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Comparison of Upper Airway Respiratory Resistance Measurements with the Esophageal Pressure/Airflow Relationship during Sleep

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Abstract— Measurement of upper airway resistance is of interest in sleep disordered breathing to estimate upper airway patency. Resistance is calculated with the airflow and respiratory effort signals. However, there is no consensus on a standard for upper airway resistance measurement. This study proposes a new benchmarking method to objectively compare different upper airway resistance measurement methods by objectively differentiating between breaths with inspiratory flow limitation (high resistance) and non-limited breaths (low resistance). Resistance was measured at peak-Pes, at peak-flow, at the linear portion of a polynomial equation, as an area comparative and as average resistance for an inspiration. A total of 20 patients with systematic, gold-standard esophageal pressure and nasal airflow acquisition were analyzed and 109,955 breaths were automatically extracted and evaluated. Relative resistance values in relationship to a reference resistance value obtained during wakefulness were also analyzed. The peak-Pes measurement method obtained the highest separation index with significant ($p < 0.001$) differences to the other methods, followed by the area comparative and the peak-flow methods. As expected, average resistances were significantly ($p < 0.001$) lower for the non-IFL than for the IFL group. Hence, we recommend employing the peak-Pes for accurate upper airway resistance estimation.

I. Introduction

After sleep onset, the loss of muscular tone of the pharyngeal muscles usually leads to upper airway (UA) narrowing and a consequent increase in UA resistance. Hence, UA resistance is frequently measured during sleep to obtain information on changes in the cross-sectional area of the UA and UA obstruction. This is of critical importance in sleep disordered breathing (SDB), because an increase in UA resistance during the inspiratory phase is usually related to and helps differentiating obstructive and central apneas/hypopneas, inspiratory flow limitation (IFL) and/or other SDB events [1].

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UA resistance R is usually defined as

$$R = \frac{P}{\dot{V}} \qquad (1)$$

where P is a valid measurement of respiratory effort and $\dot{V}$ is airflow. Currently, the gold-standard to assess respiratory effort is esophageal pressure (Pes) measurement [2], despite being a complex and invasive technique.

However, there is no consensus on a standard measurement methodology for UA resistance. In previous studies, UA resistance has been calculated at the Pes-nadir [3, 4], at peak flow [3, 4], as an average resistance [4] or even with a polynomial equation [5]. Hence, it should be of interest finding out which of these methodologies achieves the most objective and optimal representation of UA resistance.

Previous studies [6 - 8] employed the Pes-flow ($P/\dot{V}$) relationship to objectively differentiate between IFL (highly obstructive) and non-IFL (non- or mildly obstructive) inspirations. In this study we propose a novel evaluation method that employs this relationship to benchmark and compare the mentioned resistance measurement methods. The aim is to objectively determine the measurement of UA resistance that best separates the high (IFL) and low (non-IFL) obstructive groups of inspirations.

II. Methodology

A. Subjects

Twenty subjects had full nocturnal polysomnography (NPSG) with an 18-channel recorder (Somnolab sleep diagnosis system, Weinmann GmbH, Hamburg, Germany) at the sleep laboratories of Klinikum Bethanien hospital in Solingen, Germany. The clinical protocol was specifically designed and approved by the hospital's Ethics Committee. Seventeen subjects were male and three were female. All subjects were lung-healthy without asthma and COPD. The patients' demographic data can be seen in Table I.

B. Data Acquisition

To obtain the respiratory signal, a nasal cannula device (Weinmann GmbH, Hamburg, Germany) was connected to a pressure transducer system (Weinmann GmbH, Hamburg, Germany). The airflow signal was recorded with a sampling frequency of 32Hz [2] and an 8-bit resolution. No absolute

TABLE I
DEMOGRAPHIC VALUES OF THE STUDIED POPULATION

	Mean ± StdDev	Range
Number of patients	20	
Gender (F/M)	3/17	
Age [years]	48.3 ± 16	23 – 77
Body-Mass-Index [kg/m^2]	28.1 ± 4.3	22 – 37.5
Apnea/Hypopnea Index [events/h]	11.2 ± 10.1	1.1 – 42.8

physical measurement units are given for the airflow signal because nasal cannula devices cannot be calibrated. Esophageal pressure was recorded with a unidirectional pressure-tip catheter (UniTip catheter by UNISENSOR AG, Attikon, Switzerland) that consisted of a piezoresistive pressure sensor with an accuracy of +/- 0.6 mmHg, a sensitivity of 5 µV/V/mmHg and a typical resolution of [-100,...,+300 mmHg]. A separate pressure amplifier (ISOPRE-P amplifier, Standard instruments GmbH, Karlsruhe, Germany) with a resolution of [-99 mmHg,...,+200mmHg] was connected to the catheter. The Pes signal was recorded with a sampling frequency of 16Hz and a 12-bit resolution. The catheter was introduced through the patient's nostrils after spraying the nasopharynx with Xylocaine and positioned in the lower third of the esophagus [9].

Other physiological signals, like arterial oxygen saturation (SpO_2), body position, pulse, and thoracic and abdominal respiratory inductance plethysmography (ProTech, Services Inc, Mukilteo, WA, USA) were recorded with an 8-bit resolution. Also 2 electroencephalogram channels (C3-A2/C4-A1), 2 electrooculogram (right/left), 1 submental electromyogram (EMG), 1 leg-EMG and an electrocardiographic (ECG) channel were systematically recorded with a sample frequency of 256Hz and a 12-bit resolution.

C. Pre-processing and Detection of Respiratory Cycles

The airflow and Pes signals presented noise and physiological disturbances that had to be reduced. The Pes signal was interpolated to a sampling frequency of 32 Hz. Then, a low-pass moving average (MA) filter with a cut-off frequency of 2.9 Hz at -3 dB was applied to both airflow and Pes signals [10]. The MA filter was applied in forward and reverse directions to achieve zero-phase. Inspirations were automatically detected and individually extracted from the airflow and Pes signals [8] to allow a separate analysis. Phase differences between corresponding airflow and Pes inspirations were compensated as described in [8].

D. The Esophageal Pressure/Airflow Relationship

After the pre-processing, the corresponding airflow and Pes inspirational pairs for each subject were assembled in a general pool of inspirations and made available for analysis.

The $P/\dot{V}$ -relationship is the gold-standard method to assess IFL [6 – 8]. IFL has been formally defined as a minimum decrease of 1 cmH_2O (0.7356 mmHg) of esophageal

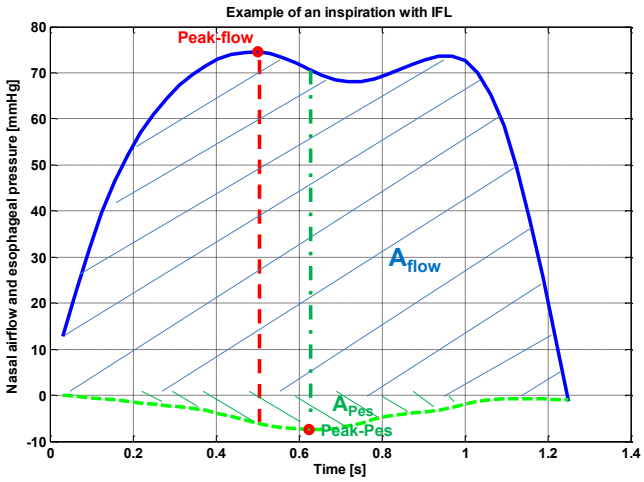

Fig. 1. Example of an inspiration with IFL: the corresponding airflow (solid blue line) and Pes signals (dashed green line) are displayed for one inspiration. Peak flow resistance is calculated with the corresponding airflow/Pes points at peak flow (see red dashed line). Similarly peak-Pes (green dash-dotted line) is calculated. Area resistance is calculated with the area of the flow curve (A_{flow}) and the area of the Pes curve (A_{Pes}), marked by the diagonal solid lines. Resistance is always calculated as $R=P/\dot{V}$.

(intrathoracic) pressure without a corresponding increase in airway flow rate [6, 7]. As all values beyond the pressure nadir do not contain IFL-related information (increasing Pes) [6, 7], each inspiration was cut at the time value of the Pes nadir to avoid hysteresis. The $P/\dot{V}$ -relationship was automatically constructed [7, 8] for each inspirational pair and the inspiration was assessed for IFL.

E. Measurement of UA Resistance

Resistance was measured for each inspirational flow-Pes pair applying equation (1) with the following methods:

- **Peak-Pes R:** resistance measurement at the peak-Pes value, see fig. 1
- **Peak-flow R:** resistance measurement at the peak-flow value, see fig. 1
- **Linear R:** resistance at the linear portion [5] was calculated with a 3rd degree polynomial equation that modeled the $P/\dot{V}$ -relationship of an inspiration. Real (not absolute) Pes values were used for its construction and the equation's coefficients were fit with a least-squares algorithm. Finally resistance at the linear portion was calculated as described in [5].
- **Area R:** in this study we also want to introduce a new resistance measurement. Resistance is calculated with the area values of the flow and Pes curves, respectively, see fig. 1. If flow had been recorded with a pneumotachograph (calibrated flow) this would be equivalent to the respiratory work performed by the patient. Even though flow was recorded here with a nasal cannula device, we still hypothesized that this measurement could be a good indicator for respiratory resistance.

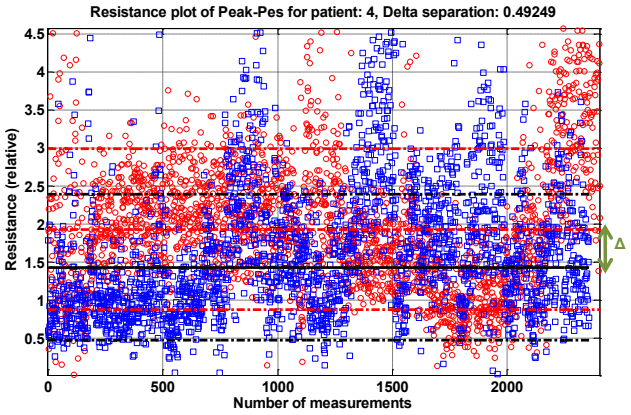

Fig. 2. Example of the measured resistance values of peak-Pes for one patient. Note the separation distance between the medians of the IFL (dotted line, red circles) and non-IFL (solid line, blue squares) resistance values. The separation index Δ is indicated by the arrow on the right side. Standard deviations are represented as dash-dotted lines. The number of resistance measurements is equivalent to the number of extracted breaths.

- **Average R:** average resistance was calculated as the mean over all resistance samples computed for a corresponding flow-Pes pair of an inspiration [4].

In some cases, extreme resistance values (defined as absolute values beyond the median with three times the standard deviation) appeared due to artifacts in the extracted inspirations and were excluded from the analysis.

The benchmarking index we propose for these resistance measurements is the separation distance between the IFL and non-IFL measurements. IFL breaths correlate with high UA resistance [6], while non-IFL breaths are low resistance events. Accordingly, the better the resistance measurement, the higher the separation between both groups should be, see fig. 2. We calculated the separation index for each patient as the normed difference of the medians of the two resistance groups (IFL and non-IFL)

$$\Delta = \left\| \frac{m(R_{IFL}) - m(R_{nonIFL})}{\left(\frac{stdev(R_{IFL}) + stdev(R_{nonIFL})}{2} \right)} \right\| \qquad (2)$$

where m is the median, $stdev$ the standard deviation, R_{IFL} the resistance measurements of IFL breaths and R_{nonIFL} the resistance measurements of non-IFL breaths. The Kolmogorov-Smirnov statistical test was employed to assess each data series for normal distribution. To evaluate if the calculated values for the five resistance measurement methods were significantly different between each other we employed the Kruskal-Wallis test.

Given the technical characteristics of nasal cannula devices, the airflow signal was not calibrated. Hence, to be able to compare resistance values between patients, each resistance measurement for a subject was referred to the median resistance of that subject obtained during a period of quiet respiration during wakefulness, as described in [3]. For this purpose the manually generated hypnogram of each patient was automatically imported and analyzed and the flow and Pes signals for the awake segments, especially at the beginning of the recordings before sleep onset, were extracted.

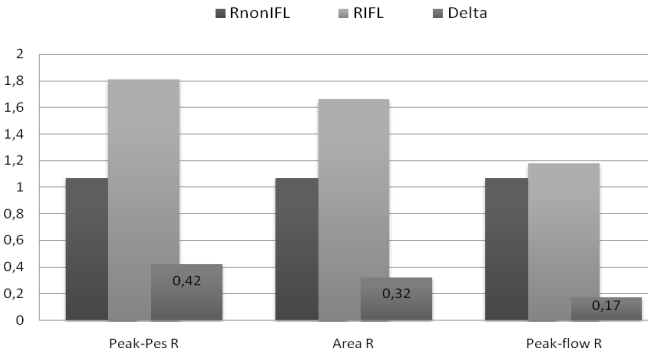

Fig. 3. Overview of the median for 20 patients of the non-IFL resistance, IFL resistance and delta separation for the best performing resistance measurement methods (Peak-Pes R, Area R and Peak-flow R).

III. RESULTS

A total of 109,955 breaths were automatically extracted and evaluated for our 20 patients. A total of 41,212 breaths (38%) had IFL, while 68,035 breaths (62%) were non-IFL. The results for all the resistance measurement methods can be seen in Table II. The maximal separation Δ value was obtained with the resistance measurement at peak-Pes (0.42), followed by the area resistance measurement (0.32), see fig. 3. The peak-flow measurement (0.17) and the average resistance (0.15) measurement obtained a similar outcome. The linear resistance measurement (0.04) presented the lowest **Δ** value of our benchmark. Similar resistance values were measured for non-IFL breaths for all five measurement methods and all were close to the measured resistance value during the wake phase (1.0). However, for IFL breaths the peak-Pes, the area and the average resistance measurement obtained significantly ($p < 0.001$) higher resistance values than the peak-flow and the linear methods. Neither one of the data series was normally distributed. The Kruskal-Wallis test that was applied respectively for the **Δ**, R_{IFL} and R_{nonIFL} data series showed significant ($p < 0.001$) differences for the values between the five resistance measurement methods.

TABLE II
OVERALL RESULTS (MEDIAN) OF THE RESISTANCE MEASUREMENTS FOR 20 PATIENTS, P < 0.001

	Peak-Pes R	Peak-flow R	Linear R	Area R	Average R
$\mathbf{R_{nonIFL}}$	1.07	1.07	1.05	1.07	1.03
$\mathbf{R_{IFL}}$	1.81	1.18	1.18	1.66	1.57
Δ	0.42	0.17	0.04	0.32	0.15

IV. Discussion and Conclusions

In this study we proposed a novel method to benchmark and objectively compare different measurement methodologies of UA resistance. This could be helpful to strengthen arguments in favor or against a certain measurement method as currently no standard for UA resistance measurement exists.

The airflow signal was obtained here with a nasal cannula/pressure transducer device. These devices are indicated by current NPSG guidelines [1, 11] for the identification of SDB events and have been routinely employed with the Pes signal for the identification and analysis of IFL [6]. Studies [6] have shown that a linear correlation between flow values obtained with a nasal cannula device and pneumotachography exists, if a square-root conversion is performed. However, as a nasal cannula device cannot be calibrated, we had to use a patient-dependent reference value, as described in [6], to compare resistance values between patients. The relative changes in UA resistance were calculated by referencing each measured resistance with a median resistance reference value obtained at the principal awake stage of each corresponding patient.

The results obtained here show that the resistance measurement at peak-Pes obtained the maximal separation Δ value between the IFL and non-IFL groups and that it was significantly ($p < 0.001$) higher than those obtained for the other measurement methods. Interestingly the newly proposed area index obtained the second highest Δ separation index, outperforming other popular measurements such as the peak-flow resistance or the average resistance measurements. As expected, the median resistance measurements obtained for the low resistance (non-IFL) group, see R_{nonIFL} in Table II, were all close to the calculated reference awake value of 1.0. This underlines the validity of the applied methodology and of the obtained measurement values. The measured median resistance values for the high resistance group (IFL), see R_{IFL} in Table II, were a multiple of the reference awake value (up to 81% higher e.g. for peak-Pes). Interestingly, the best performing measurement methods according to our Δ value also obtained the highest median R_{IFL} value, see fig.3 and Table II.

It appears that the separation performance of a measurement method is not necessarily related to the amount of information it contains on the whole breath. For instance, the area index was calculated with samples that represent the whole inspiration but it performed lower than the peak-Pes method that is only calculated at one sample point. Similarly, the average resistance value that is calculated with all an inspiration's resistance samples performed surprisingly lower than single-sample methods like peak-Pes and peak-flow. However, the area index outperformed the peak-flow method. Hence, it appears that the location and quality of the obtained information is of critical importance.

Nevertheless, the results obtained in this study should be carefully interpreted as several constraints apply. UA resistance is normally expressed as a single numerical value, providing only partial information on the intricate UA dynamics during sleep. Even a simplified human respiratory model has usually been electrically represented as an RCI-circuit [12, 13] that includes the phase delays between airflow and respiratory effort (i.e. Pes). Hence, UA impedance should be expressed as a complex number that contains the information on both UA resistance and phase shifts. As phase delays between airflow and Pes were compensated in the pre-processing phase of this study for simplification, here we only evaluated, as in most other studies [3 -5], the UA resistance part. In a future work, UA impedance should be consistently assessed without neglecting the information on flow/Pes phase delays and also include information on impedance variation over the different sleep stages.

Still, this study should be helpful on selecting the most appropriate method for the primary estimation of UA resistance. Here, the peak-Pes measurement method obtained the best overall score and should be primary considered for the purpose of clearly differentiating high and low obstructive resistances.

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