P_{CRIT}$, and becomes indeterminate with further increases in nasal pressure (above $P_{eff}$) once flow-limitation is abolished. Although a continuous sigmoid function could describe the pressure-flow relationship, it would not have been
appropriate since discrete states of upper airway occlusion, flow-limitation, and non-flow-limited breathing would not be modeled, as predicted by the Starling resistor model (31-33).

A further advantage of our analytical approach was that it allowed us to probe for methodological and physiologic sources of variability in critical pressure determinations. Statistical methods were utilized to model repeated measures of breaths at each nasal pressure level, along with summary statistics (e.g. median flow) to characterize the pressure-flow relationship. We found that two complete series of pressure-flow data were sufficient to accurately determine $P_{\text{CRIT}}$, and that a third series did not further increase our accuracy. In contrast, investigators have previously chosen the number of runs and series to be acquired (13-15,34), which may have differed substantially within and between studies. Such differences may have influenced the accuracy and precision of $P_{\text{CRIT}}$, and may lead to bias in the estimates of $P_{\text{CRIT}}$. Our methods also allowed us to account for breath effects which may be secondary to changes in lung volumes (35-37). Others and we have previously shown critical pressures to decrease over several breaths during each run (14,38,39). In the repeated measures analyses examining the effect of successive breaths on $P_{\text{CRIT}}$, no statistically significant differences in maximal inspiratory airflow were found after the first breath, suggesting that changes in lung volume following the second breath are either negligible or had minimal influence on upper airway properties.

A major focus of the present study was to develop an approach that minimized the technical expertise required for the collection and analysis of pressure-flow data without compromising our ability to accurately determine the critical pressure. In previous studies, laborious methods were employed to ensure that sufficient flow-limited breaths were available to delineate the entire pressure-flow relationship. Esophageal manometry and visual inspection of
pressure-flow waveforms (1,12,15,23,39) were required to extract the subset of flow-limited data to be used in determining $P_{CRIT}$. Investigators frequently had to acquire additional pressure-flow data to ensure that sufficient flow-limited breaths would be ultimately available for analysis. In contrast, we implemented a uniform collection protocol that did not require invasive monitoring of esophageal pressure, which can disrupt sleep. We found that a complete data set could be obtained with only two series of runs over less than one hour of sleep data acquisition, and that $P_{CRIT}$ could be accurately identified with segmented regression analysis without pre-selecting flow-limited breaths for analysis. Thus, our analytical approach eliminated the need for invasive monitoring of esophageal pressure, further simplified the data acquisition protocol, and reduced the technical expertise required for identifying the flow-limited segment and determining the critical pressure.

Several pitfalls should be acknowledged that might limit the implementation of the present approach in the clinical setting. First, the acquisition protocol required complete polysomnography and quantitative measurements of airflow and nasal pressure to generate pressure-flow data for analysis. Nevertheless, equipment for monitoring pressure and airflow are currently supported by many CPAP devices and polysomnographic recording systems. Second, personnel needed to be trained to detect stable sleep and micro-arousals in real time during data acquisition. Third, esophageal manometry was not utilized to identify flow-limited breaths, which might have allowed for more accurate identification of flow-limited breaths. Nevertheless, reliable methods for determining the presence of flow limitation based on visual inspection of flow waveforms have been established (28,29). No significant differences in critical pressure were found when the technique of segmented regression was applied to data sets that included all flow-limited and non-flow-limited breaths or only flow-limited breaths. Further development of
automated procedures for sleep stage monitoring and the detection of flow limitation on a breath-by-breath basis may overcome these limitations, and more fully automate methods for determining the critical pressure in the clinical setting.

A potential limitation of the current methodology is that we based our analysis on pressure-flow measurements generated under hypotonic conditions (14). Critical pressures measured with this protocol are primarily thought to reflect the influence of anatomic factors on upper airway collapsibility. Previously, investigators have demonstrated that critical pressures in normal individuals may be somewhat higher (less negative) under hypotonic conditions (13) than those determined under state conditions of intact neuromuscular activity (12). In contrast, the critical pressure under hypotonic conditions in our population of sleep apnea subjects appear to be remarkably similar to those described in the atonic state by Isono and colleagues (2). Thus, our protocol may be useful in examining the anatomic correlates of upper airway collapsibility that are seen in different populations (e.g. men vs. women) (40), however, our analyses will need to be extended to steady-state pressure-flow relationships assessed when neuromuscular activity is intact.

Our findings have several implications for investigators seeking to characterize upper airway pressure-flow relationships and determine critical closing pressures during sleep. First, an abbreviated protocol has been established for generating upper airway pressure-flow relationships, and consists of two series of step-wise reductions in nasal pressure for at least two breaths at each pressure level. Since less than one hour was required to obtain two series of runs, our findings indicate that upper airway function can be accurately characterized in the clinical setting during a routine CPAP titration study. Second, technical expertise in the recognition of flow-limited breaths is no longer required to determine the critical pressure, thereby simplifying
the analysis of acquired data to determine the critical pressure and the minimally effective therapeutic pressure. Third, standardizing the data acquisition and analytic methods for determining critical pressures lays the foundation for future studies examining measurements of upper airway collapsibility across clinical populations and centers. In particular, the analytical methods have potential applications for clinical trials examining the effect of therapeutic devices and pharmacologic agents on upper airway collapsibility during sleep. Finally, the minimally effective therapeutic pressure could be automatically determined from the pressure-flow relationship, and might be used during nasal CPAP titration in sleep apnea patients. Further work is required to compare results obtained with the presented approach across study centers and cohorts.
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Reference List


The male predisposition to pharyngeal collapse: importance of airway length. Am J 
Respir Crit Care Med 2002; 166(10):1388-1395.
Figure Legends

Figure 1: Theoretical plot of maximal inspiratory airflow ($V_{\text{Imax}}$) vs. nasal pressure ($P_N$) illustrating three distinct regions of the pressure-flow relationship as predicted by the Starling resistor model: an occluded (Fig. 1, segment A), a flow-limited (Fig. 1, segment B), and a non-flow limited segment (Fig. 1, segment C). The flow-limited segment is bounded by the critical pressure ($P_{\text{CRIT}}$) and by the minimally effective therapeutic pressure ($P_{\text{eff}}$).

Figure 2: The protocol for obtaining pressure-flow data is illustrated. Subjects are maintained at a “holding pressure” sufficient to eliminate apnea, hypopneas, or flow-limitation. Nasal pressure was abruptly reduced in a step-wise fashion for five breaths before returning to the holding pressure. Reductions in nasal pressure were repeated at one-minute intervals for $j$ pressure levels (runs) for $k$ breaths over a range that included zero airflow for at least three series of pressure-flow data. $j, j+1, j+2, j+3$ represent successive reductions in nasal pressure or runs.

Figure 3: (A) Example recording of one series of runs in a representative subject during NREM sleep. Flow limitation and progressive reductions in airflow are evident with step-wise reductions in nasal pressure. (B) $V_{\text{Imax}}$ vs. $P_N$ for the series displayed is plotted using all breaths. Values of slopes for consecutive pressure bins connected by (---) are shown. The solid line (—) is the regression slope of the flow-limited segment of the pressure-flow relationship bounded by the minimally effective therapeutic pressure ($P_{\text{eff}}$) and the critical pressure ($P_{\text{CRIT}}$), determined by segmented regression analysis using a minimal slope and no-flow criterion. Values on graph represent the slope of the individual segment.
Figure 4: Bland-Altman plot is presented comparing measurements of $P_{\text{CRIT}}$ by the segmented regression analyses with the expert visual identification analyses for (A) sample A (mean difference 0.09 cm H$_2$O [95% CI: -0.15 to 0.32 cm H$_2$O]; limits of agreement –1.18 cmH$_2$O [95% CI: -1.59 to –0.77 cm H$_2$O] to 1.35 cm H$_2$O [95% CI: 0.94 to 1.76 cm H$_2$O]) and (B) sample B (mean difference 0.06 cm H$_2$O [95% CI: -0.40 to 0.52 cm H$_2$O], and that the limits of agreement were –1.54 cmH$_2$O [95% CI: -2.35 to –0.74 cm H$_2$O] to 1.66 cm H$_2$O [95% CI: 0.86 to 2.47 cm H$_2$O]).

Figure 5: Bland-Altman plots are presented for $P_{\text{CRIT}}$ from consecutive series by the segmented regression method vs. expert visual analyses (A) 1 series (mean difference 0.31 cm H$_2$O [95% CI: -0.20 to 0.82 cm H$_2$O]; limits of agreement –2.60 [95%CI: -3.49 to –1.73 cm H$_2$O] to 3.23 [95% CI: 2.35 to 4.11 cm H$_2$O]), (B) 2 series (mean difference – 0.03 cm H$_2$O [95% CI: -0.37 to 0.32 cm H$_2$O]; limits of agreement –1.98 [95%CI: -2.58 to –1.39 cm H$_2$O] to 1.93 [95% CI: 1.34 to 2.53 cm H$_2$O]), and (C) 3 series (mean difference 0.07 cm H$_2$O [95% CI: -0.31 to 0.45 cm H$_2$O]; limits of agreement –2.10 [95%CI: -2.76 to –1.44 cm H$_2$O] to 2.24 [95% CI: 1.58 to 2.89 cm H$_2$O]). Note that the mean difference in $P_{\text{CRIT}}$ between the segmented regression and expert visual analysis decreased with the addition of a second series of pressure-flow measurements (-0.03 cm H$_2$O from 0.3 cm H$_2$O) to the first series, and that little change in this difference occurred with the addition of a third series of pressure-flow measurements (0.07 cm H$_2$O).
<table>
<thead>
<tr>
<th>Breath</th>
<th>Change in ( V_{\text{max}} ) (m l/s)</th>
<th>95% Confidence Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breath 1</td>
<td>36.7</td>
<td>20.3 – 53.2</td>
</tr>
<tr>
<td>Breath 2</td>
<td>16.5</td>
<td>-0.1 – 33.0</td>
</tr>
<tr>
<td>Breath 3</td>
<td>14.3</td>
<td>-2.4 – 31.0</td>
</tr>
<tr>
<td>Breath 4</td>
<td>9.5</td>
<td>-7.4 – 26.5</td>
</tr>
<tr>
<td>Breath 5</td>
<td>Reference</td>
<td>-</td>
</tr>
</tbody>
</table>

* Analyses were performed using the method of General Estimating Equations (GEE) with random intercept and slope and an exchangeable correlation structure. The change in airflow for a one cm H\(_2\)O increase in nasal pressure was 68.5 ml/s (95% CI: 58.3 – 78.6 ml/s). Breath 5 was selected as the reference value in order to express changes in \( V_{\text{max}} \) in positive units.
Figure 3a
Figure 3b
Figure 4A

Between Pair $P_{CRIT}$ Difference (cm H$_2$O) vs. Within Pair $P_{CRIT}$ Mean (cm H$_2$O)
Figure 4B

Between Pair $P_{CRIT}$ Difference (cm H$_2$O) vs. Within Pair $P_{CRIT}$ Mean (cm H$_2$O)
Figure 5A
Figure 5B

The figure shows a scatter plot with the x-axis labeled as "Within Pair P_{CRIT} Mean (cm H_2O)" and the y-axis labeled as "Between Pair P_{CRIT} Difference (cm H_2O)". The plot appears to display a distribution of data points around the x-axis, indicating no significant difference between the within-pair and between-pair measurements.
Between Pair $P_{CRIT}$ Difference (cm H$_2$O)

Within Pair Mean (cm H$_2$O)
A Simplified Method for Measuring Critical Pressures during Sleep in the Clinical Setting

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ONLINE DATA SUPPLEMENT
ON-LINE DATA SUPPLEMENT

A) Supplement to Conceptual Background, under Analytical Approach – “Modeling the Flow-Limited Segment”

**Modeling the flow-limited segment:** Under flow-limited conditions, maximal inspiratory airflow ($V_{\text{Imax}}$) is determined by the $P_{\text{CRIT}}$, resistance upstream to the flow-limiting site ($R_{\text{US}}$) and by the upstream nasal pressure $P_{\text{US}}$ as described by the following equation (equation 1):

$$V_{\text{Imax}} = \frac{(P_{\text{US}} - P_{\text{CRIT}})}{R_{\text{US}}}$$

This relationship can be modeled with linear regression as follows:

$$V_{\text{Imax}}^j = \beta_0 + \beta_1 (P_N^j) + \epsilon_j$$

In this equation, $V_{\text{Imax}}$ and $P_N$ measurements at nasal pressure level $j$ are represented, while $\epsilon_j$ represents the standard error around the mean airflow for a given nasal pressure level $j$. $P_{\text{CRIT}}$ was determined by the ratio, $-\beta_0/\beta_1$ (where $\beta_0$ represents $V_{\text{Imax}}$ when $P_j$ is zero and $\beta_1$ is the mean change in $V_{\text{Imax}}$ for a 1 cm H$_2$O increase in $P_j$), and $R_{\text{US}}$ was determined by $1/\beta_1$. This relationship is used to determine $P_{\text{CRIT}}$ and $R_{\text{US}}$ for each subject.

The standard linear regression model described above can be expanded in order to consider the influence of protocol-related factors such as breath number on $V_{\text{Imax}}$. In the data collection protocol (see Methods), repeated measurements of $V_{\text{Imax}}$ are obtained for several breaths at each nasal pressure level. In order to model overall and individual specific $V_{\text{Imax}}$ observations, additional terms can be added to equation 2 to account for differences in $V_{\text{Imax}}$ between breaths within individuals and for differences in $V_{\text{Imax}}$ between individuals, as follows (equation 3):

$$Y_{ij} = \beta_0 + \beta_1 (P_{ij}) + \left\{ \sum \limits_{k=2}^{5} \gamma_k \text{ Breath}_{ik} \right\} + U_{oi} + U_{1i} (P_{ij}) + \epsilon_{ij}$$
In equation 3, the coefficient $\gamma_k$ quantifies the differences in $V_{I\text{max}}$ across $k$ breaths for a given nasal pressure level $j$, in the $i^{th}$ individual. The terms $U_{0i}$ and $U_{1i}$ represent the deviation in the y-intercept and slope of the pressure-flow relationship, respectively, for an individual $i$, from the overall group average at a given level of $P_N$. To account for the correlation between repeated measurements within an individual, model fitting was performed using the techniques of regression analysis for repeated measures (1). Pressure-flow measurements obtained for all subjects studied were then assembled into a single database in which equation 3 was applied to determine the effects of sequential breaths on $V_{I\text{max}}$.

B) Expanded Methods

Patient Recruitment

Forty-four subjects with moderate to severe obstructive sleep apnea (apnea-hypopnea index $\geq 20$ events/hour) presenting for clinical continuous positive airway pressure (CPAP) titration were studied. Sleep apnea severity was determined by overnight polysomnography as previously described (2). Subjects were divided consecutively between a development sample (Sample A; $n=30$) and a validation sample (Sample B; $n=14$). The development and validation samples were comparable in age, BMI, NREM apnea-hypopnea index, and gender (see Results). The study was approved by the institutional review board on human research.

Experimental Protocol

Patients underwent polysomnography with pressure and airflow measurements monitored via a tight-fitting nasal mask and respiratory effort monitored through the use of piezoelectrode
abdominal and thoracic strain gauges, as previously described (3). Patients slept in the supine position with one pillow under the head.

During sleep, nasal pressure ($P_N$) was maintained at a holding pressure that eliminated flow limitation (4). Nasal pressure was abruptly lowered for five breaths (a run) through a remote control device attached to a CPAP unit designed to apply pressures between –20cm to + 20cmH$_2$O. Three series of stepwise reductions in nasal pressure that encompassed zero airflow ($P_{CRIT}$) were collected (Fig. 2). If an arousal occurred, the protocol was resumed after patients reinitiated stage II – IV NREM sleep. Breaths associated with micro-arousals from sleep were excluded from analyses.

A recording example of pressure-flow measurements is shown in Fig 3a for one series of runs at several nasal pressure levels during stable NREM sleep, with corresponding median $V_{I\text{max}}$ vs. $P_N$ plot (Fig 3b). Maximal inspiratory airflow was measured as the difference in inspiratory flow maximum and the zero or mean airflow level (average airflow between the peak expiratory flow of breaths) during a run. A $V_{I\text{max}}$ vs. $P_N$ plot was generated for each subject using all breaths analyzed, irrespective of the presence or absence of flow limitation.

Sensitivity Analyses Results of the segmented regression analyses for each individual were compared against the visual identification approach of identifying the flow-limited segment. Two experts (HS and AS) independently examined each pressure-flow curve, and identified the flow-limited segment. In order to streamline and potentially automate the process of identifying the flow-limited segment, separate analyses were undertaken to compare values of $P_{CRIT}$ and $R_{US}$ obtained from an analysis of: (a) only flow-limited breaths based on established criteria (5,6) and from an analysis of: (b) all flow-limited and non-flow limited breaths. If significant differences in $P_{CRIT}$ or $R_{US}$ were not detected between analytic methods, we
concluded that flow-limited breaths need not have been identified visually, and that the detection and analysis of the flow-limited segment could be automated.

Sensitivity analyses were performed to optimize thresholds for the minimal slope and no-flow criteria by testing specific combinations of different criteria on Sample A only. Using expert visual analysis in identifying the flow-limited segment as the gold standard, we tested combinations of different values of the minimal slope criterion (15, 20, 25, 30 ml/s/cm H2O) and the no-flow threshold (25, 50 ml/s) against the gold standard for each subject. The percent agreement between expert visual analysis and segmented regression analysis was calculated for the lower inflection point with all combinations of minimal slope and no-flow thresholds, and for the upper inflection point with each minimal slope threshold. The combination values for the minimal slope and the no-flow thresholds with the highest percent agreement were accepted, and applied prospectively in the validation sample (sample B).

Comparison of segmented regression to expert visual identification demonstrated the greatest levels of agreement for a minimal slope criterion of 20 ml/s/cm H2O and a no-flow threshold of 50 ml/s. The selected criteria were used to determine Pcrit and RUS in both samples using segmented regression, and prospectively validated these criteria in Sample B. The selected minimal slope and no-flow criteria were then applied and prospectively validated in Sample B only.

Effects of Protocol-Related Factors on the Upper Airway Pressure-Flow Relationship

In order to simplify and standardize methods for data acquisition and analysis, analyses were performed to account for protocol-related factors, such as the number of runs and duration of nasal pressure levels (number of breaths) that could increase variability in the determination of
the critical pressure. Differences in the pressure-flow relationship among the five breaths during each run were examined. The PROC MIXED procedure (SAS Software, Inc.; Version 8.2) was used to estimate the parameters of interest in equation 3 while accounting for autocorrelation in the data (1). The minimum number of series of pressure-flow measurements necessary to accurately determine $P_{\text{CRIT}}$ was also investigated. Segmented regression analysis was performed repeatedly after adding series of pressure-flow data sequentially (i.e. series 1, series 1 and 2, series 1 – 3). Results of the segmented regression analysis were then compared to the expert visual analysis of all 3 series with Bland-Altman plots of $P_{\text{CRIT}}$.

**Statistical Analyses**

Values are reported as mean ± standard deviation (SD), unless otherwise stated. Paired t-test was performed to identify significant differences between a) segmented regression analyses and expert visual analyses and between b) results obtained from the visual analysis of only flow-limited breaths compared to the automated analysis of all flow-limited and non-flow limited breaths. Bland Altman analyses were performed (7) to determine whether systematic differences existed between measurements of $P_{\text{CRIT}}$ from the expert visual and segmented regression analyses.

**C) SUPPLEMENT TO RESULTS**

Sensitivity analyses were performed to optimize thresholds for the minimal slope and no-flow criteria by testing different criteria combinations using Sample A only. Comparison of segmented regression to expert visual identification demonstrated that a minimal slope criterion
of 20 ml/s/cm H$_2$O and a no-flow threshold of 50 ml/s had the greatest levels of agreement (see Tables E1 and E2).
### Table E1. Percent Agreement for Combinations of Minimal Slope and No-Flow Criteria in Identifying the Lower Inflection Point

<table>
<thead>
<tr>
<th>No Flow Criterion (ml/s)</th>
<th>Minimal Slope Criterion (ml/s/cm H\textsubscript{2}O)</th>
<th>&lt; 15</th>
<th>&lt; 20</th>
<th>&lt; 25</th>
<th>&lt; 30</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 25</td>
<td></td>
<td>0.80</td>
<td>0.80</td>
<td>0.77</td>
<td>0.77</td>
</tr>
<tr>
<td>&lt; 50</td>
<td></td>
<td>0.87</td>
<td>0.87</td>
<td>0.83</td>
<td>0.83</td>
</tr>
</tbody>
</table>

A minimal slope criteria of < 20 ml/s/cm H\textsubscript{2}O and no flow criterion of < 50 ml/s resulted in an 87% agreement in detecting the lower inflection point of the flow limited segment when compared to expert visual identification of the flow-limited segment.
A minimal slope criterion of < 20 ml/s/cm H₂O resulted in a 70% agreement in detecting the upper inflection point of the flow-limited segment when compared to expert visual identification of the flow-limited segment.
Reference List


