Contributions of passive mechanical loads and active neuromuscular compensation to upper airway collapsibility during sleep

STUDIES ADDRESSING THE MECHANISMS underlying upper airway collapsibility during sleep are significant given the prevalence of obstructive sleep apnea (OSA) in the general population (27) and the serious public health impact of this disorder (14). A variety of factors predispose to OSA within a patient, and the relative contribution of each factor can vary between patients (23). Such predisposing factors include the mechanical properties and collapsibility of the upper airway (e.g., influenced by upper airway size and compliance) (6, 7), ability to reflexly activate pharyngeal dilator muscles during sleep (24), ventilatory control instability (22, 26), decreased lung volume (3), and the predisposition to arousal that can destabilize breathing and lead to further apneas (25). An important breakthrough in determining the underlying mechanical properties and collapsibility of the upper airway was the development of techniques to measure the critical closing pressure (Pcrit) in sleeping subjects under passive conditions, i.e., in the absence of significant tone in the pharyngeal dilator muscles (16). A series of important observations have been made using this technique (18), a technique that has also been modified for more routine clinical use (12). In this issue of the Journal of Applied Physiology, Patil et al. (13) have extended their use of this technique to include measures of Pcrit under conditions of active neuromuscular responses during sleep. This is an important advance to further address the relative contributions of anatomically imposed mechanical loads and compensatory neuromuscular responses to maintain airway patency and is relevant to mechanisms influencing collapsibility and the pathogenesis of OSA (24). Before the findings and implications of this study are discussed, however, there follows a brief introduction to the measurement of Pcrit and the factors that alter this measure of upper airway collapsibility.

The upper airway is a collapsible tube with high compliance that is vulnerable to collapse during breathing (7), especially during sleep when muscle tone is reduced (9). During inspiration, the upper airway experiences subatmospheric pressures transmitted from the thoracic cavity. Under normal physiological conditions, the maintenance of an open upper airway depends on the intrinsic collapsibility of the airway and the level of pharyngeal muscle activation that stiffens and enlarges the airspace (4). The upper airway has been modeled as a collapsible tube with maximal inspiratory flow ($V_{\text{Imax}}$) determined by upstream nasal pressure ($P_N$) and resistance ($R_N$) (18). Airflow ceases in the collapsible segment of the upper airway at the critical closing pressure, Pcrit. $V_{\text{Imax}}$ is determined by the following relationship: $V_{\text{Imax}} = (P_N - \text{Pcrit}) / R_N$. From this relationship, it is apparent that increases in $P_N$ lead to increases in $V_{\text{Imax}}$; this effect on flow is the basis for nasal continuous positive airway pressure (CPAP) therapy in OSA. In contrast, decreases in $P_N$ decrease $V_{\text{Imax}}$. Experimental reductions in $P_N$ can be produced by rapid lowering of CPAP holding pressures and measuring inspiratory airflow. The relationship between $P_N$ and $V_{\text{Imax}}$ is linear, and so Pcrit can be measured directly or via linear regression (18). Importantly, since pharyngeal dilator muscle activity decreases substantially on CPAP and is not recruited for several breaths following the decreased airway pressure and subsequent hypoventilation (11, 16, 20), then the inspiratory flow observed immediately after lowering $P_N$ reflects the mechanical properties of the passive upper airway. Subjects in whom the upper airway is closed, or nearly closed, at pressures near or above atmospheric are highly susceptible to OSA and hypopnea, and these individuals require upper airway muscle activation to permit adequate airflow.

In contrast to the typical measurement of Pcrit in the passive upper airway, Patil et al. (13) in this issue of the Journal of Applied Physiology describe measures of Pcrit under conditions of active neuromuscular responses to loading during sleep in both normal subjects and patients with OSA. The authors implemented a modification of the technique originally described to measure the active Pcrit (17, 19). With this technique, the Pcrit at airway closure was progressively more positive (i.e., indicating a more collapsible upper airway) from groups of normal sleeping subjects, to snorers, and to patients with hypopneas and OSA (2, 18). The subjects of the recent study (13) were matched for obesity, age, and sex, i.e., factors known to influence OSA. The overall aim of the study was to determine the relative contributions of mechanical loads (passive Pcrit) and dynamic neuromuscular responses (active Pcrit) to upper airway collapsibility. Accordingly, in addition to the standard measurements of passive Pcrit immediately following the reductions in CPAP, measurements of active Pcrit were also made during separate interventions. For these interventions, CPAP was decreased in a stepwise fashion and sustained for at least 10 min at different holding levels. This protocol first produced periods of stable flow-limited breathing followed by periods of recurrent apneas and hypopneas as the CPAP holding pressure was lowered further. Measurements of $V_{\text{Imax}}$ and $P_N$ were performed during breaths at the end of the 10-min period, and segmented regression was used to identify the flow-limited segment of the pressure-flow relationship to provide the measure of active Pcrit (13). Measurements were not made during the same interventions where the air space would be passive at the initial step down in pressure followed by development of active neuromuscular compensation toward the end of the prolonged interventions. Measurements of genioglossus muscle activity were also performed in a subset of subjects to determine the differences in neuromuscular activity between the active and passive conditions.

The results confirmed previous observations (2, 18) that patients with OSA, compared with normal subjects, demonstrate an elevated mechanical load as indicated by more positive closing pressures in the passive upper airway (Pcrit $= -0.05 \text{cmH}_2\text{O}$ compared with $-4.5 \text{cmH}_2\text{O}$ in the 2 groups, respectively). The slopes of the relationship between $P_N$ and $V_{\text{Imax}}$ were similar, indicating a similar upstream resistance between groups, i.e., a parallel shift in the pressure-flow response resulted in the change in Pcrit. In the active condition, the control subjects markedly lowered their Pcrit to an average of $-11.1 \text{cmH}_2\text{O}$, i.e., a significant change from the $-4.5 \text{cmH}_2\text{O}$ measured in the passive condition. Importantly, however, in the patients with OSA this ability to lower Pcrit during
loading was markedly attenuated; i.e., $P_{\text{crit}}$ decreased from $-0.05$ cmH$_2$O to only $-1.6$ cmH$_2$O between the passive and active conditions. Matching the subjects for the level of passive $P_{\text{crit}}$ further confirmed that despite comparable initial mechanical loads, the patients with OSA had significant depression of the neuromuscular compensatory responses compared with the control subjects. Despite the robust ability of normal subjects to lower $P_{\text{crit}}$ during loading, whereas OSA patients were unable to similarly lower $P_{\text{crit}}$, the results showed that the increase in genioglossus muscle activity during loading was similar between groups. Given that it is assumed that the change in $P_{\text{crit}}$ between the active and passive conditions is due to recruitment of a neuromuscular compensatory response that involves upper airway muscles, this result is surprising and without full explanation. The authors suggest that the genioglossus is one of the many muscles that can affect upper airway collapsibility and may not be fully representative of the overall neuromuscular response. In addition, since genioglossus muscle recordings were only performed in one-third of subjects, it is also possible that this part of the study may have been underpowered to detect a difference.

Determining the mechanisms underlying the lack of neuromuscular responses in OSA patients to prevent them from effectively lowering their $P_{\text{crit}}$ during loading (13) is an important direction of future research because it is directly relevant to the pathogenesis of OSA and may also be involved in the natural history of this disorder (4). For example, the magnitude of reflex pharyngeal dilator muscle activation to stimuli of negative airway pressure shows inherent differences between subjects that are consistent within and across days (5). Therefore, in addition to individual differences in mechanical loads (passive $P_{\text{crit}}$) between subjects, this variation in neuromuscular responses to subatmospheric pressures in the upper airway during loading may help explain the variability between subjects in the ability to lower $P_{\text{crit}}$ and protect the upper airway during sleep (13).

An active $P_{\text{crit}}$ of approximately $-5$ cmH$_2$O separated most patients with OSA from the normal subjects, i.e., 12 of 13 normal subjects had an active $P_{\text{crit}}$ more negative than $-5$ cmH$_2$O (less collapsible), whereas 14 of 16 OSA patients had an active $P_{\text{crit}}$ more positive than $-5$ cmH$_2$O (more collapsible). Interestingly, the passive $P_{\text{crit}}$ of some of the normal subjects was elevated and in the range normally associated with OSA from previous studies (2, 18). An important result from this study, however, is that such normal individuals with a relatively collapsible upper airway were able to mount a robust neuromuscular response during loading to maintain airway patency and effectively lower $P_{\text{crit}}$ during sleep. Recent studies in OSA patients suggest that mechanical loads on the upper airway contribute approximately only one-third to sleep apnea severity and that differences in neuromuscular compensatory effectiveness are the major determinant of the variability in OSA severity between patients (24). The results from the study by Patil et al. (13) agree with the concept that both mechanical factors and compensatory effectiveness are important in the pathogenesis of OSA. One difference, however, is that the results from Patil et al. (13) emphasize a relative inability to mount a robust compensatory neuromuscular response to loading, whereas the studies by Younes (24, 25) suggest that such patients are able to mount effective compensatory responses but that arousal from sleep preempts this orderly response, leading to ventilatory instability and recurrence of obstructions. The studies by Younes (24, 25) focused solely on patients with OSA, whereas the study by Patil et al. (13) investigated subjects with and without OSA. Patil and colleagues discuss both cohorts and propose a “two-hit” hypothesis whereby defects in both upper airway mechanical loads and neuromuscular control are important factors for the development of OSA. Since much attention in the literature has focused on the former, a reminder of the importance of the latter mechanism is of relevance to the field. In this scenario, those individuals with a robust neuromuscular response would be better able to maintain (or restore) a patent upper airway, even with a high mechanical load, compared with those individuals with low neuromuscular compensatory responses. It follows, therefore, that any decrements in neuromuscular compensatory responses could lead to an increased tendency to develop hypopneas and OSA and that individuals with already small responses would be most susceptible (4). A decrement in neuromuscular compensatory effectiveness may result from alcohol ingestion or age or may even develop over time as a consequence of the detrimental effects of snoring and OSA on the upper airway mucosa (8, 10). Changes in body mass index can also have a significant impact on upper airway collapsibility that may be relevant given the increasing rates of obesity in society, especially among the young (1, 21). Weight loss of $-15\%$ can decrease $P_{\text{crit}}$ by $-6$ cmH$_2$O, which in individuals with a $P_{\text{crit}}$ close to atmospheric pressure may be sufficient to significantly improve OSA (15). In the two-hit hypothesis, an increase in weight would increase the mechanical load on the upper airway and alter $P_{\text{crit}}$ such that previously normal compensatory neuromuscular response may not now be sufficient to keep the upper airway open or restore patency. Such important effects of obesity on mechanical loads and the interaction with compensatory neuromuscular responses may explain the increasing prevalence of OSA associated with obesity (28).

REFERENCES


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