Effects of inspiratory and expiratory positive pressure difference on airflow dynamics during sleep

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Sériesz, F., and I. Marc. Effects of inspiratory and expiratory positive pressure difference on airflow dynamics during sleep. J. Appl. Physiol. 85(5): 1855–1862, 1998.—We measured the effects of dissociating inspiratory and expiratory positive pressure (Pi and Pe, respectively) on the inspiratory flow limitation pattern and on genioglossus (GG) activity in nine sleep apnea patients. Measurements were made at two different levels of Pi with stepwise increases in Pe. Flow-limited breaths were observed during each recording session. In six of nine subjects, maximal inspiratory flow (V_{max}) was correlated with the difference between Pi and Pe (correlations were negative in 5 subjects, positive in 1 subject). In three other patients, V_{max} was not influenced by the amount of pressure difference. A positive relationship between tonic and/or phasic GG electromyographic activities and Pi-Pe difference was observed at least at one Pi level in all patients. This correlation was observed independently of the presence or absence of any relationship between V_{max} and the amount of pressure difference. Our results suggest that increasing the Pi-Pe difference (i.e., decreasing Pe) may be associated with a significant worsening in inspiratory flow limitation and that the V_{max}-pressure difference behavior is not dependent on the GG electromyographic-pressure response.

genioglossus; sleep apnea; hypopnea; upper airways; electromyography

UPPER AIRWAYS (UA) are an important determinant of airflow, especially during sleep. Numerous studies have been conducted both in animals and in humans to determine factors that influence UA resistance and the characteristics of flow pattern, i.e., the occurrence of a flow-limited regimen. In this regard, UAs during sleep are considered to behave like a Starling resistor (8). UA collapsibility is increased in the sleep apnea hypopnea syndrome (SAHS) and is responsible for the occurrence of recurrent episodes of partial or complete closure. Factors that modify UA shape or dimension, mucosal characteristics, and activity of UA muscles have been shown to dramatically influence UA collapsibility (9, 13, 26). The influence of airflow pressure on inspiratory flow has been demonstrated by several authors (19, 24). Two different mechanisms could account for the influence of positive pressure changes on inspiratory flow: the lung volume dependence of UA patenty, and the changes in neuromuscular activity of UA dilator muscles. UA patenty is lung-volume dependent (19, 22), and this dependence is probably related to changes in the position of the hyoid bone with tracheal traction (25). This can account for the decrease in inspiratory UA resistance that accompanies lung inflation, whether or not the lung inflation is associated with an increase in expiratory pressure (PE; 20). Changes in UA neuromuscular activity associated with UA pressure changes can also influence UA collapsibility: continuous positive airway pressure (CPAP) abolishes UA electromyographic (EMG) activity and increases collapsibility in sleeping SAHS patients (18, 24).

There is evidence that the end PE level may also significantly contribute to UA stability: 1) total expiratory pulmonary resistance progressively increases during the breaths that precede UA closure (16), 2) sleep-related obstructive breathing disorders partially improve with the application of a positive Pe (10), and 3) isolated inspiratory pressure (Pi) support is ineffective in this regard (15). In awake SAHS patients, the minimal UA cross-sectional areas are smaller with bilevel pressure than with constant positive pressure therapy (7). In normal subjects, UA EMG activity measured during wakefulness and sleep is differently influenced by positive Pi and Pe; i.e., alae nasi and genioglossus (GG) activities decrease with CPAP but increase with Pe (4). Therefore, dissociating Pi and Pe could differently influence the inspiratory flow regimen due to the respective effects of lung inflation and of changes in neuromuscular activity on UA patenty, but no study has specifically looked at repercussion of dissociation on airflow dynamic in sleeping subjects with SAHS. According to the results of these earlier clinical studies, Pe could, therefore, also contribute to influence inspiratory flow limitation. The aims of this study were to quantify the effects of dissociating Pi and Pe on the flow-regimen characteristics (presence and severity of flow limitation) and on GG activity in these patients by independently manipulating inspiratory and expiratory pressure levels during bilevel pressure therapy.

MATERIALS AND METHODS

Subjects. Nine SAHS patients treated at home with CPAP were included in the study. Their effective positive pressure (Peff) level, corresponding to the pressure that abolishes apnea, hypopnea, and flow-limited breathing, had to be >10 cmH2O. Patients were taking no medication and did not complain of any impediment in their nasal respiration. The protocol was accepted by the review board of our institution, and each patient signed an informed consent form for acceptance to participate in the protocol.

Protocol. An electroencephalogram (C4 A1, C3 A2, O1 A2), electrooculogram, and GG EMG were recorded continuously. The GG EMG signal was obtained with two surface electrodes mounted on a custom-made dental appliance and applied to the costs of publication of this article were defrayed in part by the payment of page charges. The article must therefore be hereby marked “advertisement” in accordance with 18 U.S.C. Section 1734 solely to indicate this fact.
the floor of the subject's mouth, as previously reported (5). EMG activity was amplified, filtered, rectified, and integrated. An esophageal balloon catheter was inserted through a nostril after local anesthesia was given, and the catheter was positioned in the distal one-third of the esophagus (1). A tightly applied nasal mask was connected through a Fleisch no. 2 pneumotachograph to a non-rebreathing valve (Whisper Swivel, Respironics, Murrysville, PA) and to a bilevel positive-pressure apparatus (ViPAP II; Resmed, Sydney, Australia) used in the spontaneous mode. One of the mask ports was connected to a pressure transducer (Validyne MP 45, ±100 cmH2O), and the other was connected to a CO2 analyzer (Ametek, Pittsburgh, PA). Esophageal pressure (Pes) was referenced to mask pressure.

Study design. After the different sensors were installed, the maximal awake GG EMG activity was measured during maximal inspiratory efforts against the occluded circuit and maximal forceful protrusion of the tongue against the maxillary alveolar ridge. Patients were then allowed to fall asleep in the supine position with the positive pressure apparatus set at the effective pressure level. Measurements were made in this supine position after a 15-min period of stable sleep with CPAP therapy. If the subject awakened during the course of the study, measurements were made after a minimum of 5 min of stable sleep.

PI and PE levels were adjusted separately by changing the corresponding pressure setting of the ViPAP machine. Measurements were made in random order at two different levels of PI that corresponded to Peff less 1 and 3–4 cmH2O, respectively. For each PI recording session, PI level was kept constant and PE was lowered to the lowest value that prevented obstructive apnea and was tolerated by the patient. The PE was then progressively raised in 1-cmH2O steps up to the PI level. Fixed PI and PE levels were maintained for at least 5 min before each recording was initiated, and 2-min recordings were obtained at each PE level. All PE recording sessions had to be completed before the PI level was changed. All variables were collected on a paper recorder, and flow, CO2, and pressure tracings were simultaneously recorded on a microcomputer.

Analysis. Breathing cycles were identified as flow limited when the inspiratory flow plateaued or decreased while driving pressure (difference between mask pressure and Pes) increased. At each mask pressure, breath-by-breath maximal inspiratory flow (VImax) for each flow-limited breathing cycle, phasic and tonic GG EMG activities, and expiratory and inspiratory CO2 fractions (FI(CO2)) were measured. Data collected during patient arousals were not retained for analysis.

All VImax measurements were obtained when the PE level had been reached. At the highest PI-Pe differences, it rarely occurred that there was no PE rise by the ViPAP machine, because the very small inspiratory flow generated during severe flow-limited breaths did not trigger the apparatus. These breathing cycles were not considered for analysis. To see whether the delay in pressure rise between PE and PI could have influenced our results, two different delays were measured at each pressure setting: 1) one was measured between inspiratory onset, identified on the flow tracing, and the beginning of the positive pressure rise from present expiratory values and 2) one was measured between inspiratory onset (defined as above) and the beginning of the PI plateau.

The relationship among VImax, GG EMG, and the difference between PI and PE obtained at each PI level was analyzed by least squares regression. To standardize the presentation of the results that were obtained at the different PI levels for the different subjects, as well as for one given subject, the changes in PE are expressed as the difference with PI (ΔP). EMG activity was expressed in percentage of maximal EMG awake value (11a).

RESULTS

Characteristics of subjects are shown in Table 1. Recordings were done during non-rapid-eye-movement sleep and predominantly in stage 2 sleep. Measurements could be obtained at two PI levels in seven subjects (PI = Peff - 3 cmH2O for 5 subjects, and -4 cmH2O for 2 subjects) and at PI = Peff - 1 cmH2O only in two of the nine subjects. The mean PI-PE difference for all recording sessions was 4 ± 1 (SD) cmH2O.

In each subject, flow-limited breaths were observed at each pressure recording session. These flow-limitation episodes were not accounted for by a delay in the rise in positive pressure from the PI to the PI values, because all VImax values were measured at PI. A representative recording of raw data obtained in one patient at different PE levels is shown in Fig. 1. In five of nine subjects (patients 1–5), VImax progressively increased with decreasing the difference between PI and PE (Fig. 2), with a negative significant relationship between these variables (correlation coefficient range: −0.32 to −0.83, P < 0.05). Three of these five patients (patients 1–3) had measurements at two different PI; the negative VImax/PI-Pe relationship was observed at both PI levels in patients 1 and 3, and an increase in PI was associated with an upward shift of the slope of the relationship (Fig. 2). In patient 2, measurements made at the higher PI level (13 cmH2O) were obtained in slow wave sleep, whereas only stage 2 sleep was recorded at 11 cmH2O. In three other patients (patients 7–9), VImax was not influenced by the amount of pressure difference at both PI levels (Fig. 2). In the last subject (patient 6), there was a significant positive relationship between these parameters at the two PI levels (r = 0.55 and 0.35, respectively; P ≤ 0.01). These different VImax-pressure difference behaviors did not correspond to any difference in body mass index, neck circumference, baseline apnea+hypopnea index, or Peff. There was no correlation between the delays in pressure rise and the maximal PI-Pe difference nor with breath-by-breath values of VImax (R ≤ 0.34, P > 0.1).

For technical reasons, sleeping GG EMG activities could not be measured in two patients (patients 6 and 7). In the others, tonic and/or phasic GG EMG activities progressively decreased with decreasing ΔP (Fig. 2). There was a positive relationship between tonic and/or phasic GG EMG activities, and the difference between PI and PE was at least at one PI level (Fig. 2) in each of them. This correlation was noted in the seven sessions

Table 1. Anthropometric and nocturnal breathing characteristics of participating patients

| Age, yr | 52±9 |
| Body mass index, kg/m² | 40.0±7.6 |
| Neck circumference, cm | 50.1±3.5 |
| Baseline apnea + hypopnea index, no/h | 69.2±28.6 |
| Effective pressure, cmH2O | 13±2 |

Values are means ± SD; n = 9 subjects.
in which $\dot{V}_{\text{Imax}}$ correlated negatively with the amount of \(\Delta P\) and in three other sessions without correlation (Fig. 2).

For the entire bilevel positive-pressure trials, $F_{\text{ICO2}}$ did not change significantly from the maximal to the minimal $P_i$-$P_e$ difference ($0.138 \pm 0.093\%$ and $0.099 \pm 0.093\%$, respectively; $P = 0.07$), and the breath-by-breath value of $F_{\text{ICO2}}$ did not correlate with the difference in the $P_i$ and $P_e$. A positive correlation between these variables was found in four trials (2 in one subject at $11$ and $13$ cmH$_2$O $P_i$, and in two other subjects at $8$ and $10$ cmH$_2$O $P_i$, respectively), with the correlation coefficient ranging from $0.61$ to $0.90$ ($P \leq 0.02$). In these last two subjects, this relationship was noted for the highest positive pressure level (10 cmH$_2$O) but not for the smallest one (8 cmH$_2$O). The $\dot{V}_{\text{Imax}}$ or EMG GG response to changing $P_i$-$P_e$ difference was not different in these trials than in the others. The average breath-by-breath end-tidal CO$_2$ fraction did not change between the maximal to the minimal $P_i$-$P_e$ difference ($5.18 \pm 0.77$ and $4.84 \pm 1.72\%$, respectively; $P = 0.9$).

**DISCUSSION**

Our results suggest that increasing the difference between $P_i$-$P_e$ levels may be associated with a significant worsening in inspiratory flow limitation and that the $\dot{V}_{\text{Imax}}$-pressure difference behavior is not related to the GG EMG-pressure response.

There is evidence that UA flow-limitation pattern is influenced by UA hysteresis during CPAP therapy (3). Our measurements were obtained at fixed $P_i$ levels and varying $P_e$ values; we are not aware of any data in the literature on the influence of $P_e$ on these hysteresis characteristics. Recordings in the present study were made at the different $P_i$ levels, in random order, with a 5-min delay separating each recording session, and positive pressure trials were always conducted with ascending $P_e$. Therefore, we believe that this study design should have limited the influence of UA hysteresis on the $\dot{V}_{\text{Imax}}$-mask pressure relationship.

CPAP is known to have a depressive effect on activity of UA muscles (24), but little is known about the effects of positive $P_e$ changes on the activity of these muscles and on their mechanical effects. Interestingly, recently published results showed that low CPAP and positive $P_e$ levels have opposite effects on alae nasi and GG activities in normal sleeping subjects (4). Therefore, the progressive decrease in GG EMG activity that we observed with increasing $P_e$ at fixed $P_i$ level suggests that the positive $P_i$ level could modulate the influence of positive $P_e$ on activity of UA muscles. However, any direct comparison between our data and those of Deegan...
Fig. 2.

A

Patient 1

Expiratory pressure: 11 cm H₂O

R: 0.33, p<10⁻⁴

Phasic R: 0.18, p<0.04

Tonic

Patient 2

Inspiratory pressure: 11 cm H₂O

R: 0.41, p<10⁻³

Phasic R: 0.72, p<10⁻⁴

Tonic R: 0.67, p<10⁻⁴

Patient 3

Inspiratory pressure: 8 cm H₂O

R: 0.56, p<10⁻⁴

Phasic R: 0.56, p<10⁻⁴

Tonic R: 0.65, p<10⁻⁴

SWS. Inspiratory pressure: 13 cm H₂O

R: 0.84, p<10⁻³

Phasic R: 0.84, p<10⁻³

Tonic

Inspiratory pressure: 10 cm H₂O

R: 0.32, p<0.04

Phasic R: 0.33, p<0.01

Tonic R: 0.30, p<0.01

Fig. 2.
Fig. 2, cont.

B

Patient 4

Inspiratory pressure: 9 cm H₂O

Patient 5

Inspiratory pressure: 10 cm H₂O

Patient 6

Inspiratory pressure: 8 cm H₂O

Patient 7

Inspiratory pressure: 7 cm H₂O

Inspiratory pressure: 10 cm H₂O
Fig. 2. Individual relationships in patients 1–3 (A), 4–7 (B), and 8 and 9 (C) among breath-by-breath values of maximal inspiratory flow ($V_{\text{I max}}$) of flow-limited breaths, tonic and phasic GG EMG activity, and inspiratory-expiratory pressure difference (delta pressure). SWS, slow-wave sleep (patient 2, right). % max awake, percentage of maximal awake value.
et al. (4) is limited by the fact that our data were obtained in sleep apnea patients and at significantly higher positive PI and Pe levels. One plausible explanation for the increase in GG EMG activity with increasing PI-Pe difference is that ventilatory central drive may have increased at the highest pressure differences. This could be accounted for by the progressive increase in inspiratory efforts with worsening flow limitation, i.e., decreasing V_{\text{max}}, that was observed in the present and other studies (23) and that has been described by other authors (12). This increase in activity of UA dilator muscles with increasing efforts has been documented during CO_{2} rebreathing (14) and correlates with increasing central respiratory drive (21). In some of our trials, this increase in ventilatory drive may have been accounted for by CO_{2} rebreathing at the highest PI-Pe differences due to increasing dead space (6), as suggested by the progressive rise in FICO_{2} with increasing PI-Pe difference in 4 of 16 trials.

The major findings of our study are that flow-limited breaths reappear during bilevel positive-pressure therapy and that these events may worsen with widening of the PI-Pe difference when the PI is set at the optimal or suboptimal level. Gugger and Vock (7) have compared the UA area during CPAP and bilevel positive-pressure therapy in awake sleep apnea patients; they found that the minimal velopharyngeal and hypopharyngeal areas were smaller with bilevel than with constant CPAP therapy. These results may be directly applicable to those obtained in the present study, because they were obtained with similar positive pressure levels. Both results could be accounted for by the lung-volume dependence of UA structures and by the intrabreath hysteresis of UA cross-sectional area. It is known that the cross-sectional area of UA is smaller in sleep apnea patients than in normal subjects, and this difference is particularly important at low lung volumes (2). The role of hysteresis on UA patency at the different UA anatomic levels is particularly important in sleep apnea patients whose UA cross-sectional area is minimal at end expiration (17). Therefore, lung deflation that is associated with the reduction in Pe should lower UA area and promote inspiratory flow limitation.

It is particularly interesting, from a mechanical point of view, to note that the changes in GG EMG activity could be dissociated from those in flow characteristics, with decreasing GG activity being accompanied by an increase, or decrease, or stability of V_{\text{max}}, of flow-limited breaths. This could be explained by a passive enlargement of UA structures due to tracheal traction and/or an improvement in UA dilator efficiency with increasing lung volumes (25). The individual variability in UA collapsibility with bilevel positive pressure could not be accounted for by differences in anthropometric or sleep-related breathing characteristics; this variability could be related to the individual UA shape and dimension response to changing lung volume.

To increase the sensitivity of our method, the dissociation between PI and Pe was made after decreasing the PI below the Peff level. It could be asked whether our results could be extended to bilevel positive-pressure therapy, in which the PI level is usually set at the Peff level (15). It is important to note that in five trials, flow limitation was noted at pressure differences >1 cmH_{2}O but was abolished at the suboptimal PI level when the Pe was equal to (n = 3) or below (n = 2) Peff (Fig. 2). This suggests that inspiratory flow limitation can occur with decreasing Pe even if PI is set at a Peff level.

We conclude that the influence of bilevel positive-pressure therapy on UA stability may differ between SAHS patients, the decrease in the Peff sometimes being associated with a progressive worsening of inspiratory flow limitation during sleep. Further studies are needed to evaluate the possible clinical repercussions of these findings in patients with different ranges of positive Peff levels.

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