INTRODUCTION

THE DIAGNOSIS OF SLEEP-DISORDERED BREATHING (SDB) IS CRITICALLY DEPENDENT ON IDENTIFICATION OF AND DISCRIMINATION BETWEEN TYPES OF RESPIRATORY EVENTS. Furthermore, the nature of the events detected may be influenced by the monitoring techniques used. Multiple techniques have been used to record the respiratory signals (e.g., thermistors, thermocouples, inductance plethysmography, esophageal manometry, pulse transit time) and various analysis strategies have been proposed to define “significant” events (e.g., those producing arousal and/or desaturation). A recent consensus statement from the American Academy of Sleep Medicine proposed standard definitions of abnormal breathing events and identified “acceptable” techniques for recording the signals used in those definitions. While this document proposed that non-invasive techniques be used for the detection of apnea and hypopnea, esophageal manometry was the only technique listed as “acceptable” for detection of events characterized by subtle reduction in flow with transiently elevated upper-airway resistance. When associated with arousal, these events were called respiratory effort-related arousals (RERAs). Despite literature to the contrary, it has been the experience of our laboratory and others that esophageal manometry is poorly tolerated by many subjects (especially those with mild sleep disorders). In addition, few clinical laboratories use this technique routinely, and it would be desirable to replace it with a more acceptable non-invasive technique for detecting RERAs.

Non-Invasive Detection of Respiratory Effort-Related Arousals (RERAs) by a Nasal Cannula/Pressure Transducer System

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Study Objectives: The published AASM guidelines approve use of a nasal cannula/pressure transducer to detect apneas/hypopneas, but require esophageal manometry for Respiratory Effort-Related Arousals (RERAs). However, esophageal manometry may be poorly tolerated by many subjects. We have shown that the shape of the inspiratory flow signal from a nasal cannula identifies flow limitation and elevated upper-airway resistance. This study tests the hypothesis that detection of flow limitation events using the nasal cannula provides a non-invasive means to identify RERAs.

Design: N/A
Setting: N/A
Patients: 10 UARS/OSAS and 5 normal subjects
Interventions: N/A

Measurements and Results: All subjects underwent full NPSG. Two scorers identified events from the nasal cannula signal as apneas, hypopneas, and flow limitation events. Two additional scorers identified events from esophageal manometry. Arousals were scored in a separate pass. Interscorer reliability and intersignal agreement were assessed both without and with regard to arousal. The total number of respiratory events identified by the two scorers of the nasal cannula was similar with an Intraclass Correlation (ICC) = 0.96, and was essentially identical to the agreement for the two scorers of esophageal manometry (ICC = 0.96). There was good agreement between the number of events detected by the two techniques with a slight bias towards the nasal cannula (4.5 events/hr). There was no statistically significant difference (bias 0.9/hr, 95%CI –0.3-2.0) between the number of nasal cannula flow limitation events terminated by arousal and manometry events terminated by arousal (RERAs).

Conclusion: The nasal cannula/pressure transducer provides a non-invasive reproducible detector of all events in sleep disordered breathing; in particular, it detects the same events as esophageal manometry (RERAs).

Key words: Respiratory monitoring; airflow; flow limitation; UARS; OSAS; hypopnea; apnea; RERA; esophageal manometry
For detection of apnea and hypopnea, the AASM task force recommended as “acceptable” the use of a nasal cannula/pressure transducer system as described in the literature. In the AASM document, identification of apnea and hypopnea was based solely on measuring the amplitude of the signal from this detector of flow. We have shown that, in addition to amplitude, the shape of the nasal cannula signal provides a non-invasive indicator of elevated upper airway resistance. During periods of partial collapse of the airway, the inspiratory flow signal develops a characteristic plateau that suggests flow limitation has occurred in the upper airway.

The present study tests the hypothesis that detection of flow limitation using the nasal cannula provides a non-invasive means to detect the same events identified by esophageal manometry (RERAs). We also evaluated the interrater reliability of event detection from both the nasal cannula and conventional esophageal manometry.

METHODS

All sequential patients presenting to the laboratory with suspected UARS or mild/moderate OSA were approached for the present study if they had no contraindication to having an esophageal catheter placed. In all, 15 subjects (13 male/2 female, age 30—70) were enrolled. Ten patients were studied because of complaints of snoring and EDS (n=9) or snoring alone (n=1), suggesting the diagnosis of sleep disordered breathing. Five additional subjects were specifically recruited based on the absence of snoring and any other reported sleep complaints. All 15 subjects underwent full night polysomnography at the NYU Sleep Disorders Center. Recordings of central and occipital electroencephalogram (EEG), electrooculogram (EOG), and submental electromyogram (EMG) were used to monitor sleep on a Biologics Sleep Scan (Mundelein, IL) digital recording system. An anterior tibialis EMG was used to detect leg movements and a unipolar electrocardiogram (ECG) was used for cardiac monitoring. Oxygen saturation was monitored with a pulse oximeter. Chest wall and abdominal movement were monitored with piezoelectric strain gauges. Respiratory airflow was simultaneously monitored using a nasal/oral thermistor and a nasal cannula connected to a 2 cmH2O pressure transducer (Validyne, Northridge, CA or Protech PTAF2, Minneapolis, MN).

The output of the pressure transducer was connected to a DC amplifier with a 5 or 10 Hz low pass filter. Esophageal pressure was measured with a catheter ending in a 10-cm latex balloon (Ackrad, Cranford, NJ) placed transnasally following local 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).

Sleep was scored on a first pass through the data using the criteria of Rechtschaffen and Kales on 30-second epochs. Respiratory scoring was performed in separate passes, without display of the other sleep scoring signals (EEG, EMG, and EOG) on the computer screen. In the first respiratory pass, obstructive respiratory events were identified from the nasal cannula flow using the following definitions: Obstructive apneas were defined as a decrease in peak inspiratory flow rate to below 10% of the surrounding baseline for at least 10 seconds. Repetitive central apneas (defined by the absence of rib/thoracic movement during the event) occurred in one subject for a period of one hour and were excluded from analysis. Hypopneas were defined as a decrease in flow amplitude to less than 50% of the surrounding baseline. Desaturation and/or arousal were not required to be present. The inspiratory airflow signal from the nasal cannula was also used to define “flow limitation events.” These consisted of two or more consecutive breaths (for an event duration generally ≥ 10 sec) that had a flattened or non-sinusoidal appearance but had peak inspiratory amplitudes that did not meet the >50% reduction requirement of hypopnea. These events were required to end abruptly with a return to breaths with sinusoidal shape. The esophageal pressure signal was not displayed on the computer screen during the scoring of the nasal cannula signal.

In the second respiratory scoring pass, during which the nasal cannula signal was not displayed on the computer screen, esophageal pressure events were identified. These were defined as a crescendo pattern of negative inspiratory pressure swings that lasted at least 10 seconds and were followed by a rapid decrease of the swings to baseline level. No attempt was made to subdivide these events into apneas, hypopneas, or RERAs.

Respiratory events were scored from the nasal cannula signal by two scorers working independently (scorers A and B) and blinded to all the other scorer’s results. Respiratory events were scored from the esophageal manometry signal by two additional scorers (scorers C and D) working independently and blinded to all other scorer’s results. After all scorers had completed scoring all studies, a reconciliation process was performed separately for the nasal cannula signal and the esophageal pressure signal: all disagreements as to presence/absence or as to event type were reviewed and a single reconciled score assigned to each event for each signal.

Figure 1 shows examples of events that were classified as a flow limitation events from the nasal cannula signal and as esophageal events from the esophageal pressure signal. The nasal cannula signal shows a decrease in amplitude simultaneously with the development of an inspiratory plateau (and loss of a sinusoidal inspiratory waveform). The esophageal pressure signal shows a crescendo increase in negative pressure swings terminating with an abrupt decrease in pressure swings at the end of the respiratory...
Figure 1—Sixty second NPSG window showing simultaneous nasal cannula and esophageal pressure events. The nasal cannula signal shows two flow limitation events with a < 50% reduction in amplitude and a flattening of the inspiratory flow contour. The esophageal pressure signal shows RERAs with a crescendo increase in pressure swings terminated by an abrupt decrease in pressure swings simultaneous with cortical arousal.

Figure 2—Sixty second NPSG window showing a flow limitation event marked on the nasal cannula signal, which is not associated with an esophageal pressure signal event.
event at the time of a cortical arousal. Figure 2 shows an example of a flow limitation event on the nasal cannula which was not clearly visible on the esophageal pressure signal. Figure 3 shows an example of an esophageal pressure event during which there was no reduction in amplitude or inspiratory flattening on the nasal cannula channel.

Interscorer reliability for each signal and intersignal agreement were assessed based on the total number of events detected and, separately, by event-by-event concordance. The interscorer comparison for the nasal cannula was made using total number of events and repeated using apnea, hypopnea, and flow limitation events treated as separate events. Agreement as to the number of events was evaluated by an intraclass correlation coefficient (ICC) based on a two-way random effects analysis of variance model. Agreement on an event-by-event basis was evaluated using the proportion of specific agreement (PSA).

Each record was then reevaluated for arousals as defined by the AASM from a computer display screen which included only the EEG, EOG, and EMG channels. This was done by two scorers working independently, who then reconciled their results to a single score for each event, and without display or other indication of the respiratory events. This reconciled arousal event was used to define respiratory effort related arousals (RERAs) from esophageal manometry events as proposed by the AASM. Arousal was similarly used to define potentially equivalent arousal-linked events from events previously scored from the nasal cannula. A comparison (intersignal) was made between RERAs and the analogous arousal-linked nasal cannula events. Finally, we compared the total respiratory event index (apnea index + hypopnea index + RERA index) using RERAs defined by esophageal manometry to the index obtained using RERAs defined by nasal cannula.

The protocol was approved by the New York University Institutional Board of Research Associates and all subjects gave informed consent prior to the performance of the NPSG.

RESULTS

The total numbers of respiratory events identified by each of the two scorers of the nasal cannula signal and by each of the two scorers of the esophageal pressure signal are shown in Table 1. The respiratory event index in the 15 subjects (average of all techniques, all scorers) ranged from 4.2 to 69.5/hr, indicating that the full spectrum of respiration from normal to severe SDB was represented in our data. As can be seen in Table 1, scorers of the nasal cannula...
La signal (A and B) identified nearly equal numbers of apneas and hypopneas. However scorer B scored 35% more flow limitation events than scorer A. Scorers of the esophageal pressure signal (C and D) also identified similar numbers of esophageal events.

Figure 4a compares the agreement between the scorers of the nasal cannula within each subject. Each point represents one subject. The open circles represent the asymptomatic subjects and the closed circles represent subjects with EDS/Snoring. The line of identity is shown. The total numbers of events identified by the two scorers are nearly identical in all subjects. Figure 4b breaks down this data by event type. There is good agreement between scorers for apnea and hypopnea. Scorer B tended to score more flow limitation events than scorer A.

Event-by-event agreement between the two scorers for each signal is shown in Table 2. For the nasal cannula signal the interscorer agreement was excellent for apnea (PSA 0.91) and moderate for hypopnea (PSA 0.69) and for flow limitation (PSA 0.64), taken individually. Because the delineation between hypopnea and flow limitation events is based on an arbitrary amplitude criteria, we also examined

### Table 2—Proportion of specific agreement between scorers.

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<th>nREM+REM</th>
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<tr>
<td>NC Hypopnea</td>
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<td>0.84</td>
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<td>NC Hypopnea/Flow Limitation</td>
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<td>0.82</td>
<td>0.81</td>
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<tr>
<td>NC Total</td>
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<tr>
<td>Reconciled NC</td>
<td>0.82</td>
<td>0.85</td>
<td>0.81</td>
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* Nasal Cannula
interscorer agreement for the combination of hypopnea and flow limitation (all non-apneic respiratory events) and found agreement to be much improved with a PSA 0.81. Agreement between scorers for identifying the esophageal events was good (PSA 0.83). In general, the results were similar for both REM and non-REM sleep.

Table 1 also shows the number of events obtained when the two scorers of each method reconciled their results. Reconciliation resulted in only very small changes in the total number of apneas and hypopneas. There was a 24% change in the number of flow limitation events relative to scorer B, and 5% change in the number of esophageal events. Overall, 15% (1999 vs. 1682) more reconciled events were identified from the nasal cannula signal than from the esophageal pressure signal.

Figure 6 compares the total number of reconciled nasal cannula and reconciled esophageal events within each subject. There was good agreement between the number of events detected by these two measures. A slight bias was present toward a higher number of nasal cannula events (mean bias 4.5/hr, 95% CI 1.0 to 7.9).

Using the scoring of events from the esophageal pressure signal as a gold standard, the sensitivity for detecting the same events by the nasal cannula was 0.88 (95% CI 0.86 to 0.89) and the selectivity was 0.77 (95% CI 0.75 to 0.79).

Because the AASM definition of RERAs requires linkage of respiratory events to arousal, we also evaluated the effect of this linkage on the relationship between nasal cannula and esophageal manometry data. Specifically, our analysis excluded apneas and hypopneas because their definition does not require linkage to arousal. Figure 7 shows the number of RERA events as defined by linkage of arousal to esophageal events (AASM criteria) vs. the number of events defined by linkage of arousal to flow limitation events identified on the nasal cannula signal. There is good agreement between the two methods with no statistically significant bias (mean bias 0.9/hr, 95% CI from -0.3 to 2.0).

When using the index proposed by the AASM for diagnosis of sleep disordered breathing (apneas + hypopneas + RERA events per hour of sleep), the two methods of defining RERAs produced the data shown on Figure 8. There is near identity between the two techniques (mean bias has the same value as for RERAs alone). Furthermore, if one dichotomizes subjects as either “normal” (no EDS or snoring) or having symptoms of SDB, the classification based on the count of total events is identical by the two methods. This is true whether one chooses a clinically used cutoff of 15 events/hr or one of 5 events/hr as recommended by the AASM.

**DISCUSSION**

The present study shows that the analysis of the shape of the nasal cannula flow signal (transient inspiratory flattening which suggests flow limitation) can be used to replace esophageal manometry in detecting the subtle obstructive events defined by the AASM as potential RERAs. Since analysis of the amplitude of the nasal cannula flow signal has been previously shown to be an acceptable technique for detecting apnea/hypopnea (AASM), the combination of analyses of flow amplitude and shape (applied to this sin-

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Figure 6—Scatterplot of the indices of reconciled events scored on the nasal cannula flow signal (apneas + hypopneas + flow limitation events) versus the esophageal pressure signal. The points tend to follow the line of identity. However, there is a slight bias between the two measures with the nasal cannula producing an average of 4.5 events/hr more than the esophageal pressure.

Figure 7—Scatterplot of the indices of flow limitation events scored from the nasal cannula signal when linked to arousal vs. RERAs on the esophageal pressure signal. The points follow the line of identity and there was no consistent bias between the two measures.
Esophageal manometry detects increases in effort, which are also reinforced by the cannula. The flattened shape of the flow signal can also be shown to correlate closely with collapsible behavior of the upper airway, which is generally accepted as the source of the transiently elevated resistance seen in an “event.” Thus, these two sensors detect different physiological aspects of the same event; therefore, it is not surprising that the same events are detected. However, neither the esophageal pressure alone nor the detection of amplitude of flow is sufficient to define increases in airway resistance; measures of both flow and effort are needed to calculate resistance. In most cases, however, the two indirect measures appear to track the transient elevations of upper airway resistance closely, and from this comes their clinical utility as single signals. In our data, we occasionally noted (primarily in one subject) situations where there were increases in esophageal pressure swings occurring out of phase with changes in shape of the flow signal. In these cases, although both events mark a period of transiently elevated resistance, changes marking the event occur at different times. The cannula detects changes in flow related to the collapse of the airway at the time this occurs. Esophageal manometry detects increases in effort, which can occur either during or after the change in flow has resolved, as due to persisting O₂ desaturation or hypercapnia. An example of this dissociation between appearance of flow limitation and a transient increase in esophageal manometry pressure is shown in Figure 9. While physiologically interesting, this divergence does not affect the classification of events or of patients.

The main object of the present study was to show that the total number of all SDB events identified by two techniques was similar. This follows from the suggestion of the AASM position paper recommendation that apneas, hypopneas and RERAs be totalled as a single index. In the present study, our definition of hypopnea from the nasal flow signal differed slightly from that proposed by the AASM recommendations, which states that any clear reduction in the amplitude of the flow followed by an arousal should be classified as a hypopnea. Because the nasal cannula is a very sensitive detector of flow, most of the cannula events in the present study would have met this definition and been called hypopneas. However, in the present study we wished to preserve a category of subtle events analogous to the RERA as defined by esophageal manometry in combination with absence of an event on a primary respiratory signal other than the nasal cannula. Thus, we chose to limit the definition of hypopnea to only those events where flow (measured by the nasal cannula) was reduced to less than 50% of baseline. For events where flow did not fall to less than 50% but showed flow limitation on the nasal cannula signal we defined flow limitation events as an independent category separate from hypopnea. Our data showed that these nasal cannula events tended to be the same events as those identified on esophageal manometry as potential RERAs (before arousal is assessed). Linkage to arousal further reinforced the identity between the arousal-linked nasal cannula event and esophageal manometry RERAs (see Figure 7).

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The choice of statistics used in this paper to quantify agreement among scorers requires comment. In the recently published AASM guidelines¹ it is recommended that Cohen’s Kappa statistic¹⁴ be used to assess event-by-event interrater reliability. However, in addition to the tabulation of the presence of events, the calculation of Kappa (and also of specificity) requires a measurement of agreement on absence of events. Thus, while agreements and disagreements as to the presence of a respiratory event can be tabulated, the number of agreements on absence of respiratory events is undefined. Solutions to this problem introduce their own difficulties, as the same metric must be used to measure both the presence and absence of a respiratory event for Kappa to be valid; the choice of the method may strongly influence the value of Kappa.¹⁵ A version of Kappa for use with transient events in a continuous time series has been described¹⁶ but would be difficult to implement for many laboratories because it is impractical without computerization. In this study we chose to describe
agreement using both the total numbers of events (a common clinical summary) and then repeated the analysis for the event-by-event agreement. The agreement between total numbers of events was evaluated by using a form of the intraclass correlation coefficient that includes the measurement of mean difference (bias) among the scorers. Event-by-event agreement was evaluated using the proportion of specific agreement (PSA), which requires only the measurement of agreement on the presence of events and does not require agreement on the absence of an event. This statistic can be interpreted as a conditional probability (i.e. the probability that if a randomly chosen scorer in a pair detects an event the other scorer will also detect the event).

An additional finding of this study, whether using esophageal manometry or the nasal cannula signal, is that normal, asymptomatic subjects may have more than five events per hour (the recommended cutoff in the AASM recommendations). All symptomatic subjects (EDS and snoring) had more than 15 events per hour. Our data also raise questions about linking respiratory events to EEG-determined arousal. Arousal has been used both to validate a poorly defined respiratory event (which may have been ambiguous because of the methodology used to detect it) and as a result of the event which explains its pathophysiological implications (EDS). Because the nasal cannula detects even subtle changes in respiratory airflow, arousal may not be as critical to validate an event’s existence. For this reason, we suggest that the nasal cannula may have a role in unattended limited studies in which no EEG signals are available. However, it is clear that the role of arousal as a consequence of respiratory events needs to be separately assessed from its role as confirmation of existence of the event. Our present data shows only that the nasal cannula provides a simple, well-tolerated non-invasive method with equivalent event detection to esophageal manometry. This allows it to be used to address these issues in a potentially larger sample of subjects, including those who would not tolerate esophageal manometry.

The data we present in this study compares reconciled scores where two scorers repeated the same scoring for nasal cannula events, esophageal events, and arousal events. This was done to maximize the reliability of the individual signals, so as to focus the data analysis on the difference between nasal cannula events and esophageal events. However, virtually all clinical laboratories score their studies only once (and in some cases multiple techs may contribute to the scoring of a single study). Our data on the variability between scorers for the nasal cannula events indicates that scoring variability was low when scorers were given rules. Thus events can be identified with confidence and the technique is generalizable to the usual clinical scoring situation. In order to address the clinical effect of interscorer variability on the nasal cannula signal on subject classification, we examined the effect of using a cut-off of 15 events/hr to classify subjects (normal vs SDB). In 10/10 of our subjects with EDS and/or snoring (patients) and 3/5 normal subjects both scorers agreed on

Figure 9—Two minute NPSG window showing repetitive apneas on the nasal cannula signal and esophageal pressure increases, which are out of phase with the apnea. There is a minimal change in esophageal pressure during the apneic event with significant increases in esophageal pressure swings following arousal. This relationship between the signals occurred in 49% of all events in one subject, but only rarely in others. They were tabulated as “agreements” for the purpose of this paper.
whether the total counts (RDI_Total) were > or < 15 events/hr. In the other 2/5 “normals” a difference in classification would have resulted from the difference between the total index obtained by the two scorers (12 vs. 18 events/hr, and 4 vs 17 events/hr), and these were primarily the result of differences in the count of flow limitation events due to decisions about separating long runs of flow limitation into multiple events. The average difference between the two scorers scoring for the nasal cannula in all 15 subjects was 3 events/hr. This small difference only has impact in the vicinity of the cut point, and will vary with its choice.

In conclusion, the present study shows that the identification of RERAs, as well as the detection of apneas and hypopneas, can be accomplished with the single modality of a nasal cannula/pressure transducer (used to detect airflow and impute changes in resistance). Although esophageal manometry may be a useful adjunct to differentiate central from obstructive apnea, our data suggest that this type of monitoring is not necessary in the routine evaluation of subjects with obstructive sleep disordered breathing. Thus, we propose that the nasal cannula is the tool of choice for monitoring respiratory airflow during sleep in both clinical and research sleep studies, especially if one wishes to detect both apnea/hypopnea and milder sleep disordered breathing events.

REFERENCES