

Test of the Starling resistor model in the human upper airway during sleep

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Stephen H. Loring,² David P. White,¹ Andrew C. Jackson,³ Ole F. Pedersen,⁴ and James P. Butler¹

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Wellman A, Genta PR, Owens RL, Edwards BA, Sands SA, Loring SH, White DP, Jackson AC, Pedersen OF, Butler JP. Test of the Starling resistor model in the human upper airway during sleep. *J Appl Physiol* 117: 1478–1485, 2014. First published October 16, 2014; doi:10.1152/jappphysiol.00259.2014.—The human pharyngeal airway during sleep is conventionally modeled as a Starling resistor. However, inspiratory flow often decreases with increasing effort (negative effort dependence, NED) rather than remaining fixed as predicted by the Starling resistor model. In this study, we tested a major prediction of the Starling resistor model—that the resistance of the airway upstream from the site of collapse remains fixed during flow limitation. During flow limitation in 24 patients with sleep apnea, resistance at several points along the pharyngeal airway was measured using a pressure catheter with multiple sensors. Resistance between the nose and the site of collapse (the upstream segment) was measured before and after the onset of flow limitation to determine whether the upstream dimensions remained fixed (as predicted by the Starling resistor model) or narrowed (a violation of the Starling resistor model). The upstream resistance from early to mid inspiration increased considerably during flow limitation (by 35 ± 41 cmH₂O·liter⁻¹·s⁻¹, $P < 0.001$). However, there was a wide range of variability between patients, and the increase in upstream resistance was strongly correlated with the amount of NED ($r = 0.75$, $P < 0.001$). Therefore, patients with little NED exhibited little upstream narrowing (consistent with the Starling model), and patients with large NED exhibited large upstream narrowing (inconsistent with the Starling model). These findings support the idea that there is not a single model of pharyngeal collapse, but rather that different mechanisms may dominate in different patients. These differences could potentially be exploited for treatment selection.

pharynx; wave speed theory; flow limitation; choke point; sleep apnea

THE HUMAN PHARYNGEAL AIRWAY during sleep is thought to collapse like a Starling resistor in patients with obstructive sleep apnea (OSA) (5, 21, 22). In a Starling resistor, when the downstream pressure drops below some critical value, a choke point develops. The choke point prevents further reductions in downstream pressure from propagating upstream past the choke point. The pressure in the upstream region (shaded area in Fig. 1) therefore remains constant. Because the pressure in the upstream region remains constant, so do the dimensions (resistance) of the upstream region. A fixed pressure gradient and resistance in the upstream segment will produce a fixed amount of airflow through the upstream segment. Because the amount of airflow through the upstream segment is necessarily

the same as the amount of airflow through the downstream segment, the flow through a Starling resistor will reach a maximum value that remains constant. This is referred to as flow limitation, or flow that is fixed and independent of downstream pressure.

However, inspiratory flow limitation in many patients with OSA is not fixed or independent of downstream pressure. Rather, in many patients it decreases as downstream pressure decreases [i.e., negative effort dependence (NED)]. Because of this inconsistency, we wanted to test the Starling resistor model in the upper airway by measuring the dimensions, or resistance, in the upstream segment (shaded region in Fig. 1) during flow limitation. A fixed upstream resistance during flow limitation would be interpreted as being consistent with the Starling resistor model, whereas an increase in upstream resistance would be interpreted as being inconsistent with the Starling resistor model.

The importance of this research is that it could improve our understanding of pharyngeal collapse, leading to more informative models. Correct models of airway collapse are useful for developing, testing, and predicting response to treatments for OSA, such as upper airway surgery, oral devices, positional therapy, etc. (7, 11, 23).

METHODS

Subjects. The subjects in this study had OSA and were recruited from the Brigham and Women's Hospital clinical sleep laboratory. OSA was defined as an apnea-hypopnea index (AHI) >10 events/hour during supine, non-rapid eye movement (NREM) sleep. Hypopneas were defined as a $\geq 30\%$ reduction in flow associated with an arousal or a 3% desaturation. Apneas were defined as a >10 s cessation of airflow. Subjects were on no medications known to affect respiration or pharyngeal muscle control. Exclusion criteria included concurrent sleep disorder, renal insufficiency, neuromuscular disease, uncontrolled diabetes mellitus, central sleep apnea, heart failure, uncontrolled hypertension, or thyroid disorder. The age range was 21–65 yr. The study was approved by the Institutional Review Board at Partners Healthcare/Brigham and Women's Hospital. All subjects gave informed, written consent before participating.

Equipment and protocol. Subjects slept in the supine position and breathed through a nasal mask attached to a modified continuous positive airway pressure (CPAP) machine (Philips Respironics, Murrysville, PA) capable of delivering positive and negative pressures. Once a patient was asleep, CPAP was set to the patient's prescribed pressure and increased as needed to eliminate residual snoring, hypopneas, or flattened inspiratory flow (holding pressure). Nasal pressure was then decreased slowly (1 cmH₂O every few minutes) to induce flow limitation. CPAP was returned to the holding pressure when awakening occurred. Multiple CPAP reductions were performed in each individual to produce flow limitation at as many nasal pressures as possible. Electroencephalography, chin electromyogra-

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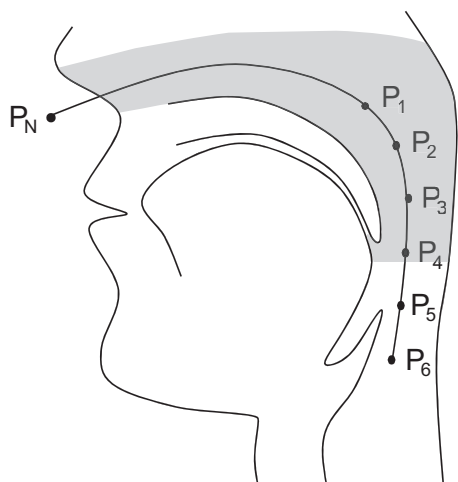


Fig. 1. Pressure measurements in the upper airway. In this study, the pressure at the nose (P_N) and several points along the airway (P_1 to P_6) was measured to test the predictions of the Starling resistor model. The upstream segment is shaded. In a Starling resistor, the pressure in the upstream segment (P_N through P_4 in this example) remains fixed after the onset of flow limitation, whereas the pressure in the downstream segment (P_5 to P_6) becomes more negative. Because the pressure gradient in the upstream segment remains fixed, so do the dimensions of the upstream segment.

phy, and electro-oculography were measured for sleep staging. Airflow was measured with a pneumotachometer (Hans-Rudolph, Kansas City, MO) and a pressure transducer (Validyne, Northridge, CA) attached to the nasal mask. Mask pressure was monitored with a pressure transducer (Validyne) referenced to atmosphere. Pharyngeal

pressure was measured with a 5-French catheter equipped with six pressure sensors either 0.75 or 1.5 cm apart, depending on the catheter (Millar Instruments, Houston, TX). The catheter was inserted through the nose 2 cm below the tongue base and adjusted as needed to ensure that the pressure sensors spanned the site of collapse. The site of collapse was identified by noting which sensors showed continued substantial decreases in pressure following the peak in airflow; these sensors were judged to be downstream. Sensors showing a pressure that remained constant or decreased only slightly after the initial peak in airflow were considered to be upstream or at the site of collapse. Arterial oxygen saturation at the finger (BCI, Waukesha, WI) and exhaled carbon dioxide in the mask (Vacumed, Ventura, CA) were also measured. Signals were sampled at 125 Hz and recorded using Spike 2 software (Cambridge, UK), and all measurements were performed during NREM sleep only.

Data analysis. Flow-limited breaths were selected at random and exported to Matlab (Natick, MA) for analysis. The two pressure sensors that spanned the site of collapse were plotted vs. flow, and peak flow and plateau flow were identified, with the plateau flow simply being the flow at peak negative downstream pressure (typically mid or late inspiration). In all breaths analyzed, the downstream pressure became more negative during the period after peak flow was reached. NED was quantified as the difference between peak and plateau flow as well as the fractional reduction in flow, (peak-plateau)/peak, expressed as a percent. The resistance of the upstream segment at peak negative downstream pressure was measured and compared with the resistance at the same flow (isoflow within the same breath) prior to flow limitation (see Fig. 2). The change in upstream resistance before and after flow limitation is a measure of the change in upstream dimensions of the airway and was the primary outcome measure in this study because in a Starling resistor, the upstream dimensions should remain constant during flow limitation.

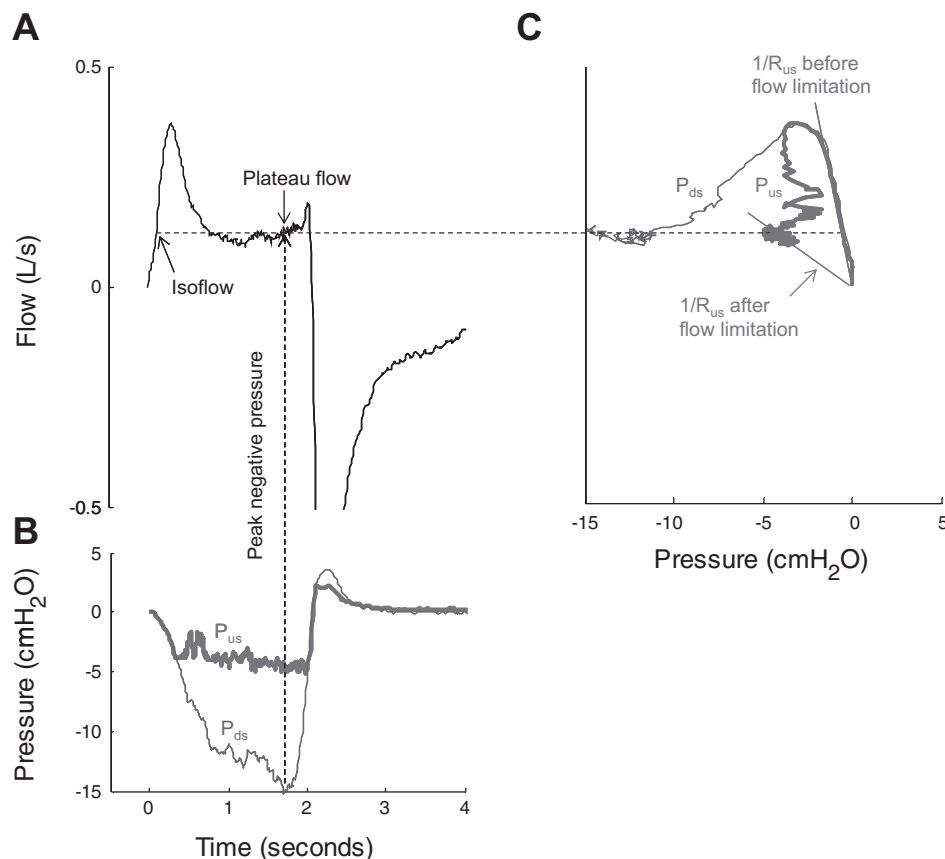


Fig. 2. Procedure for measuring upstream resistance (R_{us}) before and after flow limitation. First, in (B), the upstream and downstream pressures from adjacent sensors (e.g., P_4 and P_5) were plotted vs. time, then the peak negative downstream pressure was identified. The corresponding flow at peak negative pressure (i.e., plateau flow) was marked along with the isoflow before flow limitation (A). C: a plot of downstream (thin line) and upstream (bold line) pressures vs. flow. The resistance of the upstream segment before and after flow limitation was determined by calculating the slope of the upstream pressure (P_{us}) vs. flow relationship.

The change in each variable before and after flow limitation was compared using a paired *t*-test. A Pearson correlation analysis was also performed between the change in upstream resistance and NED to determine whether more upstream narrowing produced greater NED. Lastly, the effect of the following two variables on NED was also tested using a Pearson correlation analysis: 1) magnitude of the epiglottic pressure swings to determine whether more inspiratory effort was associated with greater NED; and 2) amount that the CPAP was dropped below the holding pressure to determine whether the level of nasal pressure affected NED. In a subset of 13 individuals, NED was measured on a second night, and the two measurements were analyzed using the intraclass correlation coefficient, as defined by the function Intraclass Correlation Coefficient (type 1-1) in Matlab (19). Data are presented as means \pm SD. $P < 0.05$ was considered significant.

RESULTS

Twenty-four individuals were studied. The participants were middle-aged (49 ± 11 yr), obese (body mass index 35 ± 8 kg/m²), and mostly men (15 men, 9 women). All had OSA, with apnea-hypopnea indices ranging from 17 to 112 episodes/hour. Those using CPAP at home used an average pressure of 10 ± 2 cmH₂O. Ten individuals were studied with the catheter that had pressure sensors 0.75 cm apart, whereas the other 14 were studied with the catheter that had sensors 1.5 cm apart. Both catheters seemed adequate for identifying the site of collapse and measuring upstream resistance. Flow-limited breaths (14 ± 5) were analyzed per subject. The average CPAP level on these breaths was 4.5 ± 2.6 cmH₂O. The average downstream pressure on the breaths used for NED determination was -14 ± 5 cmH₂O. Raw data showing the pressure-flow relationship for all transducers is shown in Fig. 3.

Negative effort dependence. There was a significant amount of NED in the population studied. The mean peak flow (on all the flow-limited breaths used for analysis) was 0.36 ± 0.1 liter/s, and the plateau flow was 0.21 ± 0.1 liter/s, yielding an average decrease of 0.15 liter/s, or 40%, from peak to plateau ($P < 0.001$). In all patients, flow limitation occurred during early inspiration, within the first 0.5 s of the start of each

breath. There was, however, a large standard deviation in NED (0.13 liter/s, or 28%), indicating considerable variability between subjects (see Fig. 4). In contrast, the standard deviation of NED within each individual was, on average, 0.06 liter/s, or 11%, indicating that the amount of NED was fairly consistent within a subject. Furthermore, this consistency persisted over a range of CPAP levels that spanned 2.0 ± 1.4 cmH₂O (i.e., flow limitation was produced over three different CPAP levels; e.g., 2, 3, and 4 cmH₂O). Data from the six participants who flow limited over the largest range of nasal pressures tested are shown in Fig. 5. Further evidence of the within-subject consistency of NED is provided by the lack of a correlation between the magnitude of the nasal pressure drop and NED ($r = 0.07$, $P = 0.20$; i.e., larger CPAP drops did not produce greater NED). There was, however, a significant but weak correlation between the magnitude of negative pressure swings and %NED ($r = -0.35$, $P < 0.001$), indicating that greater inspiratory effort tended to produce more NED, which would be expected if there were not a true plateau in flow rate. Lastly, the NED was measured on a second night in 13 individuals and exhibited good agreement, with an intraclass correlation coefficient of 0.65 (0.19, 0.88) ($P = 0.005$).

Upstream resistance. The large amount of NED observed in this study suggests that the Starling resistor, at least in some patients, may not be the best model. To address this, we directly tested a major prediction of the Starling resistor model; namely, that the dimensions of the tube upstream from the site of collapse remain constant during flow limitation. Raw pressure-flow traces for two subjects are shown in Fig. 6. We found that upstream resistance at isoflow (the flow at peak negative downstream pressure) increased from 7 ± 5 cmH₂O·liter⁻¹·s⁻¹ before flow limitation to 42 ± 39 cmH₂O·liter⁻¹·s⁻¹ after flow limitation ($P < 0.001$), indicating substantial narrowing of the airway upstream from the site of collapse. However, again there was a wide range of variability between subjects (the standard deviation of the change in upstream resistance for the study population was 41 cmH₂O·liter⁻¹·s⁻¹). Furthermore, although the change in upstream resistance was large and variable for patients with significant NED, in general, larger increases in upstream resistance were associated with greater amounts of NED, as illustrated in Fig. 7 ($r = 0.75$, $P < 0.001$).

DISCUSSION

This study tested one of the central predictions of the Starling resistor model. Whereas previous studies measured upstream resistance in the pharynx during sleep (3, 12, 18, 24), none have done so before and after the onset of flow limitation, and thus they cannot be used to evaluate the Starling resistor model. In the current study, a major finding was the substantial amount of NED observed that remained consistent within an individual across a range of nasal pressures and on separate nights, with each individual exhibiting their own characteristic flow shape, or fingerprint. We speculate that such a fingerprint could be produced by the different sites or configurations of airway collapse known to occur in different patients (8). We did find, however, that there was wide variability in the magnitude of NED between patients, with some individuals showing little or no NED, whereas others displayed considerable NED. Furthermore, the variability in NED was closely associated with the change in upstream dimensions: individuals

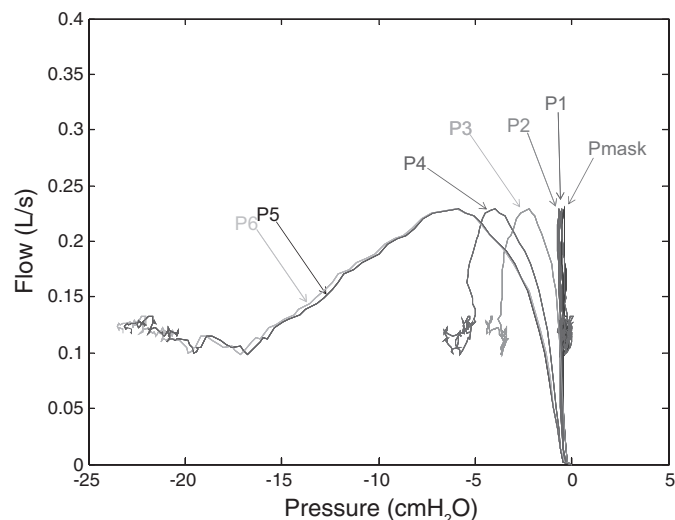


Fig. 3. Example of flow vs. pressure for all transducers. Sensors P1 and P2 are in the rigid upstream region (e.g., nares). P3 and P4 are just upstream from (or at) the choke point (P3 was used for the upstream resistance calculation in the patient). P5 and P6 are downstream from the choke point.

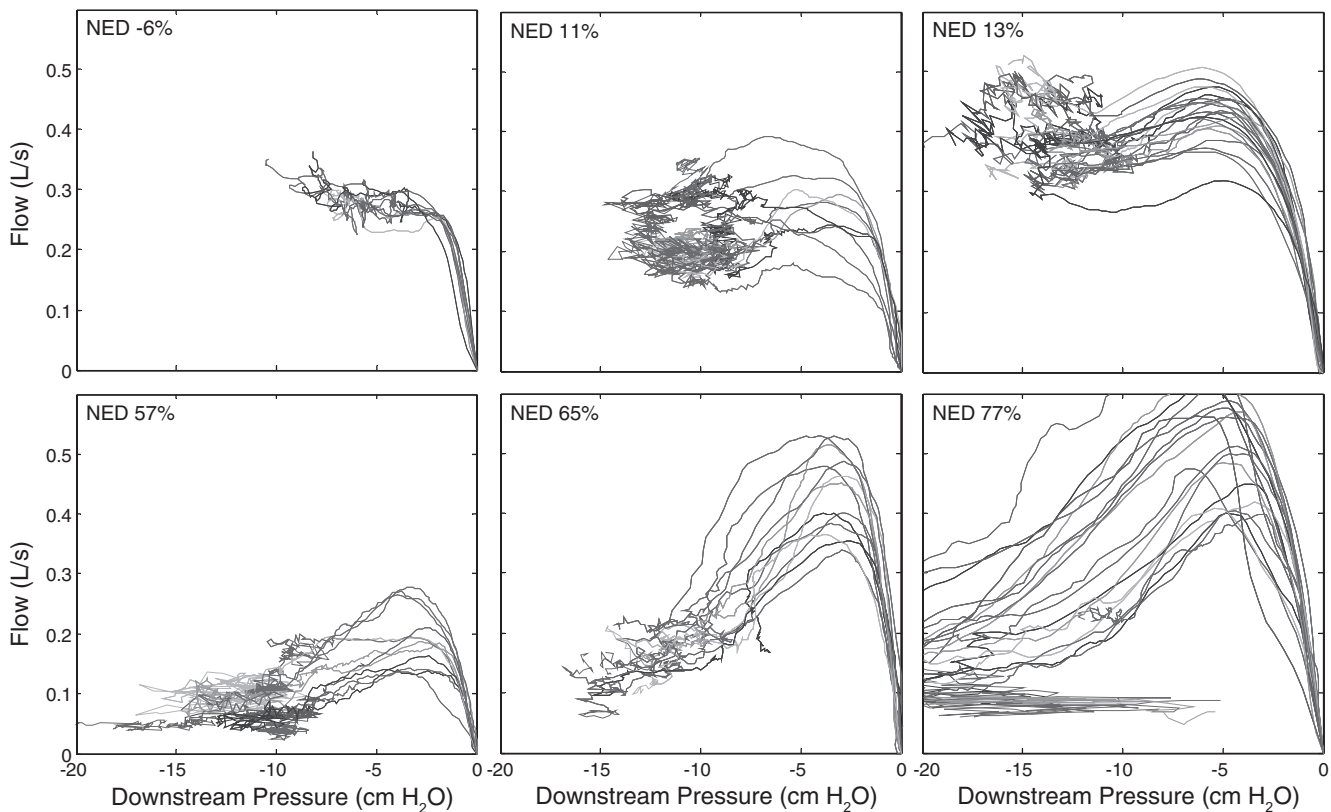


Fig. 4. There was substantial variability in the magnitude of negative effort dependence (NED) between subjects, as shown here for 6 of the 24 patients studied. Each graph shows a plot of downstream pressure vs. inspiratory flow for six different patients. Each line represents a different breath. The percent NED for each patient is shown in the upper left corner of each graph. Although flow limitation was produced at several nasal pressures in each individual, all of the flows in this and subsequent plots start at zero pressure so that the flow shapes and amount of NED can be observed.

demonstrating the greatest amounts of NED had the largest increases in upstream resistance (these patients are unlikely to collapse like a Starling resistor model), whereas those without NED had no appreciable change in upstream resistance (these patients may very well collapse like a Starling resistor model). Therefore, the most remarkable finding of this study is that there does not seem to be one model that describes collapse in all patients. Below, we describe how upstream resistance can increase during flow limitation in a collapsible tube such as the pharynx and how such an increase can produce NED.

The phenomenon of NED has been well recognized for many years. Permutt et al. (15) showed it in pressure-flow curves of the pulmonary vasculature in 1961. Elliott and Dawson (2) demonstrated NED during expiration in artificial and excised tracheas, and they described how changes in curvature at the site of collapse could cause NED (see below). Schwartz and Smith et al. illustrated it in the human upper airway in the 1980s (20, 22) and further demonstrated it in animal isolated upper airway work in the 1990s (17, 18, 24). However, NED historically has not been considered a violation of the Starling resistor model because in most cases it was small or deemphasized (1), and it could potentially be explained by phenomena such as transient effects or changes in wall curvature. However, NED in the pharynx can be quite large (13, 14), as demonstrated in this study. Furthermore, the previous explanations for NED in a Starling resistor model may not be valid for inspiratory flow limitation through the pharynx, as described below.

Volume displacement. One potential mechanism for NED in a Starling resistor model is displacement of gas from the collapsing airway. When flow through the airway begins, the walls collapse and displace gas (equal to the volume of the collapsed region) out the downstream end of the tube. This displaced gas will produce a larger amount of initial airflow out the downstream end. Hence, if flow is measured at the downstream end, it could appear to decrease from early to mid inspiration (i.e., NED). However, in inspiratory flow limitation in the upper airway, flow is measured at the upstream end of the airway. Therefore, volume displacement could not explain the NED observed in patients with OSA.

Transient overshoot. Another possible cause of NED in a Starling resistor model is related to the dynamics of the airway walls. If the airway walls have mass, it will take time for the walls to collapse and form a site of collapse. This extra time will allow a higher than maximum flow to pass through the airway before flow becomes limited, producing an initial transient overshoot in flow and the appearance of NED, as described by Knudson and colleagues for supramaximal expiratory flows (9, 10). A transient overshoot is a particularly attractive explanation for NED in the pharynx because it is reasonable to believe that the airway walls have mass and because flow often tends to plateau during mid/late inspiration, giving the impression that the initial peak flow was an overshoot and that the observed plateau is the true maximum flow. However, recent work from Owens et al. (13) has shown that fast inspirations (sharp reductions in downstream pressure) through the passive pharynx do not

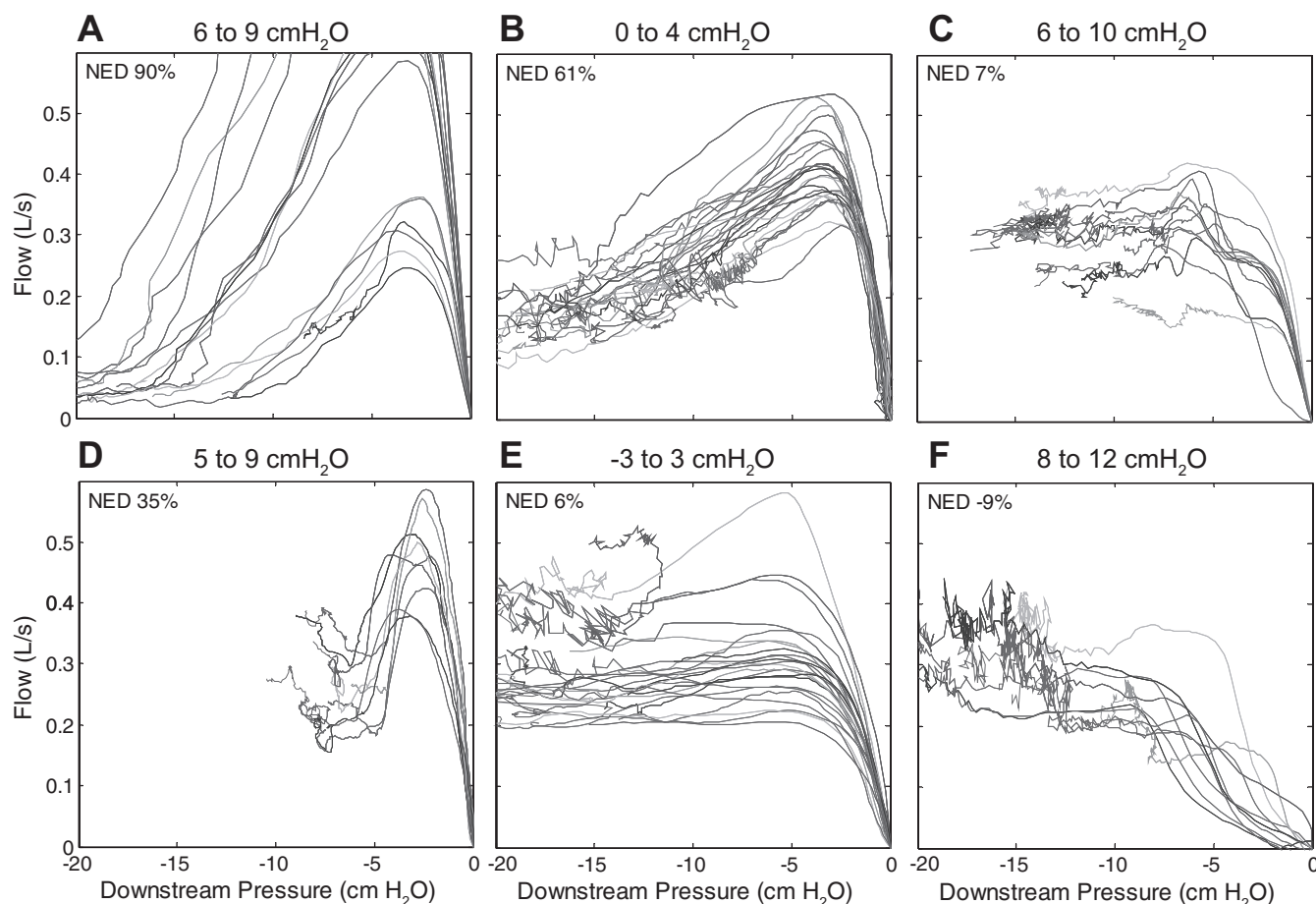


Fig. 5. The flow limitation pattern was consistent in each individual over a range of continuous positive airway pressure (CPAP) levels (the range of CPAP levels in which NED was observed in each individual appears atop each graph). Each individual seems to have a fingerprint flow limitation pattern. For example, in *subject A*, the flow pattern appears to be a scaled version of itself over a large range of peak flows, and the flow limitation pattern, which has substantial NED, is considerably different from that of *subjects C, E, and F*, who have little or no NED. Even among patients with similar amounts of NED, the flow patterns are distinguishable [e.g., note the high initial resistance in *subject E* compared with *subject F*, and how *subject D* has a steeply sloped (pinched) peak compared with *subject B*]. These features imply different models or mechanisms of pharyngeal collapse in different patients with obstructive sleep apnea.

produce larger peak flows than slow inspirations, indicating that over the time scale of interest (tenths of a second), the pharyngeal walls are essentially massless, and that the initial peak flow is not a transient overshoot.

Changes in wall curvature. To describe this mechanism, a pressure vs. distance plot for a tube (airway) that limits at the wave speed is illustrated in Fig. 8A. The wave speed theory is a more quantitative model for describing flow limitation than the Starling resistor, and dictates that flow limits when the air velocity equals the speed that a pressure wave propagates through the tube. Both models make the same prediction regarding fixed upstream resistance during flow limitation, and thus in this context they are often used interchangeably. In Fig. 8A, each line represents the pressure distribution along the tube for different levels of downstream pressure. The first line, labeled 1, would correspond to early inspiration (i.e., prior to the onset of flow limitation). When the downstream pressure is lowered one step further (to the pressure line labeled 2), the tube pinches in the most compliant region, which by design in this example is 12.7 cm from the mouth. It is assumed that the cross-sectional area of the tube closely tracks the pressure (tube law), and thus the pressure vs. distance plot is a reasonable

approximation of the corresponding area vs. distance plot. At the next incremental reduction in downstream pressure, labeled 3, airflow becomes limited. Therefore, *line 3* is termed the critical pressure and is distinguished with a bold line. When the downstream pressure drops below the critical pressure (from *line 3* to *line 4*), it becomes clear that the site of collapse is located 12.7 cm from the mouth, because the pressure upstream from this region remains fixed (note how *lines 3* and *4* overlay one another at 12 cm), whereas the pressure downstream from this region continues to decrease (note how *line 4* separates from *line 3* at 13 cm). Further reductions in downstream pressure, from *line 4* to *line 5* and *line 5* to *line 6*, produce an envelope of narrowing downstream from the site of collapse. Despite the further narrowing of this downstream region, the site of collapse remains at 12.7 cm. Also, the continued downstream narrowing does not decrease maximum flow through the tube for the following reason: the pressure gradient (and therefore the area) in the upstream segment remains fixed despite the continued downstream narrowing. Therefore, the volume flow rate through the upstream segment (which will be the same as the flow rate through the downstream segment) also remains fixed.

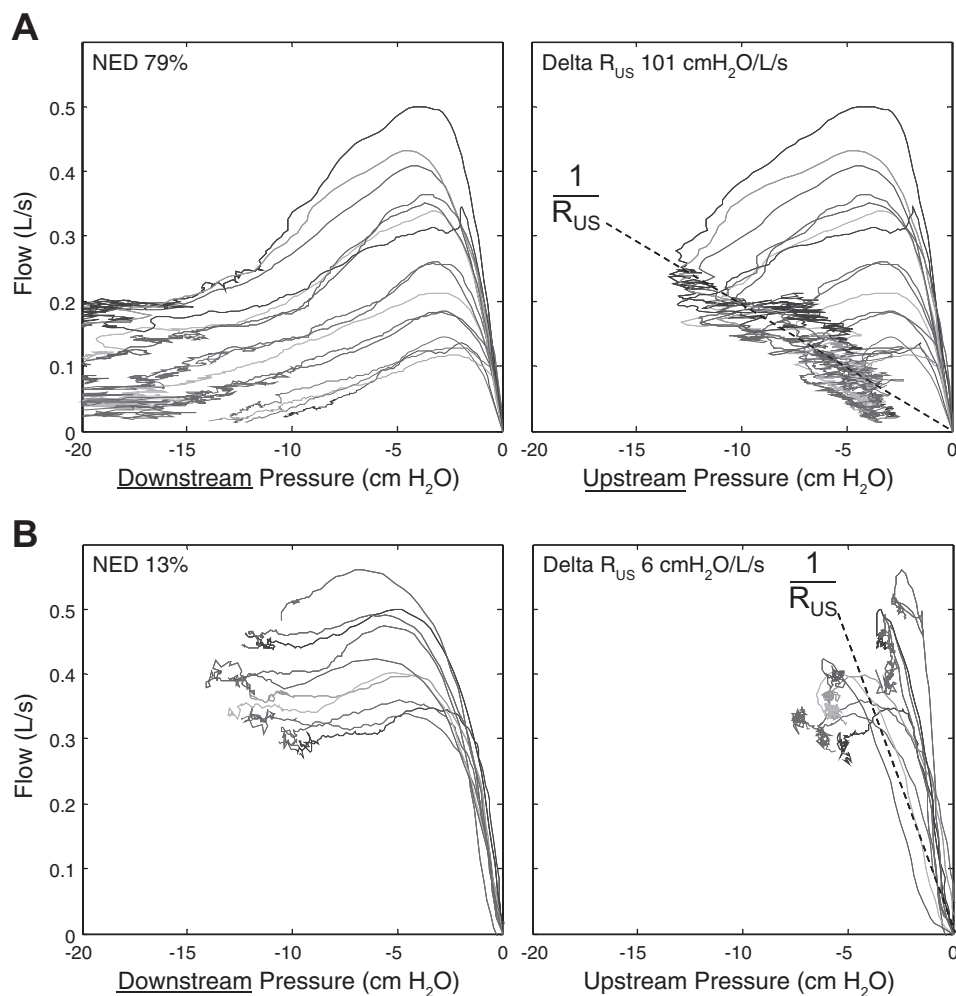


Fig. 6. A: representative subject with NED who had a significant reduction in flow vs. downstream pressure (*top left*) that is associated with a substantial increase in upstream resistance (*top right*). B: representative subject without NED. Note the flat flow vs. downstream pressure profile (*bottom left*) and the lack of further reduction in upstream pressure once flow limitation starts (*bottom right*). The dashed line represents the average reciprocal of upstream resistance at peak negative pressure.

Elliott and Dawson (2) postulated that a change in wall curvature at the choke point could cause NED. Note the relatively large amount of curvature at the site of collapse in line 3 (the angle between the upstream and downstream segments on the plot in Fig. 8 is ~120 degrees, marked by the solid arrow). However, when the downstream pressure drops below the critical pressure (to line 4), the angle between the

upstream and downstream segments on the plot now increases to 180 degrees (dashed arrow). The high degree of curvature at the critical pressure (the pinched portion of line 3) imparts more tension in the walls of the tube, making the choke point stiffer. In the wave-speed theory, the maximum flow through a tube depends on the stiffness of the choke point. Therefore, when the pressure decreases from line 3 to line 4, the stiffness

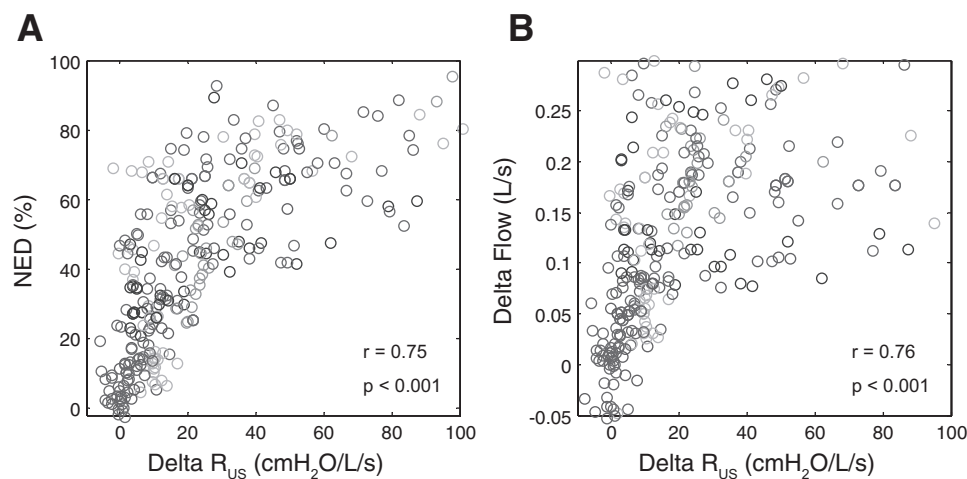


Fig. 7. A larger increase in upstream resistance (Delta R_{US}) was associated with a greater amount of NED, whether quantified as the percent reduction in flow (A) or as the change in flow (B). Data for all breaths in all patients are shown. The correlation coefficient for A was calculated after log transforming the Delta R_{US} data because of the curvilinear relationship.

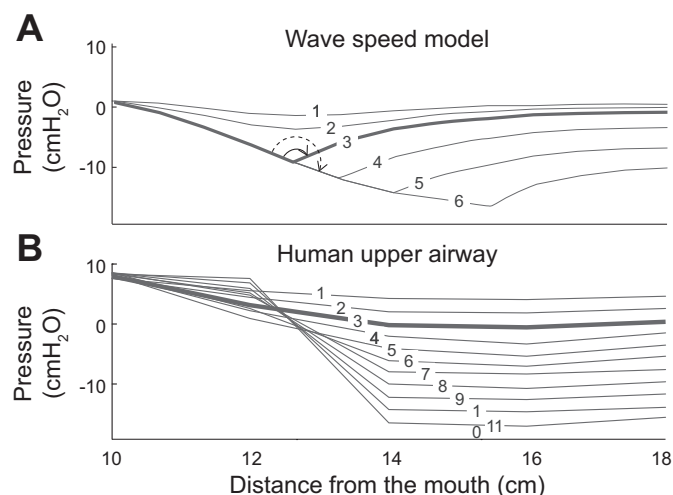


Fig. 8. Pressure-Pressure distance profile for a wave speed model (A) and a representative human upper airway (B). Each line represents an instant in time. The topmost line in each panel is early inspiration (before the onset of flow limitation). The bold line is the critical pressure at which flow limitation starts. The bottom lines are at mid to late inspiration. The choke point in both figures occurs between 12 and 13 cm from the nose. The curved arrows mark in A mark the longitudinal angle of the airway wall at the choke point before (solid arrow) and after (dashed arrow) flow limitation.

of the site of collapse also decreases and therefore so does the maximum flow rate, yielding NED.

This curvature hypothesis has never been tested but is frequently cited as a mechanism of NED in wave speed models (2, 25). The data collected in this study, we believe, speak to the likelihood that this mechanism could be contributing to NED in humans during sleep. Figure 8B shows an actual pressure distance plot for one of the participants in this study. This plot was typical of most of the subjects in the study. As in Fig. 8A, the first two lines are the pressure distributions prior to the onset of flow limitation. The bold line is the critical pressure (i.e., the pressure gradient along the pharynx at the onset of flow limitation). It is clear that when the downstream pressure drops below the critical pressure that the site of collapse in this individual is located at 12.5 cm from the mouth. Note how in lines 7–11 the pressure in the downstream segment continues to decrease, whereas in the upstream segment it does not continue to decrease but rather increases due to the reduction in flow. Note also how lines 4–6 dip slightly below the critical pressure in the upstream segment (at 12 cm), which is the upstream narrowing that has occurred during flow limitation. Importantly, there is no change in curvature at the site of collapse. Therefore, we believe that changes in curvature are an unlikely explanation for NED in the human pharyngeal airway during sleep. Furthermore, note that there is little or no pressure recovery distal to the site of collapse, suggesting that the dominant mechanism for the pressure drop is viscous losses, as opposed to convective acceleration.

Constantly evolving Starling resistor. One potential explanation for NED is a so-called constantly evolving Starling resistor, in which the mechanics of the airway at the choke point; namely, the cross-sectional area and stiffness (or, if a Starling resistor, the upstream resistance and tissue pressure), constantly change throughout inspiration. There are a number of possible reasons why this could occur. First, the pharyngeal

muscles are known to exhibit phasic activation during inspiration, which could lead to stiffening of the airway walls. Second, caudal traction on the pharynx during lung inflation could change the mechanical properties of the airway. However, these two mechanisms we believe would tend to counteract intraluminal suction pressures and reduce NED, much like the balance of forces concept proposed by Remmers and colleagues (6, 16). Moreover, recent data from Genta et al. (4) showed that a 33% reduction in phasic pharyngeal muscle activation, induced by topical pharyngeal anesthesia, produced only a 4% worsening of NED. Thus (the lack of) inspiratory phasic muscle activation does not seem to have a large effect on NED.

A third potential mechanism, which would be consistent with our current finding of an increase in upstream resistance, is if an upstream-located structure, such as the palate, is mechanically coupled to a downstream-located structure, like the tongue. Therefore, when the downstream segment narrows (e.g., moving from line 4 to 5 to 6, etc. in Fig. 8, A and B), it drags the upstream segment with it, increasing the upstream resistance (as found in this study) and lowering the pressure at the choke point. The lower pressure at the choke point will decrease the area of the choke point, which will decrease the maximum flow rate.

In this explanation, flow still limits at the wave speed (or critical pressure), yet because the wave speed (or critical pressure) is constantly changing, then so does the maximum flow rate. In this constantly evolving model, therefore, there is not a single maximum flow rate. Although our data cannot prove or disprove this model, from a practical standpoint it may not be necessary to do so because in the end, the maximum flow rate changes dramatically and thus the airway is behaving much differently than a true Starling resistor, to the point that the Starling resistor principles may no longer be applicable. For example, a true Starling resistor can be characterized by its maximum flow rate, but not if the maximum flow rate is constantly changing or is different for different levels of downstream pressure.

Limitations. There are several limitations to this study. First, we could measure pressure only at discrete locations along the airway rather than continuously. Therefore, sharp changes in pressure could potentially be missed depending on the location of the sensor. However, we studied numerous breaths with the catheter moved in or out slightly between CPAP reductions in all patients, and we used a catheter with close and wide spacing and did not observe a difference in the pressure distributions. Second, it was not always easy to determine whether the sensor was at or just upstream from the site of collapse due to the sharp pressure drop at the site of collapse. However, the Starling resistor model, as well as the wave speed model, predicts that the pressure at the choke point also remains fixed. Therefore, this should not alter the conclusions of our findings. Third, it is always possible that the catheter itself could alter the airway mechanics. We think this is unlikely because the catheter was often moved back and forth (slowly) during sleep and sometimes removed altogether without any effect on the flow rate or pattern of NED.

In summary, this paper shows that the upper airway in many (but not all) individuals does not behave as predicted by a Starling resistor model. In particular, different sites or structures involved in collapse (e.g., velum, tongue, epiglottis) (8)

could potentially produce the distinct flow patterns with varying amounts of NED. Future work identifying the structural basis of the different NED patterns is needed because it could be used to guide site-specific therapy with surgery or devices.

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DISCLOSURES

A.W. is a paid consultant for Philips Respiroics and Galleon. A.W.'s interests were reviewed and are managed by the Brigham and Women's Hospital and Partners HealthCare in accordance with their conflict of interest policies. D.P.W. is Chief Scientific Officer for Apnicure and a consultant for Philips Respiroics. D.P.W.'s interests were reviewed and are managed by the Brigham and Women's Hospital and Partners HealthCare in accordance with their conflict of interest policies. R.L.O. is a paid consultant for Philips Respiroics.

AUTHOR CONTRIBUTIONS

A.W., P.R.G., O.F.P., and J.P.B. conception and design of research; A.W. and P.R.G. performed experiments; A.W. and P.R.G. analyzed data; A.W., R.L.O., D.P.W., and J.P.B. interpreted results of experiments; A.W. and R.L.O. prepared figures; A.W. drafted manuscript; A.W., P.R.G., R.L.O., B.A.E., S.A.S., S.H.L., D.P.W., A.C.J., O.F.P., and J.P.B. edited and revised manuscript; A.W., P.R.G., R.L.O., B.A.E., S.A.S., S.H.L., D.P.W., A.C.J., O.F.P., and J.P.B. approved final version of manuscript.

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