Variability of inspiratory conductance quantifies flow limitation

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ABSTRACT
In the present study, our aim was to investigate whether the variability of conductance over the course of inspiration reflects flow limitation. Pressure/flow conditions in the upper airway were modelled by a collapsible tube within a rigid chamber and a pump simulating respiration. Instantaneous conductance was estimated every 20 ms as flow/resistive pressure, and its variability during inspiration expressed as the 90th/50th percentile ratio. Accuracy of this ratio to quantify flow limitation was evaluated by observing whether it changed predictably with adjustments of model parameters. To illustrate the potential of this ratio to quantify flow limitation in a clinical setting, we recorded pneumotachographic airflow and oesophageal pressure in 11 patients with obstructive sleep apnoea during nasal continuous positive airway pressure (CPAP) ventilation, and observed changes in the 90th/50th percentile ratio of inspiratory lung conductance induced by mask pressure titration. Rising pressure surrounding the collapsible tube from subatmospheric to positive values induced progressive inspiratory collapse and increased 90th/50th percentile ratios of inspiratory conductance as predicted. Changes in flow limitation induced by other model modifications were also correctly tracked by the 90th/50th conductance percentile ratio. Increasing mask pressure during CPAP ventilation in sleep apnoea patients from subtherapeutic to therapeutic pressure levels was associated with the expected decrease in the 90th/50th percentile ratio of inspiratory lung conductance from a mean of 6.5 ± 3.1 to 1.6 ± 0.3 (P < 0.001). We conclude that variability of inspiratory conductance quantified by the 90th/50th percentile ratio may serve as a measure of flow limitation that is independent of the absolute value of conductance.

INTRODUCTION
Flow limitation is a physiological phenomenon observed in collapsible tubes, such as blood vessels and airways. It is defined as lack of increase in flow, despite a decrease in downstream pressure (P_{downstream}) [1]. Inspiratory flow limitation occurs in the upper airways of healthy subjects during undisturbed sleep [2]. However, in certain snorers and in patients with obstructive sleep apnoea, inspiratory flow limitation might cause sleep disruption [2,3]. Quantification of inspiratory flow limitation would be desirable to investigate upper airway physiology, to identify sleep disruptive upper airway obstruction and to assess the response to treatment. Yet, there is no generally accepted standard that quantifies flow limitation.

Hudgel and co-workers [4] described the upper airway pressure/flow relationship during sleep by fitting a hyperbolic equation. Their mathematical model performed well during steady positive pressure dependence of flow. However, the equation could not account for the variable positive and negative pressure dependence observed in severe flow limitation. Based on simultaneous

Key words: inspiratory flow limitation, physiological monitoring, respiratory mechanics, sleep apnoea, upper airway, upper airway resistance.
Abbreviations: CPAP, continuous positive airway pressure; C_{St}, compliance of the collapsible segment; C_{Cap}, compliance of the capacitance; FLI, flattening index; G_{lt}, instantaneous inspiratory lung conductance; G_{ltSt}, instantaneous inspiratory conductance of Starling resistor; P_{Ch}, chamber pressure; P_{downstream}, downstream pressure; P_{el}, elastic recoil pressure; P_{res}, resistive pressure; P_{tp}, transpulmonary pressure; R_{US}, upstream resistance; T_I, inspiratory time.
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measurements of pharyngeal pressure, airflow and airway dimensions by video-endoscopy, Isono and co-workers [5] described the physiological events during flow limitation in the upper airway in detail. The need for complex measurements and extensive instrumentation of the airway made their method unpractical for clinical application. Clark et al. [6] combined a mathematical analysis of the pressure/flow relationship with classification rules to obtain a semi-quantitative grading of flow limitation. Other authors applied moment analysis, such as the peak pressure/flow ratio [7], qualitative grading scales based on visual inspection of pressure and flow recordings [8,9] or the forced oscillation technique [10], to quantify flow limitation.

The aim of the present study was to evaluate a novel approach to the quantification of inspiratory flow limitation by means of flow and driving pressure measurements. The method is based on the variation of conductance over the time course of inspiratory breath cycles during flow limitation [11]. In the absence of flow limitation, airflow/driving pressure ratios determined multiple times during inspiration (instantaneous conductance) remain constant. In mild flow limitation, the flow/resistive pressure ($P_{res}$) ratios vary, but are still clustered around their median value. During severe flow limitation, flow/$P_{res}$ ratios peak in early inspiration and fall to lower values subsequently. This results in more widely and asymmetrically distributed values of instantaneous conductance (Figure 1). We reasoned that a numerical descriptor of the distribution of instantaneous inspiratory conductance could serve as a measure to quantify inspiratory flow limitation.

We tested our hypothesis in a bench model of the upper airway. It allowed adjustment of various parameters that induced predictable changes in the degree of inspiratory flow limitation. We found that among various evaluated descriptors of the distribution of the instantaneous inspiratory conductance of the Starling resistor ($G_{IS}$), the 90th/50th percentile ratio best reflected predicted trends of changes in flow limitation. To illustrate the clinical application of this ratio as a measure of inspiratory flow limitation, we derived the 90th/50th percentile ratio of instantaneous inspiratory lung conductance ($G_{IL}$) from airflow and oesophageal pressure recordings in patients with obstructive sleep apnoea undergoing continuous positive airway pressure (CPAP) titration. In addition, the flattening index (FLI) [7,12], a surrogate of flow limitation derived from the analysis of the inspiratory flow curve contour without requirement for driving pressure measurements, was determined for comparisons.

**METHODS**

**Bench studies**

The upper airway model comprised a collapsible tube within a rigid chamber (Starling resistor) [7], a constant upstream resistor and a capacitance connected downstream (Figure 2). A piston pump simulated respiration [13] with a tidal volume of 1 litre, rate of 40 breaths/min and inspiratory/expiratory time ratio of 1:2. Airflow and $P_{downstream}$ were digitally sampled at 50 Hz. Pressure within the chamber was measured with a water manometer. The diameter of the flexible tube was assessed visually.

**Protocol**

We performed measurements at baseline and during the following three interventions: (i) increasing compliance of the collapsible segment ($C_{St}$) by inserting a longer, more flexible, tube; (ii) decreasing compliance of the capacitance ($C_{Cap}$) by external strapping; and (iii) increasing upstream resistance ($R_{US}$) by reducing the lumen with a blender. During baseline conditions and after each intervention, chamber pressure surrounding the Starling resistor ($P_{Ch}$) was systematically varied every few pump cycles from $-18$ cmH$_2$O to $+18$ cmH$_2$O in steps of 3 cmH$_2$O by an adjustable constant pressure generator.
Figure 2  Model of the upper airway
The Starling resistor consisted of a flexible tube suspended within a rigid chamber. A piston pump generated airflow. Flow rate, $P_{downstream}$ and pressure within the rigid chamber surrounding the collapsible segment ($P_{Ch}$) were measured. Predictable trends of changes in flow limitation were induced by modifying various components of the model ($P_{Ch}$, $C_{St}$, $C_{Cap}$ and $R_{US}$) one at a time. A constant pressure generator allowed titration of $P_{Ch}$. $C_{St}$ was increased by inserting a flexible tube of greater length. $C_{Cap}$ was decreased by external strapping. $R_{US}$ was increased by insertion of a blender. Vibrations and the minimal outer diameter of the collapsible segment were assessed visually through the transparent wall of the rigid chamber.

Data analysis
For each $P_{Ch}$ level, we analysed three breathing cycles. Instantaneous inspiratory conductance of the upper airway ($G_{St}$) was computed every 20 ms as the ratio of flow to $P_{res}$:

$$G_{St} = V'/P_{res}$$

where $V'$ is the flow and $P_{res}$ is the difference between atmospheric pressure and $P_{downstream}$. The distribution of $G_{St}$ values was displayed graphically and described by computing percentiles [14].

FLI, a surrogate of inspiratory flow limitation that does not require measurement of driving pressure, was computed from inspiratory time series of flow as described by Teschler et al. [12].

$$FLI = \left[\text{mean } V'_{(25\% \text{ to } 75\% \text{ T})} - \text{mean } V'_{1}\right]/\text{mean } V'_{1}$$

where mean $V'_{(25\% \text{ to } 75\% \text{ T})}$ is the mean flow over the middle portion of inspiratory time ($T_{i}$), i.e. from 25 % to 75 % of $T_{i}$, and mean $V'_{1}$ is the inspiratory flow over the entire duration of $T_{i}$. In the absence of flow limitation, when the inspiratory flow contour is rounded, FLI has values of approx. 0.3. With moderate to severe flow limitation, the flow contour becomes flat or even concave, and FLI decreases to 0 or negative values.

Statistical comparisons among values from successive phases of the experiments were performed by analysis of variance [14].

Measurements in patients
Eleven patients with obstructive sleep apnoea gave informed consent to participate in the studies, which were approved by the Hospital Ethics Committee. We obtained recordings of oesophageal pressure and airflow by a flow meter attached to a nasal mask during polysomnography and CPAP titration was performed during non-REM sleep as described previously [9].

Data analysis
For each patient, periods with therapeutic, subtherapeutic or inadequate CPAP levels respectively, were identified by visual inspection of flow and $P_{res}$ tracings, according to the degree of inspiratory flow limitation. Inspiratory flow limitation was graded in a similar way to that proposed by Clark et al. [6] and Kaplan et al. [9]. Therapeutic CPAP, corresponding to the absence of flow limitation, was scored if the inspiratory flow contour was rounded and the flow/$P_{res}$ plot was almost linear (Figure 1A, panel 1). Subtherapeutic CPAP, corresponding to mild or moderate flow limitation, was scored if the inspiratory flow contour was somewhat flattened, and the flow/$P_{res}$ plot revealed linearity, but still a steady positive pressure dependence of flow (Figure 1A, panel 2). Inadequate CPAP, corresponding to severe flow limitation, was scored in the presence of an obviously flattened or concave inspiratory flow contour in combination with large $P_{res}$ swings and a pressure independence or negative pressure dependence in the flow/$P_{res}$ plot (Figure 1A, panel 3). Periods of three successive breaths corresponding to therapeutic, subtherapeutic and inadequate CPAP were analysed for each patient. $G_{Il}$ was calculated every 20 ms as:

$$G_{Il} = V'/P_{res}$$

where $V'$ is airflow recorded by the flow meter, and $P_{res}$ is derived from transpulmonary pressure ($P_{q}$) by subtracting elastic recoil pressure ($P_{d}$) [15]:

$$P_{res} = P_{q} - P_{d} = P_{q} - \left(\text{volume} \cdot E_{L}\right)$$

Volume $\cdot E_{L}$ is the product of volume and elastance of the lung. Descriptive statistics of $G_{Il}$ were computed as for the model. FLI [12] was determined as described above.

RESULTS
Measurements in the bench model
Figure 3 shows recordings obtained in the baseline experiment during application of subatmospheric ($P_{Ch} = 18 \text{ cmH}_{2}\text{O}$) and positive pressure ($P_{Ch} + 1 \text{ cmH}_{2}\text{O}$) within the chamber surrounding the Starling resistor. During subatmospheric pressure, the time series of airflow showed a rounded inspiratory contour (Figure 3, left-hand panels). The flow/$P_{res}$ relationship was nearly linear. Accordingly, the values of $G_{St}$ were clustered around the median value, and the 90th/50th percentile ratio of $G_{St}$ was low (1.6). FLI was 0.32. In contrast,
Figure 3  Bench model recordings during application of negative (left-hand panels) and positive (right-hand panels) pressures within the chamber surrounding the collapsible segment

Upper panels, time series of airflow (flow) and $P_{res}$. Lower panels, the corresponding plots of inspiratory flow (flow)/$P_{res}$ and histograms of $G_{Is}$. As the flow/$P_{res}$ relationship is slightly curvilinear, even during $P_{Ch}$ of $-18$ cmH$_2$O, a minor degree of flow limitation occurs. Accordingly, the value of the 90th/50th percentile ratio of $G_{Is}$ indicated in the bottom left-hand panel is 1.6, i.e. greater than the theoretical value of 1 obtained in the complete absence of flow limitation. The corresponding value for FLI is 0.32 (indicated in the upper left-hand panel). At $P_{Ch}$ of $+1$ cmH$_2$O, the variable positive/negative pressure dependence, and the mid-inspiratory oscillation of flow indicates considerable flow limitation. Accordingly, the value of the 90th/50th percentile ratio of $G_{Is}$ indicated in the bottom right-hand panel is 2.8. FLI has decreased to 0.09 (upper panel).

an intermittent collapse of the Starling resistor occurred during positive chamber pressure (Figure 3, right-hand panels). Inspiratory flow reached an early brief peak and dropped to lower values thereafter. As the inspiratory flow/$P_{res}$ relationship was clearly non-linear, $G_{Is}$ varied largely over the course of inspiration, and the distribution of these values was wide and skewed. Accordingly, the 90th/50th percentile ratio of $G_{Is}$ increased to 2.8. FLI fell to 0.09.

Figure 4 summarizes the effects of systematic variation of $P_{Ch}$ from negative ($P_{Ch} = -18$ cmH$_2$O) to positive ($P_{Ch} = +18$ cmH$_2$O) values on $G_{Is}$ (Figures 4A and 4B), and on FLI (Figure 4C) during baseline conditions and after the three types of intervention. Inspection of the collapsible segment revealed that its outer diameter remained fairly stable (8–10 mm) over the breathing cycle at subatmospheric $P_{Ch}$ levels of $-18$ to $-6$ cmH$_2$O. Over this range of $P_{Ch}$, the 90th/50th percentile ratio of $G_{Is}$ underwent only minor changes. When $P_{Ch}$ was raised above $-6$ to $-3$ cmH$_2$O, vibrations and an intermittent partial collapse of the Starling resistor became apparent. These correlates of flow limitation occurred during a progressively greater fraction of the inspiratory cycle the more $P_{Ch}$ was increased up to $+3$ to $+6$ cmH$_2$O. During this phase the 90th/50th percentile ratio of $G_{Is}$ reached maximal values. When $P_{Ch}$ was increased further to $+9$ to $+18$ cmH$_2$O, the collapsible segment was compressed (minimal outer diameter 4 mm or less) over a major portion, and, finally, over the entire duration of inspiration. At $P_{Ch}$ above $+9$ to $+12$ cmH$_2$O, vibrations and movements of the compressed collapsible segment became hardly visible and finally vanished. This indicated a major stable obstruction over the entire breathing cycle. The 90th/50th percentile ratio of $G_{Is}$ decreased over the range of $P_{Ch}$ of $+6$ to $+12$ cmH$_2$O to low values, and underwent only minor additional changes thereafter, although the $P_{Ch}$ increased further (Table 1).

The plots of the median value of $G_{Is}$ during increases of $P_{Ch}$ from $-18$ to $+18$ cmH$_2$O (Figure 4B) revealed a plateau with relatively high median $G_{Is}$ at $P_{Ch}$ below $-6$ cmH$_2$O, and another plateau with relatively low median $G_{Is}$ at $P_{Ch}$ above $+6$ cmH$_2$O. In between these levels of $P_{Ch}$, the median of $G_{Is}$ decreased progressively. Thus the changes in median $G_{Is}$ did not parallel the changes in the 90th/50th percentile ratio of $G_{Is}$, the measure of inspiratory flow limitation.

At low levels of $P_{Ch}$ (from $-18$ to $-9$ cmH$_2$O), values of FLI were between 0.27 and 0.50 (Figure 4C). At intermediate and high $P_{Ch}$ levels (from $-9$ to $+9$ cmH$_2$O), the index fell to values below 0.3.
Inspiratory flow limitation

Figure 4  Effects of systematic modification of bench model parameters on the 90th/50th percentile ratio of G_{IS} (A), on the median of G_{IS} (B) and on FLI (C)

Each panel shows the data obtained during variation of pressure within the rigid chamber (P_{Ch}) over the range of -18 to +18 cmH_{2}O during baseline conditions (line without symbols), and after modification of the following model parameters, one at a time, while others were kept constant (lines with symbols): (A–C, panel 1) after increasing C_{St} (C_{St} ↑), (A–C, panel 2) after decreasing C_{Cap} (C_{Cap} ↓), and (A–C, panel 3) after increasing upstream resistance (R_{US} ↑).

Table 1  Pressure and flow characteristics at various degrees of inspiratory flow limitation

<table>
<thead>
<tr>
<th>P_{Ch} (cmH_{2}O)</th>
<th>−18 to −12</th>
<th>0 to +6</th>
<th>+12 to +18</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Visual assessment of collapsible segment</strong></td>
<td>Widely open</td>
<td>Unstable</td>
<td>Collapsed</td>
</tr>
<tr>
<td><strong>Median G_{IS}</strong> (ml·s^{-1}·cmH_{2}O^{-1})</td>
<td>261 ± 2^*</td>
<td>133 ± 43^*</td>
<td>73 ± 6</td>
</tr>
<tr>
<td><strong>90th/50th percentile ratio of G_{IS}</strong></td>
<td>1.9 ± 0.2</td>
<td>3.0 ± 0.7^*</td>
<td>2.1 ± 0.2</td>
</tr>
<tr>
<td><strong>FLI</strong></td>
<td>0.35 ± 0.01^*</td>
<td>0.12 ± 0.04^*</td>
<td>0.23 ± 0.01^*</td>
</tr>
</tbody>
</table>

Compared with baseline conditions, the various interventions did not qualitatively alter the trends of G_{IS} with changes in P_{Ch}, but they induced quantitative changes. As expected, insertion of a longer, more flexible, tube with a higher compliance (C_{St} ↑) was associated with a greater tendency for collapse and higher values of the 90th/50th percentile ratio of G_{IS} (Figure 4A, panel 1). At P_{Ch} above +9 cmH_{2}O, measurements were interrupted in order to avoid damage to the model by rigorous pump actions against a nearly completely occluded airway. Decreasing compliance of the capacitance (C_{Cap} ↓) resulted in a more pronounced inspiratory collapse of the Starling resistor compared with baseline. This was reflected in higher values of the 90th/50th percentile ratio of G_{IS} (Figure 4A, panel 2). Measurements at P_{Ch} above +3 cmH_{2}O were not feasible. Increasing upstream resistance (R_{US} ↑) reduced median G_{IS} at all levels of P_{Ch} (Figure 4B, panel 3). On the other hand, the 90th/50th percentile ratio of G_{IS} decreased relative to baseline measurements at intermediate P_{Ch} of +3 to +6 cmH_{2}O (Figure 4A, panel 3). The effect of interventions on FLI is displayed in Figure 4(C).

Measurements in patients with obstructive sleep apnoea

In a patient studied during CPAP treatment at a therapeutic mask pressure of 10 cmH_{2}O, an almost linear flow/P_{res} relationship was found (Figure 5, left-hand panels). Reducing CPAP to an inadequate level of 6 cmH_{2}O was associated with inspiratory flow limitation, as confirmed by a variable pressure dependence of flow over the course of inspirations (Figure 5, right-hand panels). The increase in the 90th/50th percentile ratio of G_{IL} from 1.2 to 3.5 and the concomitant decrease of FLI from 0.22 to 0.04 were consistent with this trend. Figure 6 illustrates the gradual
Figure 5  Time series of airflow (flow) and $P_{res}$ (upper panels) and corresponding inspiratory flow/$P_{res}$ plots and histograms of $G_{IL}$ (lower panels) in a patient with obstructive sleep apnoea during application of a therapeutic (left-hand panels) and inadequate (right-hand panels) CPAP level via a nasal mask. CPAP was 10 and 6 cmH$_2$O in the left- and right-hand panels respectively. The 90th/50th percentile ratios of conductance are presented within the histograms (1.2 and 3.5 respectively), the corresponding values of FLI are indicated below the time series of flow (0.22 and 0.04 respectively).

Figure 6  Time series of airflow (flow) and $P_{res}$ (upper panels) and the corresponding flow/$P_{res}$ plots and histograms of $G_{IL}$ (lower panels) recorded in a patient with obstructive sleep apnoea during spontaneous respiration. The histograms of $G_{IL}$ are shown for each of the successive breaths. Development of flow limitation is reflected in the steady increase in the value of the 90th/50th percentile ratio of inspiratory conductance (indicated for each breath in the corresponding histogram panel), while FLI decreases (values indicated for each breath below the flow time series).
onset of inspiratory flow limitation over the course of a few breaths in a spontaneously breathing patient. As the inspiratory flow contour flattens, $P_{res}$ swings assume a progressively larger amplitude. The trend of increasing inspiratory flow limitation is demonstrated in the flow/$P_{res}$ plots over successive breaths by the change from near-linearity to almost no pressure dependence of flow. This is reflected in the steady rise in the 90th/50th percentile ratio of $G_{IL}$ from 1.4 to 10.3 and in a decrease of FLI from 0.22 to $-0.04$. Application of CPAP at a mask pressure of 5 cm H$_2$O was inadequate for one patient, as illustrated in Figure 7. The amplitude and shape of the flattened inspiratory flow contour changed little over four breaths. Accordingly, FLI remained within a narrow range. It did not reflect the changing breathing efforts. On the other hand, as $P_{res}$ swings varied over these four breaths, the 90th/50th percentile ratio of inspiratory conductance also changed and tracked consistently the effect of variable inspiratory efforts breath-by-breath.

Individual values of the 90th/50th percentile ratio of $G_{IL}$, median $G_{IL}$ and of FLI are plotted for therapeutic, subtherapeutic and inadequate CPAP for all 11 patients in Figure 8. In the majority of patients, observed trends of the three measures were consistent with progressive
flow limitation from therapeutic to subtherapeutic and inadequate CPAP (Figure 8 and Table 2). The relative scatter of the 90th/50th percentile ratio of $G_{IL}$ is greatest at inadequate CPAP and smallest at therapeutic CPAP (Figure 8A). Conversely, the relative scatter of median $G_{IL}$ is largest during therapeutic CPAP and smaller during inadequate CPAP (Figure 8B). The relative scatter of FLI varies little over the three CPAP levels (Figure 8C).

**DISCUSSION**

In the present study, we have evaluated a novel concept for quantification of inspiratory flow limitation. In a bench model of the upper airway, the proposed measure of flow limitation, the 90th/50th percentile ratio of $G_{IL}$, consistently reflected the trend of changes in inspiratory flow limitation induced by systematic adjustments of model parameters. Application of this concept to recordings of oesophageal pressure and airflow in patients with obstructive sleep apnoea illustrated its relevance in a clinical setting. In these patients, the 90th/50th percentile ratio of $G_{IL}$ is largest during therapeutic CPAP and smaller during inadequate CPAP (Figure 8B). The relative scatter of FLI varies little over the three CPAP levels (Figure 8C).

We have validated the proposed measure of flow limitation by demonstrating accurate tracking of changes in flow limitation known to result from adjustments of the bench model parameters. Systematic variation of transmural pressure from negative to positive values revealed relatively low values of the 90th/50th percentile ratio of $G_{IL}$ at $P_{Ch}$ values below and above a critical intermediate flow-limiting range. The latter was associated with visible instability of the collapsible segment and with increases in the 90th/50th percentile ratio of $G_{IL}$ (Figure 4). These observations were consistent with those of Conrad [18], who demonstrated that the flow/$P_{res}$ relationship in a flexible tube has linear regions when the tube is either widely open or fully collapsed, and a non-linear region during intermediate states. The 90th/50th percentile ratio of $G_{IL}$ accurately reflected these expected trends. Adjustments of the model parameters in addition to variations of $P_{Ch}$ corroborated these findings: the adjustments altered the 90th/50th percentile ratio of $G_{IL}$ in the intermediate $P_{Ch}$ range associated with instability of the collapsible segment only, whereas the ratio was barely altered at the lowest and highest $P_{Ch}$ levels (Figure 4).

Insertion of a longer, more flexible, tube promoted its collapse, and we observed the expected increase of the 90th/50th percentile ratio of $G_{IL}$ at flow-limiting intermediate $P_{Ch}$ (Figure 4A, panel 1). As the compliance of the capacitance was reduced and its propensity to dissipate volume and pressure diminished, we observed the expected greater tendency of the flexible tube to collapse. Accordingly, the values of the 90th/50th percentile ratio of $G_{IL}$ increased at intermediate $P_{Ch}$ in

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**Table 2 Effect of CPAP titration on measures of inspiratory flow limitation**

<table>
<thead>
<tr>
<th>CPAP</th>
<th>Therapeutic</th>
<th>Subtherapeutic</th>
<th>Inadequate</th>
</tr>
</thead>
<tbody>
<tr>
<td>CPAP level (cmH$_2$O)</td>
<td>8.8 ± 3.2$^\dagger$</td>
<td>6.8 ± 3.2$^*$</td>
<td>5.0 ± 3.0</td>
</tr>
<tr>
<td>Median $G_0$ (ml·s$^{-1}$·cmH$_2$O$^{-1}$)</td>
<td>589 ± 406$^\dagger$</td>
<td>205 ± 195$^*$</td>
<td>50 ± 45$^\dagger$</td>
</tr>
<tr>
<td>90th/50th percentile ratio of $G_0$</td>
<td>1.6 ± 0.3$^*$</td>
<td>3.1 ± 1.1$^*$</td>
<td>6.5 ± 3.1</td>
</tr>
<tr>
<td>FLI</td>
<td>0.20 ± 0.04$^*$</td>
<td>0.09 ± 0.09$^*$</td>
<td>0.01 ± 0.07$^*$$^\dagger$</td>
</tr>
</tbody>
</table>

Values are means ± S.D.; $n$ = 11 patients. $^*P \leq 0.01$ compared with the value of the corresponding variable at adequate CPAP. $^\dagger P \leq 0.01$ compared with the value of the corresponding variable at subtherapeutic CPAP.
comparison with baseline (Figure 4A, panel 2). Insertion of a blender upstream of the collapsible segment induced a constant reduction of median conductance by more than half at negative $P_{Ch}$ (Figure 4B, panel 3). Therefore the additional variable reduction of conductance related to intermittent collapse of the flexible tube at intermediate $P_{Ch}$ was relatively minor. Consequently, the 90th/50th percentile ratio of $G_{IL}$ at intermediate $P_{Ch}$ with added upstream resistance was lower compared with baseline (Figure 4A, panel 4).

The recordings in patients with obstructive sleep apnoea illustrate the potential of the 90th/50th percentile ratio of $G_{IL}$ to track changes in inspiratory flow limitation quantitatively. The measure of intra-breath variability of conductance indicated the degree of flow limitation independent of the absolute magnitude of conductance during changes in flow limitation induced by alterations in the CPAP level. This is illustrated by opposite trends in the scatter of values of the 90th/50th percentile ratio of $G_{IL}$ and median $G_{IL}$ at therapeutic and inadequate CPAP levels (Figure 8). Thus, at therapeutic CPAP levels, the median $G_{IL}$ varied widely between individual patients according to differences in airway geometry (Figure 8B). On the other hand, the 90th/50th percentile ratios of $G_{IL}$ were clustered at low values (Figure 8A), reflecting a minor variability of inspiratory conductance in the absence of flow limitation at therapeutic CPAP. These observations are consistent with a lower variability of lung resistance and elastance reported for patients with obstructive sleep apnoea during normal compared with partially obstructed breathing [19].

FLI, a surrogate of flow limitation derived from the inspiratory flow contour [12], underwent significant mean changes with alterations in CPAP levels (Table 2). However, for individual patients, the trends of changes in FLI were not perfectly homogeneous (Figure 8C). This is not surprising, since one aspect of flow limitation, i.e. the driving pressure, is not directly reflected in the shape of the flow contour. Figure 7 illustrates this fact by demonstrating an identical FLI for breath one and two, despite differences in $P_{res}$. Nevertheless, due to its favourable performance in differentiating severe from mild degrees of flow limitation and the convenient estimation from flow or nasal prong pressure tracings, FLI has become a valuable clinical measure for assessment of sleep-related breathing disturbances [20–22].

**Conclusions**

In the present study, we aimed to quantify inspiratory flow limitation by the variability of $G_{IL}$. Our measure of flow limitation, the 90th/50th percentile ratio of instantaneous conductance, is independent of the absolute value of conductance. It indicates absence of flow limitation by values in the range of 1 to 2, corresponding to a linear or almost linear pressure/flow relationship. Higher values of the 90th/50th percentile ratio of inspiratory conductance reflect the degree of flow limitation during positive or negative non-linear pressure dependence as well as during oscillatory flow. The bench model studies confirm accurate tracking of predicted changes in flow limitation by the 90th/50th percentile ratio of conductance. Measurements in patients with obstructive sleep apnoea illustrate the potential application of the proposed measure in the diagnosis of sleep disordered breathing and for monitoring of treatment effects.

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