Upper airway collapsibility and patterns of flow limitation at constant end-expiratory lung volume

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Abstract

The passive pharyngeal critical closing pressure (Pcrit) is measured using a series of pressure drops. However, pressure drops also lower end-expiratory lung volume (EELV), which independently affects Pcrit. We describe a technique to measure Pcrit at a constant EELV. CPAP treated obstructive sleep apnea (OSA) patients and controls were instrumented with an epiglottic catheter, magnetometers (to measure change in EELV), and nasal mask/pneumotachograph and slept supine on nasal CPAP. Pcrit was measured in standard fashion and using our novel “biphasic technique” in which expiratory pressure only was lowered for one minute prior to dropping the inspiratory pressure; this allowed EELV to decrease to the drop level before performing the pressure drop. 7 OSA and 3 controls were studied. The biphasic technique successfully lowered EELV prior to the inspiratory pressure drop. Pcrit was similar between the standard and biphasic techniques (-0.4±2.6 vs. -0.6±2.3cmH2O, respectively, p=0.84). Interestingly, we noted three different patterns of flow limitation: 1) classic Starling resistor type – flow fixed and independent of downstream pressure, 2) negative effort dependence within breaths – substantial decrease in flow, sometimes with complete collapse, as downstream pressure decreased 3) and negative effort dependence across breaths – progressive reductions in peak flow as respiratory effort on successive breaths increased. Overall, EELV changes do not influence standard passive Pcrit measurements if breaths 3-5 of pressure drops are used. These results also highlight the importance of inspiratory collapse in OSA pathogenesis. The cause of negative effort dependence within and across breaths is not known and requires further study.

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Key words

Obstructive sleep apnea, Pharyngeal critical closing pressure, Starling resistor
Introduction

Obstructive sleep apnea (OSA) is a common disease characterized by repetitive collapse of the upper airway during sleep, leading to arousals, sleep fragmentation and intermittent hypoxemia. Although OSA may have multiple contributing factors, poor upper airway anatomy is likely the dominant factor in most cases. (13) Anatomy has been quantified in many ways during wakefulness and sleep, but one of the more useful methods has been the measurement of upper airway collapsibility. (6) The pressure required to collapse the upper airway is the pharyngeal closing pressure, or Pcrit, and this can be thought of as the equivalent pressure surrounding the upper airway lumen. (26) Higher pressures indicate greater collapsibility, and Pcrit has been shown to correlate with OSA and OSA severity. (5)

Pcrit can be measured in a relatively passive airway (minimal upper airway muscle activity) by abruptly lowering the airway or mask pressure to sub-therapeutic levels of continuous positive airway pressure (CPAP) for 3-5 breaths. Although relatively easy to perform, this method of determining upper airway collapsibility is imperfect. The reduction in mask pressure also causes a decrease in end-expiratory lung volume (EELV), which falls in relation to the pressure change. (18) EELV is known to independently affect Pcrit. (18, 27, 29) Increased lung volume stabilizes the upper airway, possibly through increased caudal traction, with a reduced (more negative, less collapsible) Pcrit. Conversely, decreased lung volume can potentiate collapse and an increased (less negative, more collapsible) Pcrit. Our group and others have attempted to measure Pcrit independently of changes in EELV. However, these methods are cumbersome (often using a head-out rigid shell or “iron lung”) and anticipate, but do not prevent, the changes in lung volume that occur during the pressure drop. Thus, an easy methodology to change
airway pressure while lung volume is constant could eliminate a confounding variable in the true measurement of Pcrit.

Such a technique would also answer a second related question. To account for changes in EELV, breaths 1 and 2 of a pressure drop are often discarded, and only peak flows during breaths 3-5 (if flow limited) are used in the determination of Pcrit. Although EELV may equilibrate rapidly (within 1-2 breaths), the effects of EELV on the airway might not be immediate, i.e. there may be lingering effects on breaths 3 and 4 through the temporal behavior of tissue stress adaptation (either relaxation or recovery). Comparison of Pcrit measurements made in a standard fashion and with EELV held constant could answer this question. Phrased another way, if EELV were held constant for all 5 breaths of the pressure drop, rather than decreasing over the first few breaths, would the measured Pcrit be the same?

During a pressure drop, breath by breath peak inspiratory flows typically “roll-off” – that is, peak inspiratory flow decreases with each successive breath – until reaching an approximate steady state (see FIGURE #1). It is assumed, but not known, that the initial roll-off in peak flow during breaths 1-3 is related to the change in lung volume that occurs with the pressure drop.(24) However, we have observed similar roll-offs in peak flow during more prolonged pressure drops, well after any changes in EELV would be expected to have occurred.(30) Moreover, these “late” roll-offs in flow occur while minute ventilation is below eupnea and ventilatory drive (PCO₂) is increased, which should stimulate upper airway muscle activity to improve flow.(11, 28) This observation suggests that the initial roll-off in flow might not be due solely to changes in EELV.
Thus, increasing respiratory effort or some other unidentified mechanism may be contributing to both this early and late decrement in peak flow.

Here we propose a technique to measure Pcrit at a constant end-expiratory lung volume, termed the “biphasic” technique: pressure is dropped first only in expiration to allow EELV to fall and equilibrate, then inspiratory pressure is also dropped and inspiratory flow is assessed to determine Pcrit. By comparing the traditionally measured Pcrit with the Pcrit measured using the biphasic technique, we sought to determine whether changes in EELV that occur during the pressure drop affect the Pcrit, and whether waiting until breaths 3-5 adequately accounts for EELV changes. In addition, this technique allowed us to test the hypothesis that a progressive fall in EELV is the cause of the “roll-off” in inspiratory flow after a pressure drop. Specifically, if the roll-off after a pressure drop is due to changes in EELV, we would expect no roll-off in flow while EELV is held constant. By contrast, persistence of the roll-off would suggest that factors other than changes in EELV are leading to decreases in flow.

**Methods**

**Ethical Approval:** All subjects gave written, informed consent before participation in this study, which was approved by the Human Research Committee of the Brigham and Women’s Hospital and conformed to the standards set by the Declaration of Helsinki.

**Subjects:** A total of 13 subjects (10 OSA, 3 controls) were recruited for the study. Subjects included previously diagnosed OSA patients using CPAP therapy for greater than 3 months, and healthy controls not known to have a sleep disorder. No study subject had ever smoked, had any
other respiratory disorder, or took medications known to affect respiratory or airway/muscle function. Two patients were on medication for the treatment of hyperlipidemia, one was on medication for treatment of hypertension, one used a proton-pump inhibitor, and one was on a stable dose of thyroid hormone replacement. While some of the OSA subjects in this study participated in other studies conducted in our laboratory, none of the findings of the present study have been previously published.

**Equipment:** The study consisted of a single overnight experiment. Patients arrived two hours before their usual bedtime to be instrumented. Wakefulness and sleep stages were determined using standard electroencephalogram, chin electromyogram, and electro-oculogram. Airway pressure was measured at the level of the epiglottis using a pressure-tipped catheter (Millar MPC-550, Millar Instruments, Inc., Houston, TX) passed through the nose and advanced 1.5 to 2 cm below the base of the tongue under direct visualization. Prior to insertion, both nostrils were sprayed with 0.05% oxymetazoline hydrochloride, a decongestant, and the more patent nostril was then anesthetized with 4% lidocaine topical spray. A nasal mask (Profile Lite or GoldSeal, Respironics, Murraysville, PA) was placed over the nose and airflow was measured with a pneumotachograph (model 3700A, Hans Rudolph Inc., Kansas City, MO) and a differential pressure transducer (model MP45, Validyne Corp., Northridge, CA). Two pairs of magnetometers (EOL Eberhard, Oberwil, Switzerland) were placed on the front and back of the subject along the midline at the level of the sternum and just above the umbilicus. Calibration was performed during wakefulness by comparison with tidal volumes recorded by the pneumotachograph. Expired CO₂ was continuously recorded from a catheter placed in the nostril with a capnograph (Vacumed, Ventura, CA). Arterial blood oxygen saturation via pulse
oximetry (BCI, Waukesha, WI) and the electrocardiogram were monitored throughout the study
for safety purposes. During the night, positive pressure was provided using either a modified
CPAP machine (Respironics, Murrysville, PA) capable of providing positive or negative
pressure, and able to switch rapidly between settings, or a commercially available BiPAP®
Synchrony™ device (see below).

Data were acquired on a 1401 plus interface and Spike 2 software (Cambridge Electronic Design
Ltd, Cambridge, UK).

Protocol: When subjects were awake and lying comfortably in bed, magnet calibration was
performed. CPAP was then applied and subjects were allowed an opportunity to sleep. CPAP
was initially set at the therapeutically prescribed level for OSA patients and at 4 cmH₂O for
controls, and it was increased if needed during sleep to eliminate flow limitation (flattened
inspiratory flow, dissociation between mask and epiglottic pressure), snoring, or chest-abdomen
paradox. This level of CPAP is referred to as the holding pressure. Once stable non-REM sleep
had been achieved, passive Perit measurements were made using either standard pressure drops
or “biphasic” drops (described below), in random order. Repeated Perit measurements were
made using both methodologies as many times as possible during stable non-REM sleep.

Patients were given time to re-enter stable sleep after brief arousals, but if they awoke the
measurement was aborted until stable sleep resumed. Patients slept supine.

Standard pressure drops: Using the modified CPAP machine, standard Perit measurements were
made by abruptly dropping the airway pressure for 3-5 breaths from the holding pressure to
progressively lower CPAP levels, typically starting 1 or 2 cmH2O below the holding pressure and progressing in decrements of 0.5 or 1 cmH2O per drop. If necessary, negative airway pressure was applied. Pressure drops were separated by at least one minute.

Biphasic pressure drops: At the start of the biphasic pressure drop, the expiratory pressure only was reduced to the drop pressure of interest for 1 minute. The inspiratory pressure remained at the holding pressure during this “bilevel period.” During the bilevel period, EELV should fall yet ventilation should be maintained. After 1 minute the inspiratory pressure was also decreased to the drop pressure – the “CPAP period” (see FIGURE #2). The drop pressure was initially 1-2 cm H2O below the holding pressure and was decreased with each successive drop by 0.5 to 1 cmH2O. For pressure drops to 4 cmH2O or above, the BiPAP® Synchrony™ was used in Spontaneous (S) mode. During the bilevel period, inspiratory positive airway pressure was set at the holding pressure and expiratory positive airway pressure (EPAP) set to the drop pressure. At the end of the bilevel period, the ventilator mode was switched to CPAP and set at the drop level. As commercially available systems do not allow an EPAP of less than 4 cmH2O, for pressure drops below this level, we used the modified CPAP machine to switch manually between holding and drop pressures during the bilevel period. Pressure was increased to the holding pressure just after the start of inspiration, and decreased to the drop pressure as inspiratory flow approached zero. The “CPAP period” was continued until stable flow limitation developed for approximately 1 minute or apnea or arousal occurred, at which point pressure was returned to the holding pressure.
Analysis: Data were analyzed on a breath-by-breath basis using custom-designed semi-automated software. Analyzed variables included: inspiratory time, expiratory time, tidal volume, peak flow, mask pressure, and rib cage and abdominal anterior-posterior distance (provided continuously by each respective magnetometer pair). For each breath, magnetometer distances were measured just prior to inspiratory flow. If flow was obstructed, then the first negative deflection in epiglottic pressure was used to define the end of expiration and the start of the breath.

To determine Pcrit, mask pressure and peak inspiratory flow from breaths 3-5 during each pressure drop series were plotted only if the breaths were flow limited. Breaths 3-5 of the CPAP period, if flow-limited, were used to determine the Pcrit using the biphasic technique. A linear regression model of peak inspiratory flow vs. mask pressure was used to extrapolate the pressure at zero flow, defined as Pcrit. The multiple Pcrit values in each condition were averaged to determine a Pcrit using standard pressure drops and a Pcrit using biphasic pressure drops.

Changes in end-expiratory lung volume were determined using a previously validated relationship between magnetometer readings and lung volume. During each breath of a standard pressure drop, the magnetometer distances at the start of inspiration were compared with the average of these distances during the 5 breaths immediately preceding that drop. The differences in distance and the previously determined calibration factor were used to measure acute changes in lung volume during Pcrit measurement. For each pressure drop, the lung volume changes during breaths 3-5 were plotted against the change in mask pressure (measured at end expiration) from the holding pressure, and a linear regression model was fitted to the data.
For the biphasic pressure drops, the 5 breaths immediately preceding the drop were also used as baseline. The last five breaths during the bilevel period were used to assess changes in lung volume, tidal volume, and CO2 that occurred during the bilevel period. Similar to the standard pressure drops, the relationship between the change in lung volume for a given change in expiratory pressure was determined. Once the inspiratory pressure was also decreased to the drop pressure, EELV was assessed for further change during the breaths of the CPAP period.

Statistical Analysis: Paired Student’s t-test was used to compare Pcrit values obtained using standard and biphasic pressure drops. Tidal volume and end-tidal CO2 at baseline and at the end of the biphasic period were similarly compared. A p-value of <0.05 was considered statistically significant. Values are presented as mean ± standard deviation unless otherwise indicated.

Results

Subject Characteristics: Complete data could not be obtained in 3 subjects due to poor sleep or major mask/mouth leaks. A single OSA subject’s abdominal girth exceeded the upper limit of the magnetometer range, and changes in lung volume are not reported for this individual. The anthropometric and polysomnographic data for the 10 remaining subjects (7 OSA, 3 controls) in whom data could be obtained are shown in Table 1.

Lung Volumes: As expected, during standard pressure drops, EELV fell in proportion to the change in mask pressure. EELV during breaths 3-5 fell on average 55 ± 12mL for each 1cmH2O drop from the holding pressure. Similar (p value non-significant) changes in EELV were seen
when only the expiratory pressure was dropped during the bilevel period; an example from a
single subject is shown in FIGURE #2. By the end of the bilevel period, EELV fell by 59 ±
18mL for each 1cmH2O drop in the expiratory pressure below the holding pressure. Importantly,
once inspiratory pressure was also reduced to the drop pressure at the start of the CPAP period,
further changes in lung volume were negligible. EELV decreased only an additional 6.3 ±
2.8mL for each cmH2O drop in inspiratory pressure.

Pcrit: On average, standard Pcrit measurements were made 3.4 ± 1.3 times per subject, and
biphasic measurements were made 2.0 ± 1.2 times per subject. Pcrit measured using the standard
and biphasic technique are shown in FIGURE #3. There was no difference in Pcrit between the
two techniques (p = 0.84). During the biphasic measurements, at the end of the bilevel period,
tidal volume was slightly greater than baseline (561 ± 13 vs. 537 ± 12mL, NS), and end-tidal
CO2 slightly lower (39.6 ± 2.8 vs. 40.6 ± 2.8mmHg, NS).

Early roll off in flow goes away when EELV remains essentially constant: As expected, most
standard pressure drops showed an initial roll-off in peak flow during breaths 1-3. With biphasic
drops, with little change in EELV during the CPAP period, there was no initial roll-off. Rather,
flow initially increased during the first few breaths after the transition from the biphasic drop to
the CPAP period. However, after these first few (>3) breaths there was often a late roll-off or
decrease in peak or mean flow and the development of flow limitation, despite little or no
changes in EELV (FIGURE #4).
Patterns of late flow limitation: An interesting and unexpected finding was that when flow limitation developed, it did so in 1 of 3 different patterns (FIGURE #5). In 3 subjects (2 OSA, 1 control), flow within a breath initially increased then became constant and independent of changes in downstream pressure (panel A) – as predicted by the Starling Resistor model. Successive breaths were identical (inspiratory time, peak flow, mean flow) and minute ventilation was stable (Table 2). In 4 subjects (2 OSA, 2 control), flow within a breath increased but subsequently decreased as the downstream pressure continued to decrease. The peak flows of successive breaths were nearly identical (panel B), however mean flow was progressively lower with each breath and ventilation was only preserved through an increase in the respiratory duty cycle. We have called this pattern “negative effort dependence within breaths only.” The remaining 3 subjects (all OSA) exhibited what we have termed “negative effort dependence both within breaths and across breaths.” Within breaths, flow initially rose with increasing effort, but later decreased. With each subsequent breath, the peak flow fell further (panel C). Mean flow and minute ventilation also decreased, despite an increase in the duty cycle. Importantly, for the range of drop pressures tested in each subject the pattern of flow limitation was consistent across the night. Again, regardless of flow patterns, EELV remained fairly constant during the prolonged sub-therapeutic CPAP periods.

Discussion

Our biphasic technique was designed to allow measurement of passive upper airway collapsibility after changes in end-expiratory lung volume had already occurred. As expected, lung volume changes occurred mostly during the early bilevel period of the biphasic drops, and there was little additional change in EELV during the subsequent CPAP period. We have used this technique to make several novel physiological observations.
Pcrit measured at constant EELV

There was no difference between the Pcrit measured in the standard fashion and the Pcrit measured with the biphasic technique, using breaths 3-5 of each pressure drop (during the standard drop or during the CPAP period). The individual differences in Pcrit are within the generally accepted repeatability of the measurement.(10, 17) This confirms prior work that suggests that most of the lung volume change occurs within the first 2 breaths.(18) It also suggests that the effects of EELV on Pcrit are immediate. These data are consistent with the hypothesis that tracheal traction is the mechanism by which increased EELV directly exerts an increased mechanical caudal traction that stabilizes the upper airway.

Of note, we used the biphasic technique to shift the timing of the lung volume change associated with pressure drops. However, subjects were still maintained at a different EELV than their supine, sleeping functional residual capacity (FRC). Determining upper airway collapsibility at supine FRC during sleep is of interest, but is difficult since patients with OSA are typically studied on positive pressure and are thus above FRC, while control subjects are studied using negative pressure and are below FRC. Because of the effect of EELV on Pcrit, these deviations from FRC cause the airway to appear artifically more stable in OSA patients and more collapsible in controls. In future experiments the biphasic technique could be modified to assess Pcrit at or near FRC (provided there is not substantial expiratory obstruction): the expiratory pressure would be lowered to 0cmH2O, and peak flow could be assessed at a variety of inspiratory pressures.
The early roll-off disappears when EELV remains essentially constant

A second motivation for the current work was to study the early roll-off in peak flow that occurs during a standard pressure drop. Earlier work by Schwartz and colleagues had implicated changes in lung volume as the cause of this roll-off. In their study, they compared the peak flow from breath 1 vs. breath 2 vs. breath 3 during a pressure drop to determine Pcrit, with simultaneous measurement of genioglossus EMG. (24) They hypothesized that peak flow would improve from breath 1 to 3 as muscle recruitment occurred. Surprisingly, they found that peak flow actually decreased. They concluded that lung volume changes, which were inferred from changes in esophageal pressure, were the most likely factor mediating this change. In our experiment, with EELV held constant, the early roll-off in peak flow disappeared. This finding seems to support the lung volume hypothesis proposed by Schwartz and colleagues. However, it should be noted that during the bilevel period respiratory drive and effort were slightly reduced. As a result, the first few breaths of the subsequent CPAP period were often small and non-flow limited. Thus, the disappearance of the early roll-off in peak flow could have been because of less effort producing less flow, as opposed to EELV-related changes in the mechanical properties of the airway limiting flow. Further studies are needed to confirm if the early roll-off is indeed due to changes in lung volume.

Late roll-off in flow even when EELV is constant

During the initial breaths of the CPAP period, as respiratory effort increased, so too did peak inspiratory flow (see FIGURE #5). However, when flow limitation developed in subsequent breaths 3 patterns were observed: 1) that predicted by the Starling resistor model, 2) negative effort dependence within breaths only, and 3) negative effort dependence both within breaths and
across breaths. With the last two patterns of flow limitation, there was a late roll-off in mean inspiratory flow, despite constant EELV and increasing respiratory effort. This observation was unexpected since a prolonged drop to sub-therapeutic CPAP will cause hypercapnia and/or hypoxemia that should stimulate upper airway dilator muscles to stiffen or open the airway, and thereby maintain or potentially increase (rather than decrease) inspiratory flows. Increasingly negative intrathoracic or intraluminal pressures are also expected to help maintain or increase flow, not decrease it, via reflex stimulation of the upper airway muscles. Unlike a Starling resistor, in which flow becomes independent of downstream pressure (once more negative than some threshold) we saw that flow decreased with increasingly negative downstream pressure in most of our subjects. That is, more effort produced less flow ("negative effort dependence"), not only within a breath but also progressively over a series of breaths.

Negative Effort Dependence: Patterns and possible causes

Two patterns of negative effort dependence were seen. In the first pattern, subjects exhibited negative effort dependence "within breaths only". In these individuals, flow initially increased with increasing respiratory effort to a point. Instead of plateauing, flow then decreased as downstream pressure became more negative (see FIGURE #5, panel B). In some cases, flow even increased again during late inspiration as downstream pressure returned to baseline ("terminal peak"). Importantly, with each successive breath in these individuals, peak flow was the same, and the relationship between downstream pressure and peak flow was maintained across many breaths (FIGURE #6, panel B). These individuals were "sweeping out" the same pressure-flow curve on each breath. Because there is negative effort dependence in the pressure-flow curve, the mean flow rate with each successive breath decreases but the peak flow does not
(see Table 2). Up to a point, these subjects were able to maintain a stable minute ventilation by prolonging the inspiratory time. These data suggest that the upper airway is narrowing during inspiration, but that it returns to the same baseline level by the start of the next breath. In fact, the “terminal peak” suggests that some improvement takes place even during late inspiration, as downstream pressure subsides. Importantly, these results differ from imaging studies performed in OSA patients during wakefulness, which showed airway dilation during inspiration and the greatest narrowing at end-expiration.(23) Finally, as shown in Figures #5B and #6B, the degree of negative effort dependence, as assessed by the difference between the peak flow and the flow during mid-inspiration, can be substantial. Although small amounts of negative effort dependence, with slight down-sloping of the pressure-flow curve of the upper airway have been previously been recognized, the individual variability and the potential magnitude of this effect has, we believe, been under-appreciated.(25) In some subjects, the magnitude is large enough to constitute, we believe, a deviation from the Starling resistor as a model of the dynamics of the upper airway.

Historically, negative effort dependence has most often been described in the context of isovolumetric expiratory flow limitation (specifically in isovolume pressure flow relationships) in which flow, which usually plateaus, sometimes exhibits a slight decrease with increasing effort. This is found to hold even after accounting for artifacts due to gas compression. Mead and colleagues used the “equal pressure point (EPP)” concept to explain expiratory flow limitation.(14) They proposed that negative effort dependence could be produced by movement of the EPP back toward the thoracic outlet, i.e. downstream relative to expiratory flow. In particular, since flow limited expiratory flow is the ratio of driving pressure to resistance
upstream of the EPP, and since driving pressure remains the same at a given lung volume, decreased flow can only be the result of increased upstream resistance due to lengthening of the upstream segment. However, in the upper airway, it seems unlikely that the EPP could move enough to increase upstream resistance sufficiently to decrease flow to the extent seen here. Indeed, it is not clear whether an EPP even exists in the upper airway, since upstream driving pressure (ambient pressure at the nares) and extraluminal tissue pressure are not linked as in the lower airways. Alternatively, Dawson and Elliott proposed wave-speed limitation to account for expiratory flow limitation. To explain negative effort dependence, which again was quite small in their experiments, they suggested that airway narrowing downstream of the choke point could reduce wall curvature at the choke point. This would reduce stiffness and cross-sectional area at the choke point, thereby reducing maximum flow. Again, we believe that this mechanism would produce small amounts of negative effort dependence in contrast to the substantial amounts we find. Compared with the mechanism that produces mild reductions in flow during forced expiration, the mechanism underlying these profound levels of negative effort dependence seen in the upper airway must therefore involve other factors, and currently remains an open question.

In contrast to negative effort dependence within a breath, negative effort dependence “within and across breaths” has not previously been described. Here, peak flow decreases with each successive breath, i.e. each breath sweeps out a different, progressively deleterious, pressure-flow curve (FIGURE #6, panel C). Morrell and colleagues speculated that progressive narrowing of the upper airway was due to a progressive reduction in EELV that negatively affected upper airway mechanics. Our study, however, shows that the worsening of the
upper airway anatomy does not require changes in EELV. Additionally, in their experiment, respiratory drive fluctuated, and thus the observed hypopneas and apneas may have partially resulted from reductions in drive and upper airway muscle activity following arousal and transient hyperventilation. (7, 32) Here we have shown that progressive narrowing across breaths can occur without arousals and in the setting of an increasing respiratory drive, i.e. the progressive narrowing is not simply due to passive collapse of the airway. We even saw progressive collapse when nasal pressure was greater than the Pcrit (for example, the mask or upstream pressure in **FIGURE #6, panel C** is 5.5cmH₂O, with measured Pcrit lower at 3.7cmH₂O). Thus, we speculate that similar to within breath negative effort dependence, the airway collapses during inspiration but does not fully recover during expiration: with each successive breath there is a new, worse pressure-flow relationship of the upper airway. The cause of this incomplete recovery is unknown, but could be due one or more of the following. First, airway elastic recoil may be slow, or not quick enough to re-expand the airway before the next inspiration. This effect may be exacerbated when inspiratory time lengthens relative to expiratory time during flow limitation. (8, 22) Second, the tongue or other structure may be pulled progressively further into the airway and fail to return to its original position during expiration. Third, repetitive collapse during each inspiration may induce changes in surfactant composition and surface tension that promote further collapse. (9) Whatever the mechanism, minute ventilation is not maintained despite changes in the duty cycle (**Table 2**). In these subjects, flow limitation will eventually lead to an arousal since increasing respiratory effort only worsens ventilation.
We and others have focused on understanding OSA as a multi-factorial disorder, with different traits having variable importance in individual patients. The presence of one of the described patterns of negative effort dependence (or lack thereof) may be a separate factor, or may reflect some of these traits. Better characterization of such sleep apnea “phenotypes” and timing of collapse could help personalize OSA treatment. Although speculative, we hypothesize that those patients with negative effort dependence within breaths might do best with bilevel positive airway pressure and fail with nasal expiratory resistance valves, which are thought to prevent collapse primarily during expiration. Alternatively, such patients might be minimally affected or even improved by sedative medications (such as benzodiazepines and narcotics) that reduce respiratory drive, compared to those with extremely poor airway anatomy whose OSA severity might worsen substantially. Further research is needed to determine the clinical relevance of our findings.

Limitations

Limitations of our study include first the small number of subjects studied. We also did not study subjects with untreated OSA: the relationship between EELV and Pcrit might be different in untreated OSA (perhaps with upper airway edema) compared to treated OSA. Second, we do not have a measure of upper airway muscle activity or direct visualization of the motion of the tongue or other pharyngeal structures. Third, this technique requires the use of bilevel PAP/pressure support, which will increase minute ventilation and thus reduce respiratory drive. However, most of the increase is transient, and after 1 minute of pressure support ventilation the changes in tidal volume and end-tidal CO2 were minimal compared to baseline. Furthermore, the slight hyperventilation that occurs would tend to make the upper airway muscles more...
“passive” and thus is less likely to change the passive Pcrit substantially. Finally, although the biphasic technique was slightly less well tolerated than the standard passive Pcrit pressure drops, it is likely better tolerated than the use of an iron lung to control EELV using extra-thoracic pressure.

Conclusion
End-expiratory lung volume changes do not influence standard passive Pcrit measurements if breaths 3-5 of a pressure drop are used. Progressive reductions in mean and peak flow can develop in the absence of EELV changes, and more negative downstream pressures during inspiration are associated, in some patients, with substantial decreases in flow. Although the cause remains unknown, the within breath negative effort dependence is associated with airway collapse during inspiration. However, negative effort dependence across breaths likely results from decreased airway size breath to breath due to incomplete recovery of airway dimension during expiration.

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Disclosures

DJE is a consultant for Apnex Medical. AM is a consultant for Philips Respironics, SHC, SGS, Apnex, Apnicure and Pfizer,. DPW is the chief medical officer for Philips Respironics. AW is a consultant for Philips Respironics, SOVA Pharmaceuticals and Apnex Medical. All other authors do not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript.

Author Contributions

RLO, BAE, AM and AW contributed to the conception and design of the experiments. RLO, BAE, DJE, AM, DPW and AW were involved in the collection, analysis and interpretation of data. RLO, BAE, SAS, DJE, JPB, DPW, AM, and AW were involved with drafting the article or critically reviewing it for important intellectual content. All authors have approved the final version of this article.


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Figure Legends

Figure 1. Example of progressive decrease in peak flow during a pressure drop from our laboratory.

Figure 2. Example of the biphasic drop in a single subject, illustrating the change in lung volumes. During the biphasic drop, only the expiratory pressure is dropped from the holding pressure for 1 minute (the bilevel period). Later the inspiratory pressure is also lowered to the same drop pressure (the CPAP period). At the start of the bilevel period, there is an immediate decrease in lung volume (as measured by rib cage and abdominal magnotometers). A new equilibrium is reached by the end of the bilevel period. Compared to the end of the bilevel period, there is no further change in lung volume during the CPAP period.

Figure 3. Passive Pcrit measured in standard fashion and using the biphasic technique in OSA (□) and controls (▲).

Figure 4. Changes in EELV during the Bilevel Period and CPAP Periods. Panel A) By the end of the bilevel period, EELV has fallen ~410mL from baseline. Panel B) During the CPAP period, after a 1-2 breath further decline of approximately 30mL, EELV changes very little on a breath by breath basis, even as flow initially increases then decreases.
Figure 5. Epiglottic pressure vs. inspiratory flow in 3 subjects, exhibiting the different patterns of negative effort dependence. In all cases, flow initially increases with increasing effort. However, above a certain inspiratory effort, three patterns are seen. Panel A) No negative effort dependence. Subject behaves as a perfect Starling Resistor. Panel B) Negative effort dependence within a single breath. After reaching a maximum, flow decreases within a breath as epiglottic pressure becomes more negative. Note that each successive breath reaches the same peak inspiratory flow. Panel C) Negative effort within and across breaths. As in panel B, flow decreases within each separate breath, but the peak flow is also reduced with each successive breath.

Figure 6. Pressure-flow curves of successive flow-limited breaths. Each insert highlights the breaths that are plotted, with darker curves representing later breaths. Panel A) Each separate breath shows a similar curve, with flow reaching a maximum and then becoming independent of further decreases in downstream pressure. Panel B) Each separate breath shows a similar curve, with decreases in downstream pressure associated with decreased flow. Panel C) Here each separate breath sweeps out a different curve.
Table 1. Subject Characteristics

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>n (M/F)</th>
<th>Age years</th>
<th>BMI kg/m²</th>
<th>AHI Events/hour</th>
<th>CPAP Rx cmH₂O</th>
<th>Holding Pressure cmH₂O</th>
</tr>
</thead>
<tbody>
<tr>
<td>OSA</td>
<td>2/5</td>
<td>49.7 ± 8.0</td>
<td>39.2 ± 5.7</td>
<td>35.9 ± 13.6</td>
<td>9.1 ± 1.7</td>
<td>9.3 ± 2.2</td>
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<tr>
<td>Control</td>
<td>2/1</td>
<td>47.7 ± 10.6</td>
<td>26.5 ± 5.0</td>
<td>4.6 ± 2.7</td>
<td>6.0 ± 1.7</td>
<td></td>
</tr>
</tbody>
</table>

Values are mean ± standard deviation.
Table 2. Quantification of respiratory variables during the three patterns of flow limitation, using the highlighted breaths in Figure 7 panels A-C. Flow limited Starling resistor breaths have similar peak flow, similar mean flow, and preserved tidal volume and minute ventilation. Negative effort dependence within a breath only has similar peak flow, but decreasing mean flow; ventilation is relatively preserved through increase in the duty ratio (Ti/Ttot). In contrast, in negative effort dependence across breaths, the increase in the duty ratio does not compensate for decreasing peak and mean flows.

<table>
<thead>
<tr>
<th></th>
<th>Breath 1</th>
<th>Breath 2</th>
<th>Breath 3</th>
<th>Breath 4</th>
<th>Breath 5</th>
<th>Breath 6</th>
</tr>
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<tbody>
<tr>
<td>Starling Resistor</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ti (s)</td>
<td>1.83</td>
<td>1.78</td>
<td>1.97</td>
<td>1.79</td>
<td>1.86</td>
<td>1.79</td>
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<tr>
<td>Ti/Ttot</td>
<td>0.52</td>
<td>0.49</td>
<td>0.50</td>
<td>0.49</td>
<td>0.52</td>
<td>0.52</td>
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<tr>
<td>Peak Flow (L/s)</td>
<td>0.34</td>
<td>0.31</td>
<td>0.29</td>
<td>0.32</td>
<td>0.31</td>
<td>0.31</td>
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<tr>
<td>Mean Flow (L/s)</td>
<td>0.25</td>
<td>0.23</td>
<td>0.22</td>
<td>0.24</td>
<td>0.23</td>
<td>0.22</td>
</tr>
<tr>
<td>Tidal Volume (L)</td>
<td>0.45</td>
<td>0.41</td>
<td>0.43</td>
<td>0.42</td>
<td>0.42</td>
<td>0.40</td>
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<tr>
<td>Respiratory Rate (bpm)</td>
<td>17.05</td>
<td>16.48</td>
<td>15.28</td>
<td>16.23</td>
<td>16.82</td>
<td>17.36</td>
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<tr>
<td>Instantaneous Ventilation (L/min)</td>
<td>7.70</td>
<td>6.79</td>
<td>6.57</td>
<td>6.87</td>
<td>7.06</td>
<td>6.96</td>
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<tr>
<td>Negative Effort Dependence within a breath only</td>
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<td></td>
<td></td>
<td></td>
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<tr>
<td>Ti (s)</td>
<td>1.80</td>
<td>1.84</td>
<td>1.94</td>
<td>1.95</td>
<td>2.10</td>
<td>2.24</td>
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<tr>
<td>Ti/Ttot</td>
<td>0.38</td>
<td>0.40</td>
<td>0.40</td>
<td>0.47</td>
<td>0.48</td>
<td>0.49</td>
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<tr>
<td>Peak Flow (L/s)</td>
<td>0.27</td>
<td>0.26</td>
<td>0.25</td>
<td>0.25</td>
<td>0.23</td>
<td>0.24</td>
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<tr>
<td>Mean Flow (L/s)</td>
<td>0.21</td>
<td>0.18</td>
<td>0.18</td>
<td>0.17</td>
<td>0.15</td>
<td>0.14</td>
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<tr>
<td>Tidal Volume (L)</td>
<td>0.38</td>
<td>0.34</td>
<td>0.35</td>
<td>0.34</td>
<td>0.32</td>
<td>0.32</td>
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<tr>
<td>Respiratory Rate (bpm)</td>
<td>12.38</td>
<td>13.62</td>
<td>13.26</td>
<td>13.14</td>
<td>13.75</td>
<td>12.91</td>
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<tr>
<td>Instantaneous Ventilation (L/min)</td>
<td>4.69</td>
<td>4.56</td>
<td>4.68</td>
<td>4.42</td>
<td>4.35</td>
<td>4.07</td>
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<tr>
<td>Negative Effort Dependence within and across breaths</td>
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<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Ti (s)</td>
<td>1.27</td>
<td>1.52</td>
<td>1.46</td>
<td>1.76</td>
<td>2.01</td>
<td>1.96</td>
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<tr>
<td>Ti/Ttot</td>
<td>0.41</td>
<td>0.55</td>
<td>0.55</td>
<td>0.59</td>
<td>0.61</td>
<td>0.67</td>
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<td>Peak Flow (L/s)</td>
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<td>0.10</td>
<td>0.06</td>
<td>0.06</td>
<td>0.01</td>
<td>0.01</td>
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<tr>
<td>Mean Flow (L/s)</td>
<td>0.10</td>
<td>0.09</td>
<td>0.08</td>
<td>0.06</td>
<td>0.03</td>
<td>0.02</td>
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<tr>
<td>Tidal Volume (L)</td>
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<td>0.17</td>
<td>0.15</td>
<td>0.15</td>
<td>0.09</td>
<td>0.03</td>
</tr>
<tr>
<td>Respiratory Rate (bpm)</td>
<td>19.49</td>
<td>21.75</td>
<td>22.40</td>
<td>20.09</td>
<td>18.28</td>
<td>20.40</td>
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<tr>
<td>Instantaneous Ventilation (L/min)</td>
<td>3.08</td>
<td>3.74</td>
<td>3.34</td>
<td>2.93</td>
<td>1.55</td>
<td>0.55</td>
</tr>
</tbody>
</table>
$p = 0.84$
Panel B: Breath to breath changes in EELV

Mask Pressure (cmH$_2$O)

Epiglottic Pressure (cmH$_2$O)

Flow (L/s)

Change in EELV from prior breath

+5ml  -34  -9  0  +7  +8  +14  +7  -11  -21  -29

Time (s)
Panel A: Starling Resistor

EEG C3-A2 (mV)

Mask Pressure (cmH\(_2\)O)

Epiglottic Pressure (cmH\(_2\)O)

Flow (L/s)

Time (s)
Panel B: Negative effort dependence within breaths

- EEG C3-A2 (mV)
- Mask Pressure (cmH2O)
- Epiglottic Pressure (cmH2O)
- Flow (L/s)

“Terminal peak”
Panel C: Negative effort dependence within and across breaths

Airway closes during mid-inspiration
Panel A: Starling Resistor
Panel B: Negative effort dependence within breaths
Panel C: Negative effort dependence within and across breaths