Relative Prolongation of Inspiratory Time Predicts High versus Low Resistance Categorization of Hypopneas

Anne M. Mooney, M.D.; Khader K. Abounasr, M.D.; David M. Rapoport, M.D.; Indu Ayappa, Ph.D.

NYU School of Medicine, Division of Pulmonary, Critical Care, and Sleep Medicine, New York, NY

Study Objectives: Sleep disordered breathing events conceptually separate into “obstructive” and “central” events. Esophageal manometry is the definitive but invasive means of classifying hypopneas. The purpose of this project was to identify noninvasive markers for discriminating high vs. low resistance hypopneas.

Methods: Forty subjects with obstructive or central sleep apnea underwent diagnostic polysomnography with nasal cannula airflow and esophageal manometry; 200% resistance relative to reference breaths was used to define “high” resistance. Noninvasive parameters from 292 randomly selected hypopneas in 20 subjects were analyzed and correlated to resistance. The best parameter and cutoff for predicting high relative resistance was determined and tested prospectively in 2 test sets in the 20 remaining subjects. Test Set A: 15 randomly selected hypopneas in each subject; Test Set B: all hypopneas in 7 subjects.

Results: In the development set, prolongation of inspiratory time during the 2 smallest breaths of a hypopnea (T_i) relative to baseline had the best correlation to high relative resistance. In the

Test Set A, relative $T_i > 110\%$ classified obstructive events with sensitivity = 72%, specificity = 77%, PPV = 64%, NPV = 83%. Similar numbers were obtained for classification of hypopneas based on presence of flow limitation (FL) alone. When either relative T_i or presence of FL were used to define high resistance, sensitivity = 84%, specificity = 74%, PPV = 65%, NPV = 89%. Similar results were obtained for Test Set B.

Conclusions: Relative prolongation of T_i is a good noninvasive predictor of high/low resistance in a dataset with both FL and NFL hypopneas. Combination of FL and relative T_i improves this classification. The use of T_i to separate obstructive and central hypopneas needs to be further tested for clinical utility (outcomes and treatment effects).

Keywords: Sleep disordered breathing, obstructive sleep apnea, central sleep apnea, hypopnea, diagnosis

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Sleep disordered breathing (SDB) is a term which includes both obstructive sleep apnea/hypopnea (OSAHS) and central sleep apnea (CSAS) syndromes, which are both prevalent conditions.¹⁻⁶ Although CSAS is most commonly seen in congestive heart failure (CHF), OSAHS is also often seen in these patients.⁴⁻⁶ At the root of defining whether a patient has CSAS or OSAHS is the categorization of the individual events as central or obstructive; there are both diagnostic and therapeutic implications of the distinction. In concept, obstructive events are defined by high upper airway resistance, whereas central events are defined by low “drive.” However, high resistance and low drive may not be mutually exclusive. There is increasing recognition that both types of events may exist within the same patient⁶ and that both etiologies may be invoked in the pathogenesis of some events, leading to difficulty in the overall categorization of a patient’s disorder as “obstructive” vs. “central.” Despite this, it is currently assumed that the distinction between OSAHS and CSAS has clinical significance, and may have important implications for both diagnosis and treatment. Thus establishing a noninvasive algorithm to characterize individual events which is useful in general polysomnography remains an important target.

For apnea, distinguishing the central vs. obstructive etiology is usually possible noninvasively by the presence/absence of thoraco-abdominal movement (effort). In contrast, for hypopnea (which accounts for the majority of events in SDB), distinguish-

BRIEF SUMMARY

Current Knowledge/Study Rationale: On polysomnography it is difficult to separate central from obstructive hypopneas without invasive monitoring. The purpose of the current project was to separate hypopneas into central (low resistance) and obstructive (high resistance) using non-invasive criteria derived from the flow signal alone.

Study Impact: An algorithm based on the inspiratory time and presence of inspiratory flow limitation on the airflow signal was useful in separating obstructive from central hypopneas. This non-invasive technique has the potential to improve clinical decision making and influence research design.

ing the etiology is much more problematic. Esophageal manometry combined with measurement of airflow is the accepted gold standard,⁷⁻⁹ as the ratio of effort to flow defines resistance. However, this technique is invasive, disruptive of sleep, and considered by most clinical laboratories as unrealistic for routine use.

Pulse transit time has been shown in a small study to be a useful noninvasive tool for recognition of central hypopneas,^{10,11} but this data is not routinely collected. Noninvasive techniques based on airflow exist to identify collapsible upper airway behavior; this collapsible behavior generally identifies elevated upper airway resistance.¹²⁻¹⁴ In particular, we and others have shown that the presence of inspiratory flattening on a nasal cannula/pressure transducer tracing¹⁵ strongly suggests flow limitation (FL) which

Figure 1—Each panel shows airflow and esophageal pressure obtained from the PSGs in 3 different subjects

Increasing effort and resistance during a hypopnea with flow limitation indicated by the presence of unequivocal flattening of the flow contour (**A**). Non-flow limited hypopnea with decreased relative effort and resistance (**B**). Non-flow limited hypopnea, but with increased relative effort and resistance (**C**). While the presence of subtle changes in the shape of the inspiratory flow curve may be identified by some observers, it is our experience that this represents cardiogenic oscillations, suggesting low resistance.

Table 1—Patient characteristics

	N	Years of age Avg $\pm$ SD	Gender (%male)	BMI Avg $\pm$ SD	Obstructive apnea index Avg $\pm$ SD	Central apnea index Avg $\pm$ SD	RDI Avg $\pm$ SD	Narcotic use (% set)
Development Set	20	50.9 $\pm$ 14.3	95%	35.6 $\pm$ 9.8	16.9 $\pm$ 24.2	11.4 $\pm$ 27.7	62.8 $\pm$ 33.5	15%
Test Set	20	55.9 $\pm$ 16.8	90%	33.9 $\pm$ 10.6	19.5 $\pm$ 24.6	3.3 $\pm$ 5.6	56.4 $\pm$ 31.1	5%

Subjects encompassed a wide range of sleep disordered breathing. There were no significant differences between severity of SDB, central or obstructive indices between subjects in the development and test sets.

corresponds to inappropriate (obstructive) Starling resistor behavior of the airway. Despite this, it is unclear whether *absence* of FL on a breath implies a central etiology for a given breath.¹² **Figure 1** illustrates flow and esophageal data in events with and without FL and demonstrates both high and low resistance in at least some events where there is an absence of FL.

The classification of hypopneas (defined by reduced ventilation), even by invasive means, is not without ambiguity. One conceptual approach is to use changes in “effort” alone during the hypopnea relative to stable breathing during sleep for separation of “central” versus “obstructive” etiologies. Relative increase in effort or maintenance of effort at a time of reduced airflow reflects obstruction of the upper airway. However, events with a relative *decrease in effort* can be associated with unchanged resistance (proportional decrease in airflow) or increased resistance (disproportionate decrease in airflow); thus decreased effort can be associated with both central or obstructive pathology and effort alone is not sufficient to separate central from obstructive hypopneas. For these reasons, a relative increase in resistance during a hypopnea may be the most appropriate measure for classifying hypopneas as obstructive, but this requires an invasive measurement not usually available in routine polysomnography.

The purpose of the current project was to develop an approach to separating hypopneas into central (low resistance) and obstructive (high resistance) using *noninvasive* criteria de-

rived from the flow signal alone and validate this in a dataset enriched for central/ambiguous etiology.

METHODS

Subjects

The dataset consisted of 40 subjects selected from patients seen in the NYU Sleep Disorders Center. These subjects were chosen with the target of obtaining a wide spectrum of hypopneas with (FL) and without (NFL) inspiratory flow limitation. Twenty-two of these patients had previously undergone an NPSG with esophageal manometry as part of other research protocols for suspected obstructive sleep apnea (19) or suspected central sleep apnea (3). The remaining 18 patients were recruited because they had a clinical presentation suggestive of central sleep apnea and on NPSG had > 25% of hypopneas without flow limitation. No patient was taking sedative or hypnotic medication, but 4 subjects were on narcotic medications at the time of study (3 in development set, 1 in test set). Aggregate patient characteristics are shown in **Table 1**.

The study was approved by the Institutional Review Board of New York University School of Medicine, and all subjects signed informed consent prior to being included in this study.

NPSG Protocol

Polysomnography was performed using the standard clinical protocol recommended by the AASM⁸ with the addition of esophageal manometry. A nasal cannula pressure transducer system transducer (Protech PTAF2) was used to measure airflow along with an oral thermistor to detect mouth breathing.¹⁵ An esophageal catheter consisting of a thin catheter ending in a 10-cm latex balloon (Ackrad Labs, NJ) was placed transnasally following lidocaine anesthesia, and positioned in the lower third of the esophagus. Esophageal pressure measurements were made with a 100 cm H₂O pressure transducer (Validyne, Northridge, CA). Chest wall and abdominal movement were monitored with uncalibrated respiratory inductance plethysmography. A single technician scored all sleep studies for sleep and respiration. Sleep was scored according to AASM criteria.⁸ Hypopneas were defined as events ≥ 10 sec where the square root of the airflow signal on the nasal cannula was reduced to $< 70\%$ regardless of desaturation or arousal, but not reduced to $< 10\%$ (in which case the event was rescored as an apnea). To become proportional to actual flow (which was needed to calculate resistance), the pressure change in the nose obtained with a nasal cannula needs to be linearized with a square root transform.^{16,17}

Data Analysis

Each hypopnea used in the development and test set (see below) was characterized as FL or NFL using visual assessment. Specifically we examined the shape of each breath on the airflow/time curve for inspiratory flattening, which we have previously shown to be a reliable surrogate for actual detection of flow limitation on a flow/pressure curve.^{18–20} While subtle changes in the inspiratory flow curve may be detected by some observers, our experience suggests that when these are inconsistent or ambiguous (e.g., **Figure 1B, C**), the correlation to the flow/pressure curve deteriorates. Each hypopnea was reviewed visually by 2 experienced researchers and classified as FL only if the 2 researchers agreed. For each hypopnea, the 2 consecutive breaths with the lowest flow were identified. Two consecutive reference breaths with the highest flow were identified from the 30 sec before or after the event. For each breath the following variables were extracted: Flow (peak value of square root of nasal cannula signal for NFL breaths, value of square root of nasal cannula signal during the plateau phase for FL breaths), Δ Esophageal Pressure (from end expiratory baseline [Δ Effort]), Resistance (Δ Effort / Flow), Inspiratory Time (T_i), Duty Cycle (T_i/T_{tot}), and Inspiratory/Expiratory duration (T_i/T_e). For each variable, the values for the 2 breaths within the hypopnea were averaged. Similarly, for each variable the values for the 2 reference breaths were averaged. Data were expressed as the ratio of hypopnea-to-reference values in order to represent relative effort, relative resistance, relative T_i , relative T_i/T_{tot} and relative T_i/T_e .

Development and test sets

The 40 sleep studies available for analysis were divided equally into 2 sets—one for development and one for testing of the algorithms. Each set contained 10 patients whose diagnostic PSG suggested primarily obstructive sleep apnea, and 10 patients where the esophageal manometry suggested predominantly central sleep apnea (CSA) or Cheyne Stokes respiration (CSR). In the development set, 5 events with inspiratory flatten-

Figure 2—For each NFL event ($n = 219$) in the development set, relative resistance is plotted against relative effort of events

Relative resistance is highly correlated to relative effort. Relative resistance and relative effort are calculated as the ratio of the values for the 2 smallest breaths within each respiratory event and the 2 largest breaths within 30 seconds of the event (see methods).

ing of the flow/time signal and 10 without inspiratory flattening (where available) were selected from each study. The development set contained 73 FL and 219 NFL events. Equal numbers of events (where available) were selected from each patient in order to avoid overrepresentation from any given patient while generating rules for categorization of events. Data for the test set subjects were not analyzed until after analysis on the development set (and final definitions of noninvasive criteria) were completed. Test Set A contained 15 randomly selected hypopneas from each patient in parallel fashion as extracted from the development set (5 events with inspiratory flattening of the flow/time signal and 10 without inspiratory flattening [where available]). Test Set A contained 72 FL and 185 NFL events. Test Set B contained *all* the hypopneas observed in a subgroup of 7 patients. Four of these patients had classical obstructive sleep apnea, and 3 of these patients had atypical sleep disordered breathing with periodic breathing and predominantly NFL hypopneas. Test Set B contained 223 FL and 410 NFL events. Events in the development set and all test sets were chosen randomly without respect to body position during sleep.

Reference definition of individual events as “high” and “low” resistance

As stated in the introduction, relative resistance or relative effort are alternative ways to define obstructive vs central events using the “gold standard” invasive methodology of esophageal manometry. However, events with a relative decrease in effort do not all have a low resistance, and can be associated with either a proportional decrease in airflow (unchanged resistance) or disproportional decrease in airflow (representing increased resistance)²¹; thus decreased effort can be associated with both central or obstructive pathology. For the present analyses, we chose to define events as obstructive vs. non-obstructive using relative resistance and not relative effort. The relationship between these parameters in our da-

Figure 3—Distribution of the relative resistance for FL and NFL events

Bars represent events having relative resistance within the bin indicated on the x axis. The height of each bar indicates the percentage of all events of that flow type (FL vs. NFL). There were a total of 73 FL events and 219 NFL events.

taset is shown in **Figure 2**. The high correlation (0.87) suggests similar results would be obtained when either relative resistance or relative effort is chosen as the basis for a reference classification of hypopneas, but importantly, 63% of events with reduced relative effort, i.e., < 100%, (a possible definition of “central”) have relative resistances in the 100% to 200% range. Thus, given our choice of relative resistance as the defining variable for separating “low” and “high” resistance events, a decision needed to be made with respect to the cut point separating inappropriately obstructive from central hypopneas. Whereas the breaths chosen within events were clearly during sleep, our reference breaths were chosen from periods surrounding SDB events that were usually but not always associated with subcortical arousal (e.g., heart rate acceleration without clear EEG arousal), cortical arousal, or awakening. A doubling of airway resistance has been described in normal subjects at sleep onset,²² and for this reason, we used > 200% as the cut point to define an inappropriate (above that seen with normal sleep) increase in relative resistance. This definition should identify the level of increased relative resistance having potential clinical significance for inappropriate obstruction of the upper airway. Thus, hypopneas were defined as obstructive if relative resistance of the hypopnea breaths was > 200% compared to the resistance of the reference breaths, and non-obstructive if relative resistance was < 200% compared to the reference breaths.

To test the dependence of our conclusions on the cut point chosen to define “high” relative resistance, we repeated our analyses using 150% relative resistance to separate “obstructive” from “non-obstructive” events in defining “truth” in the reference data set against which we compared our noninvasive markers.

Analyses and Statistics

Within the development set, correlations between relative resistance, relative effort and each relative noninvasive parameter (T_i , T_i/T_{tot} , T_i/T_e) were first examined only in NFL events. The noninvasive parameter with the highest correlation to relative resistance was submitted to ROC analysis in order to identify the best cutoff for noninvasive classification of resistance or effort. Sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) for high relative resistance (> 200%) were calculated for the NFL events of the development set and Test Set A. An additional analysis was performed after inclusion of FL events in Test Set A and stratified by sleep stage (NREM/REM). Analyses were repeated using presence/absence of FL as the noninvasive parameters, and for the combination of relative T_i and presence of FL. These analyses were repeated for Test Set B. To test the sensitivity of our definition of “obstruction,” Test Set A was also analyzed according to alternative definitions (effort > 100% = obstructive, resistance > 150% = obstructive).

RESULTS

Development Set

As previously shown,²³ events *with* inspiratory flow limitation (FL) showed an overall high ($289\% \pm 142\%$) relative resistance. Events *without* flow limitation (NFL) showed a significantly lower relative resistance than FL events ($151\% \pm 100\%$, $p < 0.001$), but, as shown in **Figure 3**, there was a substantial overlap of relative resistance between FL and NFL events. Thus flow contour alone was not sufficient to noninvasively predict low relative resistance.

Figure 4 shows the relationship of the noninvasive flow parameters (relative T_i , relative T_i/T_{tot} and relative T_i/T_e) to relative resistance in NFL events. All 3 noninvasive parameters were significantly correlated ($p < 0.001$) with relative resistance; the highest correlation was observed between relative T_i and relative resistance. This was also true when the noninvasive parameters were examined against relative effort (data not shown).

Figure 5 shows an ROC curve for all NFL events in the development set using a cutoff of > 200% relative resistance (solid line) to define obstructive events. Relative $T_i > 110\%$ (i.e., prolongation of T_i) was the best cutoff to predict high relative resistance, with an AUC of 0.82. Using an alternative reference definition of obstructive events as relative effort > 100% (dotted line), ROC analysis identifies a similar T_i (> 104%) as the best cutoff to predict high effort, with an AUC of 0.76.

Table 2 shows a classification analysis for NFL events in the development set. Sensitivity, specificity, PPV, and NPV are listed for using relative $T_i > 110\%$ to identify obstructive events defined as relative resistance > 200%. The table also lists a classification analysis for using relative $T_i > 104\%$ to identify obstructive events when these are defined as relative effort > 100%. By either criterion, relative T_i shows a high negative predictive value: in NFL events, *absence* of relative lengthening of T_i strongly suggests that an event is not obstructive. However, in NFL events, relative lengthening has little predictive value (PPV = 32% to 36%).

Figure 4—Utility of using noninvasive parameters of flow (x axis) to estimate relative resistance (y axis) of breaths

Data is shown for NFL events in the development set. Relative T_i (A); relative T_i/T_e (B); Relative T_i/T_{tot} (C). Best correlation is with relative T_i (A).

Table 2—Development Set (219 NFL events)

NFL events only (n = 219)	Sens	Spec	PPV	NPV
Obstructive event defined as Relative Resistance > 200%	67%	75%	32%	93%
Test positive = Relative T_i > 110%				
Obstructive event defined as Relative Effort > 100%	75%	70%	36%	93%
Test positive = Relative T_i > 104%				

Validation of Development Set Results in Test Sets

Test Set A

In NFL events in Test Set A (15 randomly selected hypopneas/patient from 20 patients distinct from patients in the development set), relative prolongation of T_i was again significantly correlated with relative resistance ($r = 0.48$, $p < 0.001$), although the correlation was lower than in the development set (where $r = 0.65$, $p < 0.001$).

Table 3A shows a classification analysis for NFL events (n = 185) in Test Set A. Sensitivity, specificity, PPV, and NPV for NFL events are shown for the same cutoffs and definitions used for the development set in **Table 2**. Results are similar to those seen in the development set. **Table 3B** shows results from a similar classification analysis when both NFL and FL events from Test Set A are included. Of note, the NPV (prediction of central events) remains high, despite the inclusion of the predominantly obstructive events implied by the presence of FL.

Because of the known reduction of effort associated with REM, a separate classification analysis of using T_i to predict resistance by sleep stage is shown in **Table 4**. The data show that in REM there is an exaggeration of the above findings (in all sleep), with a very high negative predictive value (i.e., a short relative T_i is strongly predictive of a low relative resistance in NFL).

Table 5 shows a classification analysis for events in Test Set A with and without flow limitation (FL and NFL), when the presence or absence of flow limitation alone is used to predict high or low resistance. These results are further analyzed with respect to sleep stage (REM/NREM). The absence of flow limitation in REM has very high negative predictive value.

Figure 5—ROC analysis for relative T_i to predict high vs. low relative resistance (solid line) or high vs. low relative effort (dotted line)

Using a cutoff of > 200% relative resistance to define obstructive events, ROC analysis identifies $T_i > 110\%$ (relative prolongation of T_i) as the best cutoff to predict high resistance with an AUC of 0.82. With obstructive events defined as effort > 100% of baseline breaths, ROC analysis identifies relative $T_i > 104\%$ (prolongation of relative T_i) as the best cutoff to predict increased effort with an AUC of 0.76.

As a test of the sensitivity of our findings to the definition of “high” relative resistance (> 200%), we repeated the classification analysis of T_i as a predictor of resistance using a cutoff of 150%. **Table 6** shows these data and suggests similar trends.

To incorporate all of the observations made above for noninvasive prediction, we present a combined classification analysis (**Table 7**) for predicting relative resistance > 200% for events

Table 3—Test Set A

A NFL events only (n = 185)	Sens	Spec	PPV	NPV
Obstructive event defined as Relative Resistance > 200%	63	83	52	89
Test positive = Relative T_i > 110%				
Obstructive event defined as Relative Effort > 100%	68	69	39	88
Test positive = Relative T_i > 104%				
B NFL + FL events (n = 257)	Sens	Spec	PPV	NPV
Obstructive event defined as Relative Resistance > 200%	72	77	64	83
Test positive = Relative T_i > 110%				
Obstructive event defined as Relative Effort > 100%	82	60	49	88
Test positive = Relative T_i > 104%				

Table 4—Test Set A, effect of sleep stage (REM/NREM) on test validity

NFL events only (n = 185)	Sens	Spec	PPV	NPV
REM (n = 44)				
Obstructive event defined as Relative Resistance > 200%	50	88	17	97
Test positive = Relative T_i > 110%				
NREM (n = 141)				
Obstructive event defined as Relative Resistance > 200%	64	81	57	86
Test positive = Relative T_i > 110%				
NFL + FL events (n = 257)	Sens	Spec	PPV	NPV
REM (n = 57)				
Obstructive event defined as Relative Resistance > 200%	60	79	38	90
Test positive = Relative T_i > 110%				
NREM (n = 200)				
Obstructive event defined as Relative Resistance > 200%	74	76	69	80
Test positive = Relative T_i > 110%				

Table 5—Test Set A, classification results using presence or absence of flow limitation alone

NFL + FL events (n = 257)	Sens	Spec	PPV	NPV
All Events (n = 257)				
Obstructive event defined as Relative Resistance > 200%	56	88	74	78
Test positive = Flow limitation present				
REM (n = 57)				
Obstructive event defined as Relative Resistance > 200%	80	89	62	95
Test positive = Flow limitation present				
NREM (n = 200)				
Obstructive event defined as Relative Resistance > 200%	54	88	76	72
Test positive = Flow limitation present				

Table 6—Effect of an alternative definition of resistance as > 150% in Test Set A

NFL events (n = 185)	Sens	Spec	PPV	NPV
Disease present = Relative Resistance > 150%	48	85	64	75
Test positive = Relative T_i > 110%				
NFL + FL events (n = 257)	Sens	Spec	PPV	NPV
Disease present = Relative Resistance > 150%	63	80	76	68
Test positive = Relative T_i > 110%				

Table 7—Test Set A, two-tiered classification analysis

NFL + FL events (n = 257)	Sens	Spec	PPV	NPV
Obstructive event defined as Relative Resistance > 200%	84	74	65	89
Test positive = Flow limitation present or if NFL then Relative T_i > 110%				

in Test Set A using *either* the presence of FL or $T_i > 110\%$. By these criteria, sensitivity rises to 84%, while specificity, PPV and NPV remain similar at 74%, 65%, 89%.

Figure 6 compares the validity of each test (1-presence of flow limitation alone, 2-relative prolongation of $T_i > 110\%$ alone, 3-either presence of flow limitation *or* relative prolongation of $T_i > 110\%$) to predict relative resistance $> 200\%$.

Test Set B

In contrast to Test Set A, which consisted of an equal number of hypopneas randomly selected from all patients, Test Set B evaluated *all* hypopneas in 7 patients. Four of the patients demonstrated classic loud snoring and flow limitation throughout the majority of the night. The other three patients had predominantly non-flow limited hypopneas occurring in a periodic pattern. There were 633 hypopneas in Test Set B (410 NFL, 223 FL). **Table 8** shows that the 3 noninvasive predictors (presence of FL, relative $T_i > 110\%$, and the combination of the two criteria) show good sensitivity, specificity, PPV, and NPV in the data from Test Set B.

DISCUSSION

The present analysis shows that useful predictions about whether a hypopnea is “obstructive” or “central” (defined by relative resistance) can be made from airflow alone. Our data show that the relative prolongation of T_i can be used to correctly classify the majority of hypopneas without use of invasive monitoring in a dataset enriched for ambiguous (non-flow limited) hypopneas. In this dataset, the combined assessment of relative T_i and inspiratory flow limitation had greater accuracy than either alone. An algorithm categorizing each hypopnea event first according to FL and then according to relative T_i not only helps classify individual events, but may also help in the clinical classification of patients and thus potentially inform treatment decisions.

The present study was predicated on the assumption that there is a clear dichotomy between “central” and “obstructive” etiologies that can be applied to each individual hypopnea, and that this was represented by the relative resistance obtained using the invasive measurement of esophageal manometry. We acknowledge that there may be considerable overlap in the pathophysiology underlying a given event, and as a result there may not exist an unambiguously correct distinction between an obstructive and a central hypopnea. However, it is currently assumed that this distinction exists and has clinical significance as well as implications for treatment and prognosis²⁴⁻²⁸; a dichotomous classification scheme is currently standard clinical practice.⁸

In the absence of consistent definitions of hypopnea,²⁹⁻³¹ we chose to use a very inclusive definition of hypopnea based on reduced airflow alone for our analysis,⁹ rather than one that disregards events without 4% desaturation or EEG arousal.⁸ In addition, our methodology for classifying hypopneas requires comment. The signals we used for flow are not calibrated. Thus all measurements (such as resistance) were not absolute, and needed to be related to a “baseline.” By calculating *relative* resistance, and *relative* T_i we build on the logic used to define hypopnea using the accepted change in *relative* amplitude. We used high vs. low relative resistance as the variable to provide the reference categorization of each SDB event, with $> 200\%$ being the cut point between obstructive and non-obstructive (see justification in methods).

Having chosen a definition for “correctly” classifying hypopneas as “obstructive” or “central,” the second component of our analysis was to use the now classified events as a test of various noninvasive algorithms to accomplish the same classification. Although relative prolongation of T_i alone provided a highly specific marker for high resistance (similar to flow limitation), it lacks sensitivity. Using the presence of either flow limitation or the prolongation of T_i (relative $T_i > 110\%$) improves sensitivity while maintaining NPV for classifying events as “obstructive.” An automated technique utilizing discriminant analysis of flow limitation and other features extracted from the airflow signal was recently reported to demonstrate similar accuracy in predicting relative changes in effort^{32,33} and supports our conclusions.

Figure 6—Comparison of the sensitivity, specificity, PPV, and NPV for each noninvasive predictor of high resistance, in Test Set A events (FL and NFL)

A two-tiered classification analysis using *either* the presence of flow limitation *or* relative prolongation of $T_i (> 110\%)$ demonstrates the highest sensitivity while NPV is preserved.

Table 8—Classification results using the 3 noninvasive predictors in Test Set B

NFL + FL events (n = 633)	Sens	Spec	PPV	NPV
All hypopneas in 7 Patients (n = 633)				
Obstructive event defined as Relative Resistance $> 200\%$				
Test positive = Flow limitation present	71%	89%	81%	82%
Test positive = Relative $T_i > 110\%$	72%	81%	72%	81%
Test positive = Either FL present or Relative $T_i > 110\%$	84%	77%	71%	88%

The observed low sensitivity for detecting events in Test Set A with high relative resistance is predictable from the choice made in constructing this dataset. We specifically enriched the data set with hypopneas without flow limitation as we felt that these posed the highest ambiguity based on prior work.¹² The sensitivity of our algorithm to high resistance events necessarily increases as one includes more patients (and events) that are flow limited and this is confirmed by the higher sensitivity seen in Test Set B that has greater number of FL events.

There are obvious advantages to an algorithm for separating obstructive from central events based on noninvasive measurements. Patient willingness, use of lidocaine, sleep effects, potential extension to home study data and, finally, cost, all favor a noninvasive test over esophageal manometry if comparable classification of events can be achieved. A possible limitation of our data is that quantitative flow was not measured using a pneumotachograph, and thus resistance cannot be quantitatively determined. Our choice of the nasal cannula signal was intentional in this regard, as we were trying to develop a technique that was generalizable to routine clinical use, and pneumotachographs are generally reserved to specialized research applications. We and others^{14,18,34,35} have previously shown that the nasal cannula qualitative flow signal can accurately determine presence or absence of flow limitation. Furthermore, breath duration (used to define the respiratory variables we examined relative T_i , relative T_i/T_{tot} , relative T_i/T_c) does not require quantitative airflow measurement. While quantitative resistance cannot be calculated from the nasal cannula signal, relative resistance should not suffer from this limitation.

Other aspects related to our methodology require comment. First, since airflow was collected with a nasal cannula/pressure transducer system where the calibration is only valid across short time periods (3 min) we needed to define “baseline breathing” for each event rather than using one single baseline period per subject. We chose periods of breathing within 30 seconds of the hypopnea. Second, in order to maximize reproducibility of breaths chosen for analysis we use the 2 biggest breaths for use as reference and 2 smallest breaths within the hypopnea.

An interesting and striking finding in our study was the behavior of our algorithm specifically in REM. In this state, absence of flow limitation was almost always associated with low resistance. Thus, in REM there was little need to explore additional noninvasive parameters beyond flow limitation to classify hypopneas. One possible explanation is that the upper airway during REM is so susceptible to collapse that any increase in effort brings out flow limitation. In NREM the lesser collapsibility of the airway makes for more overlap between the level of effort and the expression of flow limitation.

A limitation of our dataset is the predominance of male patients. Gender related differences in load response and arousal threshold may affect the appearance of FL and relative prolongation of T_i .³⁶ However, data from Pillar, et al.³⁷ show that despite the greater prevalence of flow limitation and the reduced ventilation seen in men with inspiratory resistive loading, men and women had similar prolongation of inspiratory time. Further testing in a dataset with more women may be desirable before generalizing our conclusions.

In conclusion, we describe a noninvasive algorithm applied to data derived solely from the nasal cannula flow signal which

is easily automatable and has good sensitivity and specificity for prediction of relative resistance of hypopneas. The utility of this algorithm lies in its ability to noninvasively classify obstructive and central hypopneas in clinical and research data sets of NPSGs, and thus test the utility and implications of this distinction for diagnostic, therapeutic and long term-outcomes.

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Address correspondence to: Anne M. Mooney, M.D., NYU Sleep Disorders Center, 462 First Ave, NBV7N3, New York, NY 10016; Tel: (212) 263-8423; Fax: (212) 562-4677; E-mail: anne.mooney@nyu.edu

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