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Developing Quantitative Physiological Phenotypes of Sleep Apnea for Epidemiological Studies

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Abstract:

Existing physiological databases have not been sufficiently detailed to provide relevant and important information for characterizing the pathophysiology of obstructive sleep apnea. Critical collapsing pressure (P_{CRIT}) is a standard method for determining upper airway patency during sleep, however is labor intensive and prohibits large-scale studies. Based on previously published data indicating R_{US} does not significantly vary between groups, our aim was to develop an approach to estimate the P_{CRIT} from airflow at atmospheric pressure (V_{atm}). In a dataset of 126 subjects, where P_{CRIT} and R_{US} were measured using standard techniques. We then determined the minimum sample size required to estimate the R_{US} mean and variance by utilizing a bootstrap procedure (30 times for n=3 to 126). We first estimated the minimum number of subjects needed for obtaining a group for a two-tailed (z=1.96) standard error for R_{US} in the population. Then in 75 individuals, quantitative estimates of airflow were obtained at atmospheric pressure. Using the estimated R_{US} and atmospheric , we determined an estimated P_{CRIT} (ϵP_{CRIT}). Bland-Altman plots were generated to determine the agreement between the measured P_{CRIT} and ϵP_{CRIT}. For the entire population the mean±SEM R_{US} was 23±1cmH_2O/L/s (±95% CI: 21, 25). ~40 subjects represent the minimum sample required to estimate the population variance within ±2 SEM. In the subsample with atmospheric flow measurements, a linear regression model (ϵP_{CRIT} [cmH_2O]=$V_{@PN}$ [L/s]x-23[cmH_2O/L/s]), ϵP_{CRIT} ranged from 0 to -9.6cmH_2O. In the Bland-Altman analysis there was no mean difference between the measured P_{CRIT} and ϵP_{CRIT} (-0.01cmH_2O; p=0.8) with upper and lower limits of agreement at ±2.3cmH_2O. The variance of upstream resistance approaches a constant value in groups with approximately 40 subjects. Utilizing a fixed up-stream resistance to estimate P_{CRIT} from the airflow at atmospheric pressure agrees with the measured values. These data suggest that measurements of quantitative airflow during standard polysomnography can be used to determine upper airway properties in large cohorts.

Keywords: physiologic databases, upper airway, obstruction, flow limitation, ventilation, obstructive sleep apnea, sleep.

I. INTRODUCTION

Large epidemiological studies demonstrated the increased health burden such as increased morbidity and mortality of obstructive sleep apnea (OSA). However little is known of the pathogenesis of OSA. Knowing and identifying physiologic and genetic factors predisposing to sleep apnea would unload the health burden associated with sleep apnea.

Recently investigator discovered quantitative physiological traits that can identify patients at risk for developing OSA. The main physiologic traits that have been identified for developing OSA are 1) an impairment in upper airway function during sleep [1-3] and 2) specific ventilatory parameters predisposing to hypoventilation [4-6]. Large scale studies however are necessary to determine the predictive value of these intermediate physiologic traits for the development of OSA and identifying factors that can prevent OSA.

Current techniques to obtain physiologic traits for OSA are too cumbersome to use in larger scale studies. For the assessment of upper airway properties in healthy and apneic individuals requires certain physiologic experiments making these methods inadequate for use in observational studies. In contrast, current techniques of standard sleep study are tailored to tabulate the apnea event rate, but are inadequate for quantifying physiology traits that causes OSA. Thus, research on pathogenesis of OSA are hampered by either the measurement burden associated to obtain physiologic phenotypes of OSA or the lack of appropriate techniques and algorithms to retrieve quantitative traits from standard sleep studies.

We have developed a novel technique [7;8] that can bridge this conundrum. By means of a light weighted, low resistive and low dead space pneumotachograph, we are able to quantify airflow during standard sleep studies. The quantification of airflow allows us to determine the physiologic traits that constitute to the development of OSA. In the current manuscript we describe the algorithm and the validation studies for how to determine upper airway critical closing pressure (P_{CRIT}), a measure of mechanical properties of the upper airway, from airflow measures at atmosphere.

II. METHODOLOGY

1. Conceptual Approach: The following conceptual framework forms the basis for our approach to determine the upper airway collapsibility from quantitative airflow signals during polysomnography. Using the Starling Resistor pressure-flow relationship model during airflow limitation: Where P_N= nasal pressure, airflow (V_{Imax}) and upstream resistance (R_{US})

$$P_N = V_{Imax} \cdot R_{US} + P_{CRIT} \quad (1)$$

For groups of individuals with increasing severity of upper airway collapsibility the pressure-flow relationship shifts to right from normal to apnea.

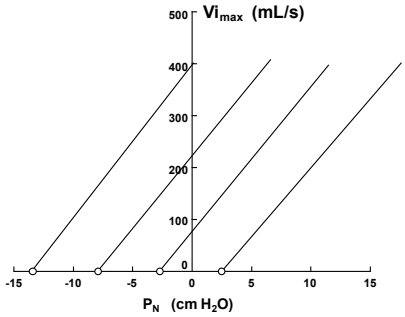

Figure 1. Pressure-flow relationship in subject groups across a spectrum of health and disease.

Pressure-flow relationships are obtained by sequential measurements of airflow across a spectrum of P_N levels (see *Experimental Methods*), however, during a polysomnographic study nasal pressure is atmospheric (i.e. P_N=0) which can be obtained utilizing a small, light-weight pneumotachograph [8].

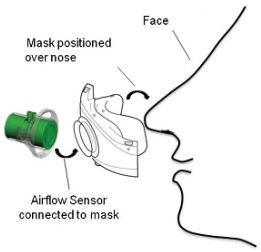

Figure 2. Light-weight, low dead-space, low resistance pneumotachograph attached to nasal mask.

Therefore, with substitution and rearrangement of equation 1, we can establish a linear relationship upper airway collapsibility, airflow and upstream resistance:

$$P_{CRIT} = -V_{Imax} \cdot R_{US} - (2)$$

Following from equation 2, if we can meet the assumption that R_{US} is constant, at least for a given population, the upper airway collapsibility is primarily dependent upon the airflow. Based on substitution of a constant value for R_{US} and measured airflow values at atmospheric pressure into equation 2 an estimated value for P_{CRIT} can be obtained as illustrated in Figure 3.

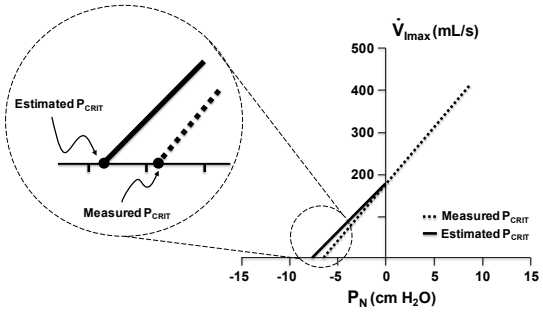

Figure 3. Illustrated approach to estimate P_{CRIT} using constant value for R_{US}.

Specific Aims: 1) Determine the minimum sample size with which upstream resistance performs as a constant and 2) develop and validate an approach to estimate upper airway collapsibility utilizing measurement of quantitative airflow.

2. Subjects: One hundred and twenty six individuals with and without sleep disordered breathing were recruited for this study.

3. Experimental Protocol: Individuals were subjected to CPAP and the nasal pressure was initially maintained at +5 cmH_2O, and reduced intermittently by steps of 1-2 cmH_2O for five breaths to induce upper airway obstruction as illustrated in Figure 4.

5. Analytic Methods: Data were obtained for the five breaths at each Pn level during non-REM sleep. Limitation in inspiratory airflow was considered to be present when inspiratory airflow reached a maximal level ($V_I$max) and plateaued as respiratory effort continued to increase. Breaths associated with micro-arousals from sleep were excluded from analyses. The peak inspiratory airflow from breaths 3-5 at each run was plotted against P_N to determine P_{CRIT} and R_{US} in each individual.

Sample Size Estimate and Population Value of R_{US}. For the entire group the mean, standard deviation and confidence intervals were determined. Bootstrap sampling (with replacement) was performed to determine the estimates of R_{US} variance for group sample sizes from n=3 to n=126. Group mean R_{US} and SD of thirty random estimates was plotted against the group size in order to determine sample size whereby estimated standard deviation was encompassed by the population confidence interval.

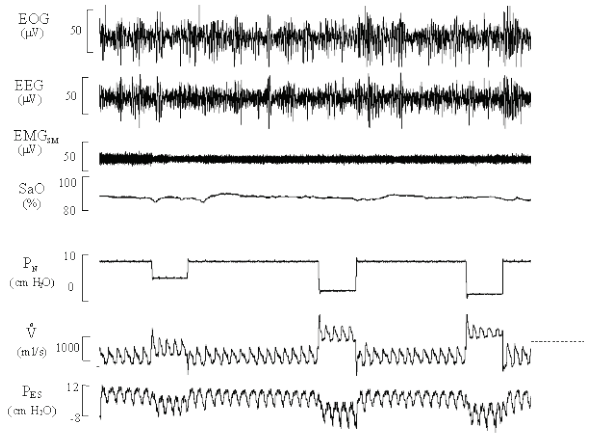

Figure 4. Raw data recording of the measurement of P_{CRIT} and R_{US} during sleep.

Modeling Upper Airway Collapsibility from Airflow. In a subgroup of 65 subjects, who had V_{Imax} >0 L/s, we estimated P_{CRIT} ($\hat{C}P_{CRIT}$) using the population estimate of R_{US} as a constant. Bland-Altman plots of the difference between measured and estimated P_{CRIT} vs. the average of the two values were examined for evidence of systematic

bias, the presence of heteroscedasticity, and to identify the limits of agreement that bound the mean difference between ϵP_{CRIT} and measured P_{CRIT} measurements (mean difference ±2 SD).

Validation of Upper Airway Collapsibility Model. In order to determine whether the assumptions developed in the model of estimated P_{CRIT} hold true we examined the agreement between ϵP_{CRIT} and P_{CRIT} in an independent group of subjects. Similarly, In a subgroup of 40 subjects, who had V_{Imax} >0 L/s, we determined ϵP_{CRIT} using the previous developed model and performed Bland-Altman analysis to compare the difference in measurements vs. the average of the two measurements.

III. RESULTS

Sample Size Estimate and Population Value of R_{US}. For the entire group (n=126) R_{US} was 22.9±1.0 cm H_2O/L/s with lower and upper confidence intervals of 21.0 cm H_2O/L/s and 24.8 cm H_2O/L/s respectively. The variability in R_{US} as a function of sample size is illustrated by the boot-strap sampling method plotting the mean and standard deviation (Figure 5).

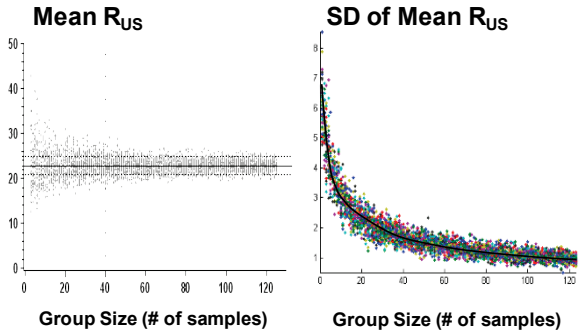

Figure 5: The distribution of mean (left hand panel) and standard deviation (right hand panel) for sample R_{US} values plotted against the sample group size. In the left hand panel, the population mean (solid line), upper and lower confidence intervals (dashed lines). In the right hand panel for a group size of approximately 40 subjects the SD primarily less than 2 cm H_2O/L/s (i.e. within the population confidence interval).

Modeling Upper Airway Collapsibility from Airflow: The Bland-Altman analysis did not demonstrate a systematic bias between measured P_{CRIT} and estimated P_{CRIT} values, with a mean difference of -0.1±1.6 cm H_2O; P=0.93 (see Figure 6) and lower and upper limits of agreement of -3.2 and +3.0 cm H_2O, respectively (Figure 6).

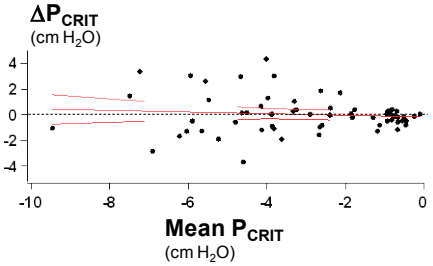

Figure 6. The difference Bland-Altman plots displaying ΔP_{CRIT} (the difference between measured P_{CRIT} and estimated P_{CRIT}) plotted against the average of the two values.

Validation of Upper Airway Collapsibility Model. In the validation series of subjects Bland-Altman analysis did not demonstrate a systematic bias between measured P_{CRIT} and estimated P_{CRIT} values, with a mean difference of -0.1±1.4 cm H_2O; P=0.96 (see Figure 7) and lower and upper limits of agreement of -2.9 and +2.7 cm H_2O, respectively (Figure 7).

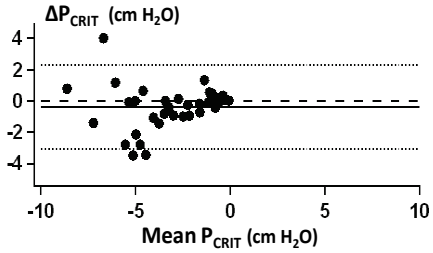

Figure 7. The difference Bland-Altman plots displaying ΔP_{CRIT} (the difference between measured P_{CRIT} and estimated P_{CRIT}) plotted against the average of the two values.

IV. DISCUSSION

In the current study we demonstrate that airflow measures at atmosphere are sufficient to estimate P_{CRIT} in a spectrum of patients from health to disease. This estimation of P_{CRIT} is equivalent to current techniques for determining P_{CRIT}. Thus, quantitative airflow measures during a standard sleep study would allow for determining physiologic upper airway traits in large scale studies.

Quantitative differences in P_{CRIT} determine sleep apnea disease status and can distinguish patients with and without sleep apnea. Like the measure of arterial pressure, P_{CRIT} is a measure from health to disease, while the apnea event rate is only an indicator for subjects who have the disease (like having symptoms of high blood pressure). Thus, P_{CRIT} is a continuous quantitative variable allowing to examine risk factors and pathogenetic factors for the development of sleep apnea.

Our approach for determining P_{CRIT} from atmospheric pressure requires a sample size of 40 subjects. Thus, accurate estimates for P_{CRIT} are only available for population based research but not for determining P_{CRIT} in single individuals. Translational research and epidemiologic studies, as well as clinical trials examining the efficacy or effectiveness of therapeutic agents, all require a large sample size. Thus, our novel technique is best suited for these kind of studies.

Rather than initiating new large studies to address pathogenic questions, the NIH has mandated investigators to utilize existing data sources. Compared to earlier epidemiological studies, current data sources are available in electronic format, however, there are limited tools for extracting relevant physiologic pathogenetic factors. If one could extract these parameters from large scale studies, one could identify the genetic basis of these physiologic pools of existing polysomnographic studies and could ask questions such as how do some diseases interact with

sleep apnea or what factors help to prevent the development of the disease.

To address these needs computational algorithms, scientific instrumentation, software analysis tools and a relational database that contains all elementary information for complex time series and data mining are required and facilitate a high through-put of translational research studies.

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V. REFERENCES

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