Effect of chemoreceptor stimulation and inhibition on total pulmonary resistance in humans during NREM sleep

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Badr, M. Safwan, James B. Skatrud, and Jerome A. Dempsey. Effect of chemoreceptor stimulation and inhibition on total pulmonary resistance in humans during NREM sleep. *J. Appl. Physiol.* 76(4): 1682–1692, 1994.—We investigated the effect of chemoreceptor stimulation and inhibition on total pulmonary resistance (RL) during non-rapid-eye-movement (NREM) sleep in healthy subjects. Chemoreceptor stimulation was accomplished with brief isocapnic hypoxia ($n = 8$). Minute ventilation increased to 150% of room air control. RL at peak inspiratory flow decreased to 66% of room air control. Resistive pressure-inspiratory flow plots demonstrated lower resistive pressures for a given inspiratory flow. Chemoreceptor inhibition was accomplished by abruptly terminating brief hypocapnic hypoxia with 100% O_2 ($n = 7$). Minute ventilation decreased to 63% of room air control. RL calculated at peak inspiratory or fixed flow did not change significantly, and pressure-flow plots at nadir ventilation showed no systematic change from room air control. We conclude that *1*) hypoxic chemoreceptor stimulation is associated with decreased RL and enhancement of pressure-flow relationships, suggesting increased upper airway caliber; *2*) upper airway patency is not compromised during periods of low ventilatory drive in normal subjects; and *3*) upper airway dilating muscles and thoracic pump muscles are optionally coordinated with increased and decreased ventilatory drive.

hypoxia; hypocapnia; upper airway patency

CHEMORECEPTOR STIMULATION or inhibition may affect upper airway patency by altering upper airway dilating muscle activity or by nonneuromuscular factors such as vasomotor tone (34) or the caudal traction generated by thoracic inspiratory muscles (30). Hypercapnic chemoreceptor stimulation is associated with decreased upper airway resistance (Ruaw) in dogs (20) and in humans during wakefulness (2, 27) and non-rapid-eye-movement (NREM) sleep (2). Hypoxic chemoreceptor stimulation is also associated with decreased Ruaw in awake seated humans (19) and laryngeal resistance in anesthetized cats (3). However, the effect of hypoxic stimulation on upper airway patency has not been studied in sleeping humans. Whereas mild hypocapnic inhibition is associated with increased Ruaw in awake supine humans (27, 28), little information is available on the effect of chemoreceptor inhibition on upper airway patency in sleeping humans, particularly those with a high propensity for upper airway narrowing or collapse.

The purpose of this study was twofold: *1*) to determine the effect of hypoxic chemoreceptor stimulation on upper airway patency during NREM sleep in healthy subjects spanning the spectrum of Ruaw from nonsnorers to healthy snorers and *2*) to determine the effect of chemoreceptor inhibition on upper airway patency in sleeping humans. Total pulmonary resistance (RL) was measured as an index of Ruaw. The bronchoconstricting effect of hypoxia or hypocapnia may confound data interpretation if RL is used as an index of Ruaw. Therefore, simultaneous esophageal (Pes) and supraglottic pressure measurements were obtained in two subjects.

METHODS

Subject Selection

Nine healthy nonobese subjects were studied (age range 19–25 yr). Three subjects were habitual snorers. All subjects were free of excessive daytime sleepiness, sleep-related breathing disorders, and any cardiopulmonary disease. The study protocol was approved by the Human Subject Committee in our institution. Subjects were instructed to restrict their sleep the night before the study (total sleep time 4–6 h). The study was done during regular sleep hours.

Breathing Circuit

The subject was connected to the circuit with an airtight silicone rubber mask strapped and glued to the face to prevent leaks. The mask was attached to a unidirectional low-resistance valve with a heated pneumotachometer on the inspiratory line. The total dead space of the mask and valve combined was ~125 ml. The valve allowed inspiration from ambient air or from one of three large gas bags containing pure N_2, 8% O_2, or 100% O_2. To maintain isocapnia, three similar bags [identical inspired O_2 fraction (FI_{O_2})] with supplemental CO_2 were attached in parallel with the non-CO_2-containing bags by manual two-way valves.

Measurements

Ventilation and timing. Inspiratory and expiratory flows were measured by a pneumotachometer attached to the mask as described above. Tidal volume (VT) was obtained by integrating the inspiratory flow signal. Respiratory cycle timing was obtained from the flow signal.

Mechanics. Pes was measured using a pressure transducer-tipped catheter (model TL-500, Millar Instruments, Houston, TX). The catheter was positioned to best reflect pleural pressure (4). Pes was measured instead of pharyngeal pressure to maximize subject comfort and to ensure detection of hypopharyngeal pressure changes. Lung elastic pressure, measured at points of zero flow, was subtracted from total intrapleural pressure to obtain resistive pressure. Inspiratory flow rate was plotted against resistive pressure throughout the breath under each experimental condition. In addition, RL was measured throughout the breath by dividing the resistive pressure by the corresponding inspiratory flow (32). Two points for measurement of RL were selected: peak inspiratory flow (RL_{pf}) and several fixed flow rates (RL_{ff}).

Chemical stimuli. End-tidal P_{CO_2} ($P_{ET_{CO_2}}$) was measured

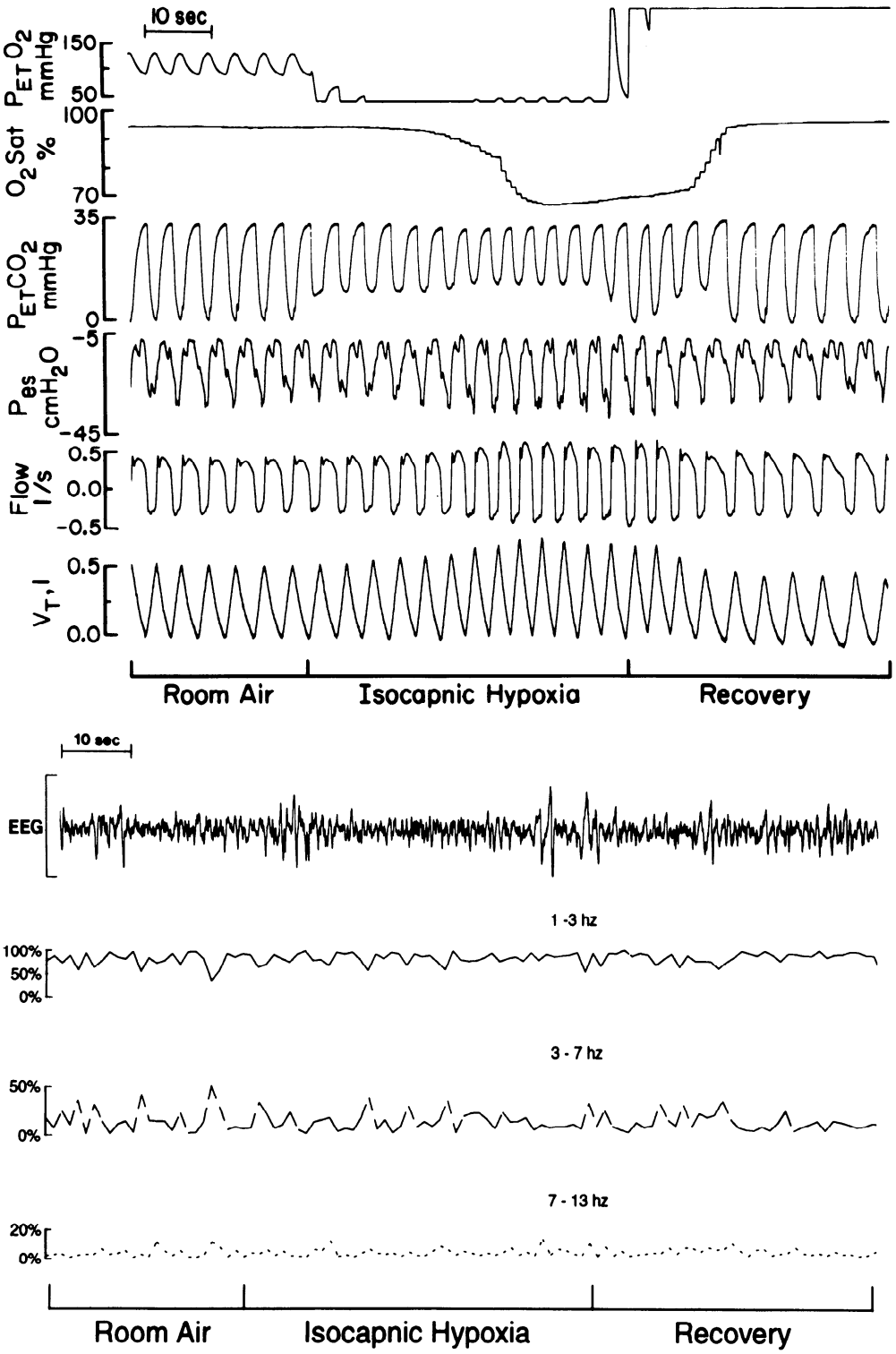

FIG. 1. *Top*: polygraph tracing depicting effect of brief isocapnic hypoxia on ventilation and pulmonary mechanics. $P_{ET_{O_2}}$, end-tidal P_{O_2}; O_2Sat, oxyhemoglobin saturation; $P_{ET_{CO_2}}$, end-tidal P_{CO_2}; Pes, esophageal pressure; VT, tidal volume. Note that $P_{ET_{CO_2}}$ remained constant throughout the trial. Sleep state was also unchanged. *Bottom*: EEG spectral analysis. Note stability of EEG during hypoxia and recovery period. Relative contribution of α-frequency (8–12 Hz) remained constant.

breath by breath (Beckman LB-2, Fullerton, CA). End-tidal P_{O_2} was measured breath by breath with an O_2 analyzer (Beckman OM 11).

Sleep stage. Electroencephalogram (EEG), chin electromyogram (EMG), and electrooculogram were recorded (model 7D, Grass Instruments). Sleep stage was analyzed according to the criteria of Rechtschaffen and Kales (25). Subtle sleep state changes were detected using the fast Fourier transformation (10). The EEG signal was low-pass filtered with an antialiasing filter and was sampled by an analog-to-digital conversion board into a personal computer at 64 samples/s. The digitized EEG signal was divided into segments (epochs) of 64 samples/s for fast Fourier transformation analysis. Mean frequency, total power, and relative power contribution were determined for every epoch. This analysis was performed on 10 representative trials. Trials were included in the analysis if sleep state remained constant throughout the trial.

Protocols

Two separate protocols were conducted in random order. One or two nights were required for completion of both protocols. Some subjects underwent only one protocol and did not return for a second night in the laboratory.

TABLE 1. *Effect of brief hypoxic stimulation on ventilation and mechanics*

	Room Air	Hypoxia
$\dot{V}_E$, l/min	6.12±1.5	9.24±2.70*
V_T, liter	0.42±0.15	0.59±0.25*
Frequency, breaths/min	16±6	17±6
$P_{ET_{O_2}}$, Torr	101±5	54±14
$P_{ET_{CO_2}}$, Torr	44.3±1	43.9±1.1
$R_{L_{pf}}$, $cmH_2O \cdot l^{-1} \cdot s$	34.5±7.0	22.5±3†

Values are means ± SD; $n = 8$ subjects. $\dot{V}_E$, minute ventilation; V_T, tidal volume; $P_{ET_{O_2}}$ and $P_{ET_{CO_2}}$, end-tidal P_{O_2} and P_{CO_2}, respectively; $R_{L_{pf}}$, total pulmonary resistance at peak inspiratory flow. * $P < 0.001$; † $P < 0.05$.

Effect of hypoxic chemoreceptor stimulation on RL during NREM sleep. Brief isocapnic hypoxia was performed for 1 min in eight subjects. To induce brief isocapnic hypoxia, the subject received several breaths of N_2 (range 4–7 breaths) supplemented with CO_2 (inspired CO_2 fraction 2–2.5%) followed by 8% O_2 supplemented with CO_2 (inspired CO_2 fraction 2.5–3.5%). The total duration of hypoxia did not exceed 1 min. Care was taken to ensure isocapnia; trials that were not isocapnic were excluded from this analysis.

Effect of chemoreceptor inhibition on RL during NREM sleep. Chemoreceptor inhibition was induced by abruptly terminating brief hypocapnic hypoxia with hyperoxia. In seven subjects, brief hypoxia (1 min) was induced with six breaths of N_2 followed by six breaths of 8% FI_{O_2}. The number of breaths was empirically adjusted to achieve O_2 saturation of 80%. Hypoxia was abruptly terminated with 100% FI_{O_2}, and the effects on ventilation and RL during the ensuing recovery period were determined.

Data Analysis

All similar trials were averaged, and a mean pressure-flow loop was plotted for each subject per condition. The effect of brief isocapnic hypoxia was determined by combining the pressure-flow loops from every subject to form a composite loop. $R_{L_{pf}}$ was also calculated per subject. The room air control period was defined as the last 10 room air breaths preceding hypoxia; the hypoxia period was defined as the last 5 hypoxic breaths. Paired t test was used to compare $R_{L_{pf}}$ between room air and hypoxia (8).

To illustrate the effect of abrupt hyperoxic termination of hypoxia, the nadir hyperoxic breath [the recovery breath with the lowest minute ventilation ($\dot{V}_E$)] was plotted on the same graph as the preceding room air control and hypoxic composite breaths for each subject. Paired t test was used to compare

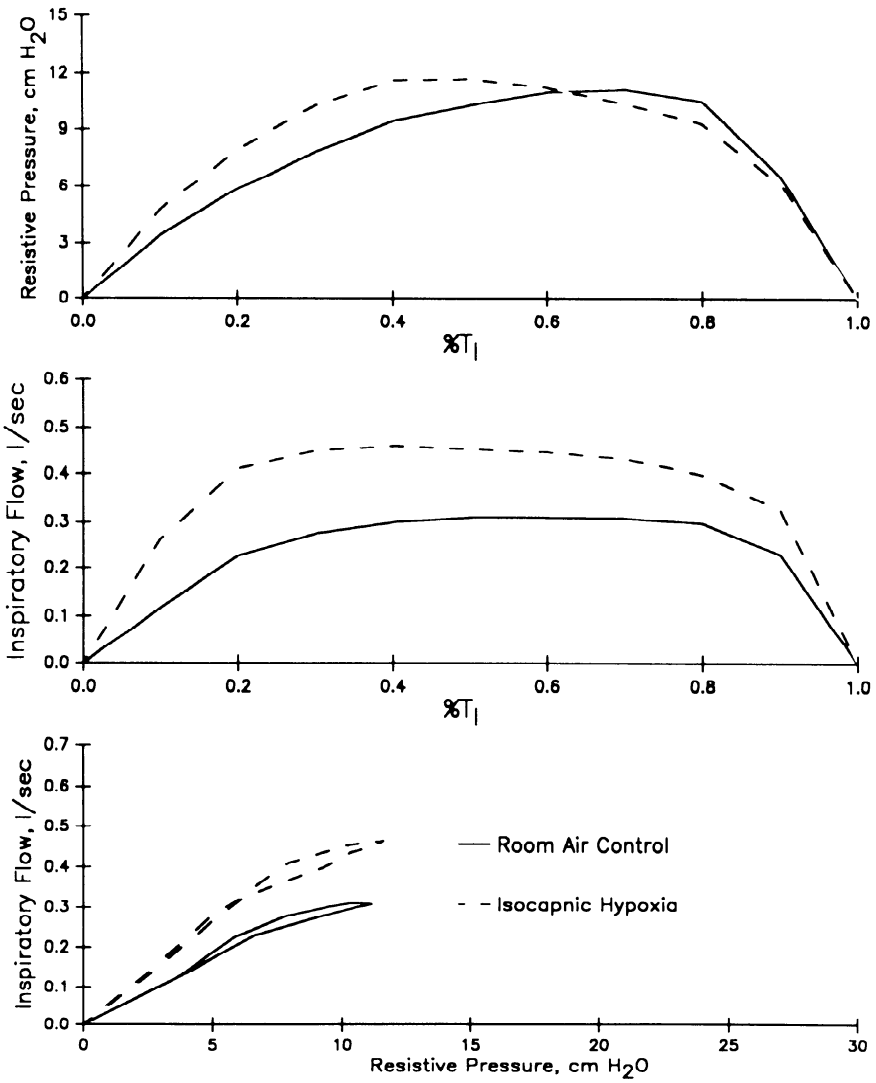

FIG. 2. Composite plot showing group effect of brief isocapnic hypoxia on pulmonary mechanics ($n = 8$). Resistive pressure increased slightly (*top*) and inspiratory flow increased (*middle*) throughout breath with hypoxia. Also note diminished magnitude of flow limitation (see text for details). Less resistive pressure was required for a given flow (*bottom*). %TI, percent inspiratory time.

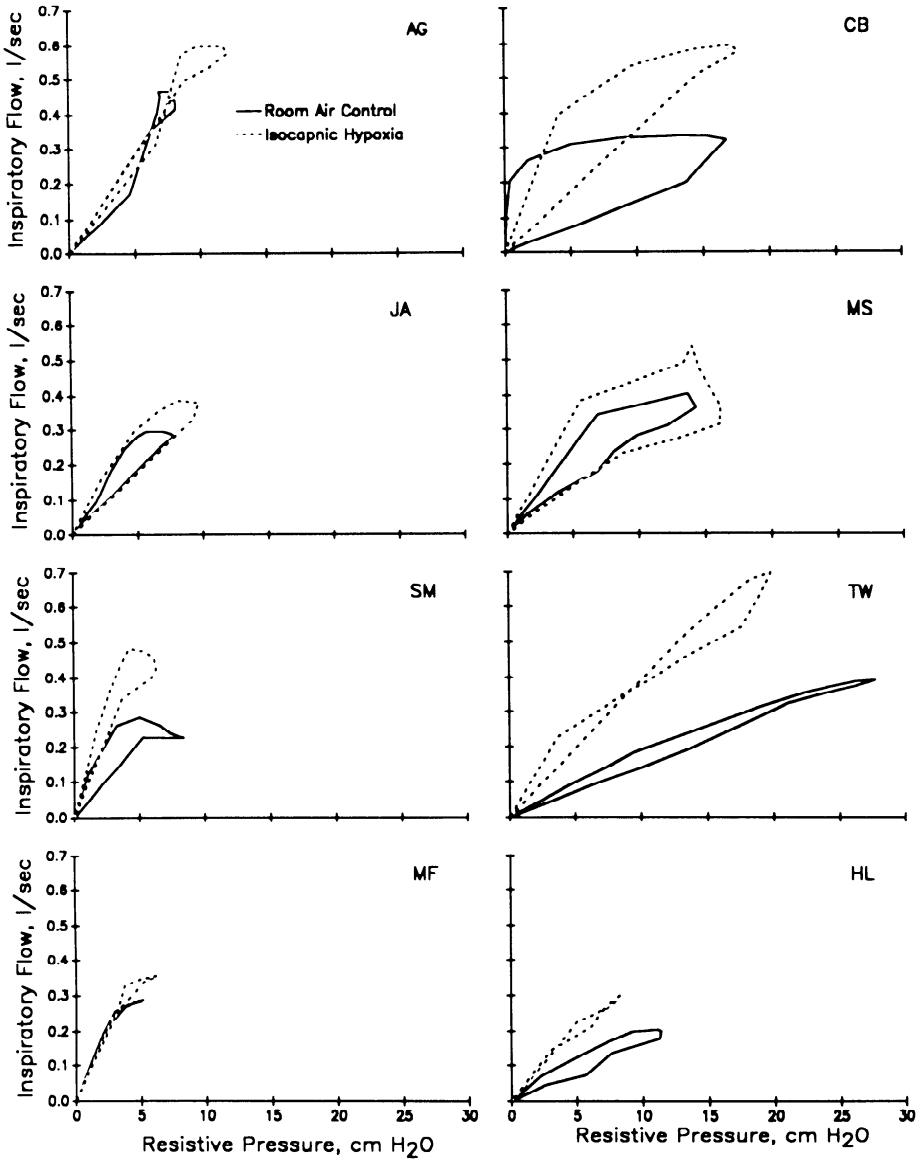

FIG. 3. Effect of isocapnic hypoxia on total pulmonary resistance. Note increased slope of resistive pressure-inspiratory flow loops, indicative of reduced total pulmonary resistance.

changes in RL between room air and the nadir breath at a flow rate of 0.15 l/s.

RESULTS

Effect of Hypoxic Chemoreceptor Stimulation on Ventilation and Mechanics

Hypoxic chemoreceptor stimulation was maintained for 1 min and was abruptly terminated with hyperoxia in eight subjects. A representative trial is shown in Fig. 1. Isocapnia was maintained within 1 Torr of room air control. VT increased and stabilized at the end of the trial; Pes and inspiratory flow rates were also augmented. Sleep state remained stable by conventional criteria and by EEG spectral analysis. The relative α-frequency contribution was stable throughout the trial. Likewise, end-expiratory lung volume was constant throughout the trial. The results for the group are shown in Table 1. Brief isocapnic hypoxia (end-tidal P_{O_2} 55 Torr, $P_{ET_{CO_2}}$ within 1.5 Torr of room air control) was associated with increased $\dot{V}_E$ (from 6.1 ± 1.5 to 9.2 ± 2.7 l/min, 151% of room air control), which was due mainly to increased VT (from 0.42 ± 0.15 to 0.59 ± 0.25 liter, 140% of room air control). During room air breathing, RL_{pf} was 34.5 ± 7 $cmH_2O \cdot l^{-1} \cdot s$ (range 10–50 $cmH_2O \cdot l^{-1} \cdot s$) and decreased to 22.5 ± 3 $cmH_2O \cdot l^{-1} \cdot s$ (66%) of room air during hypoxic stimulation.

The group effect of brief isocapnic hypoxia on the pressure-flow relationship relative to room air breathing is shown in Fig. 2. During room air breathing, inspiratory flow increased initially, reaching a plateau between 40 and 70% of inspiratory time, whereas resistive pressure continued to increase (flow limitation). Hypoxic chemoreceptor stimulation did not change the overall pattern of inspiratory flow; however, maximal resistive pressure was synchronous with maximal inspiratory flow at 40% of inspiration (no flow limitation). The relationship between inspiratory flow and resistive pressure is shown in Fig. 2, *bottom*. Less resistive pressure was required for a given inspiratory flow during hypoxia. The effect of iso-

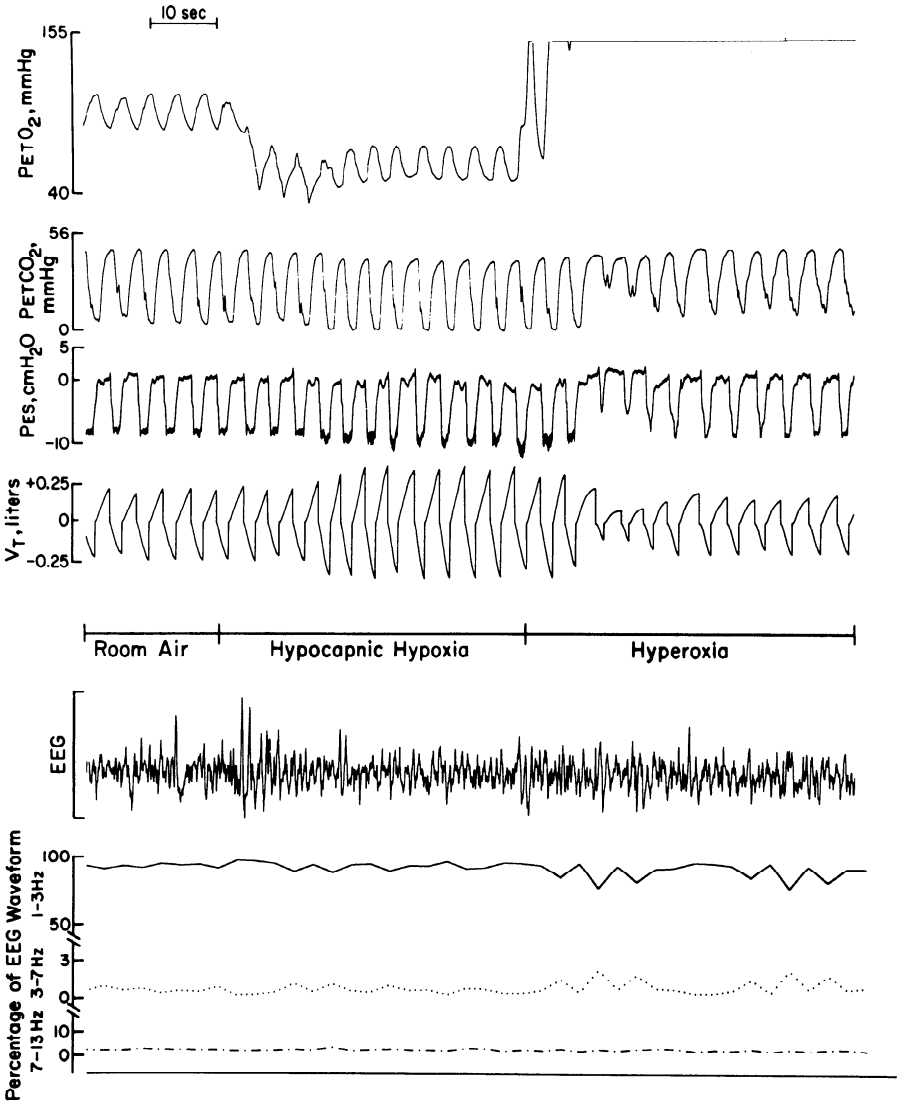

FIG. 4. Polygraph record depicting effect of chemoreceptor inhibition during hyperoxic recovery after brief hypocapnic hypoxia. Note reduction in Pes and VT during hyperoxia. Also note stability of EEG by spectral analysis, indicating unchanged sleep state.

capnic hypoxia is shown in Fig. 3 for each subject, spanning the spectrum from subjects with high resistance such as *subject TW* (RL_{pf} 74 $cmH_2O \cdot l^{-1} \cdot s$) to subjects with low resistance such as *subject SM* (RL_{pf} 13 $cmH_2O \cdot l^{-1} \cdot s$). The decreased resistance was more pronounced in subjects with high baseline resistance (*subjects CB, HL, MS,* and *TW*). In summary, brief isocapnic hypoxia had salutary effects on lung mechanics evidenced by an enhanced resistive pressure-inspiratory flow relationship and decreased RL_{pf}.

Effect of Chemoreceptor Inhibition on Ventilation and Mechanics

Chemoreceptor inhibition was accomplished in a separate protocol by abrupt termination of brief hypocapnic hypoxia. A representative example is shown in Fig. 4 from a heavy snorer (*subject TW*). VT and Pes were reduced during the recovery period. Sleep state remained constant by conventional criteria and by EEG spectral analysis; the relative contribution of the α-frequency to

TABLE 2. *Effect of chemoreceptor stimulation and inhibition on ventilation and timing*

	$\dot{V}E$, l/min			VT, liter			Frequency, breaths/min			RL_{pf}, $cmH_2O \cdot l^{-1} \cdot s$		
Subj	Room air	Hypoxia	Recovery nadir	Room air	Hypoxia	Recovery nadir	Room air	Hypoxia	Recovery nadir	Room air	Hypoxia	Recovery nadir
AG	8.2±0.2	10.1±1.6	7.2±0.6	0.5±0.0	0.6±0.1	0.5±0.0	16.6±0.3	18.3±0.3	14.7±1.3	19.0±3.6	18.7±5.9	13.6±6.7
JA	8.6±0.1	10.8±1.0	6.4±1.3	0.3±0.0	0.3±0.0	0.2±0.1	32.4±0.2	34.7±0.6	28.6±1.2	21.1±0.9	21.0±1.6	16.6±2.3
SM	5.4±0.3	6.2±0.8	3.7±1.0	0.4±0.0	0.5±0.0	0.3±0.1	13.0±0.7	13.0±0.8	11.7±3.5	9.4±0.8	10.5±3.7	10.0±3.7
MS	7.5±0.8	11.6±1.1	2.3±1.2	0.6±0.1	0.8±0.1	0.5±0.1	11.9±0.7	14.6±1.9	6.4±1.9	12.1±6.8	10.7±2.4	14.2±15.0
CB	6.5±0.3	10.1±1.5	3.5±2.1	0.6±0.0	0.7±0.1	0.3±0.1	11.7±0.7	13.6±0.9	10.5±3.5	38.4±12.6	38.9±16.6	59.6±7.2
TW	7.2±0.3	11.7±0.9	3.6±0.7	0.5±0.0	0.7±0.1	0.4±0.1	14.4±0.5	16.1±0.7	10.4±0.6	74.6±4.6	42.0±10.3	61.2±9.1
DW	3.7±0.5	4.6±0.5	2.6±0.4	.23±0.0	0.28±0.0	0.16±0.0	16.0±0.2	16.6±0.2	17.1±1.1	31.7±4.5	26.1±3.1	31.3±6.6
Mean ± SD	6.6±1.7	8.9±2.6	4.5±1.7	0.4±0.1	0.5±0.2	0.3±0.1	17.3±6.9	18.7±7.4	15.5±6.3	29.5±20.7	24.0±11.6	29.5±20.5

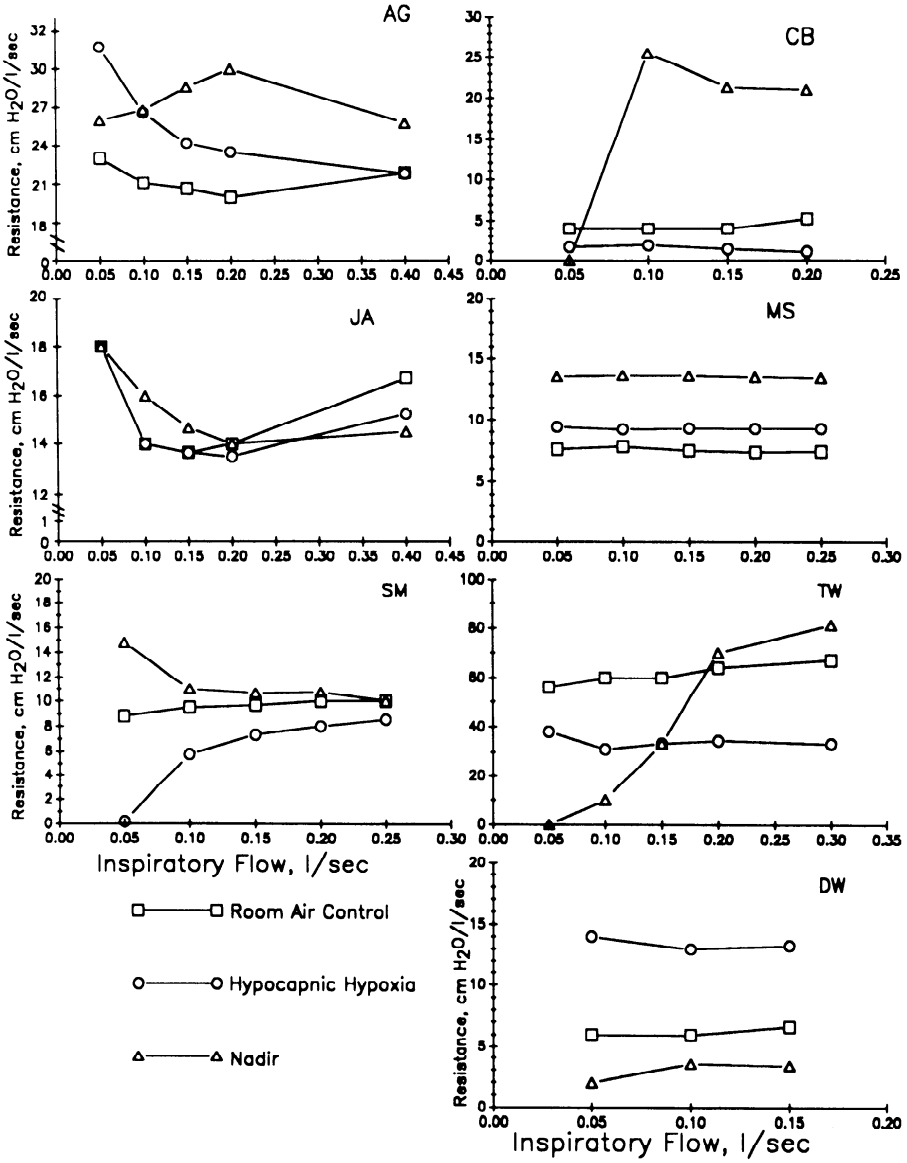

FIG. 5. Effect of hypocapnic chemoreceptor inhibition on total pulmonary resistance at several fixed flow rates (RL_{ff}). No significant change in RL_{ff} was noted at nadir breath relative to room air control. Baseline values did not predict response to reduced ventilatory drive.

the total power (8–12 Hz) was stable throughout the trial and the hyperoxic recovery period. For the group, brief hypocapnic hypoxia resulted in moderate hypocapnia (PET_{CO_2} decreased from 44.0 ± 1.8 to 40.5 ± 1.5 Torr, range 2.5–5 Torr reduction in PET_{CO_2}). During room air breathing, $\dot{V}E$ was 6.6 ± 1.7 l/min and decreased to a nadir of 63% of room air (Table 2). The decrease in $\dot{V}E$ was due to decreased VT (75% of room air) and frequency (86% of room air). The subjects spanned the spectrum of nonsnorers with low baseline RL_{pf} (*subject SM*) to heavy snorers with high RL_{pf} (*subject TW*) during room air breathing (Table 2). No significant change in RL_{pf} was noted at the nadir breath. The effect of chemoreceptor inhibition on RL_{ff} is shown in Fig. 5. There was no significant change in resistance at any flow rate ($P > 0.05$).

The effect of chemoreceptor inhibition on the resistive pressure-inspiratory flow relationship is shown in Fig. 6 for the group. There were increases in pressure and flow during hypoxic stimulation and a symmetrical reduction at the nadir breath. The pressure-flow relationships did not change between the room air control period and the nadir breath. Individual pressure-flow plots are shown in Fig. 7. No change in the pressure-flow relationship was noted between room air and the nadir recovery breath except in *subject CB*. The response to hypocapnic chemoreceptor inhibition was not affected by baseline RL or the magnitude of ventilatory inhibition.

In summary, chemoreceptor inhibition was not associated with increased RL in normal healthy subjects whether they were heavy snorers with high RL or nonsnorers with low RL.

Resistive Pressure vs. Supraglottic Pressure

Simultaneous measurements of Pes and supraglottic pressure were performed in two subjects (*subjects MS* and *JA*) to determine whether the effects of chemoreceptor stimulation or inhibition on RL were due to supraglottic or intrathoracic airway changes (Fig. 8). Pressure-flow loops were plotted using resistive or supraglottic pressure. The slope of both loops at the nadir breath was similar to the slope during room air control. Thus, changes in total pulmonary mechanics were representative of changes in upper airway mechanics.

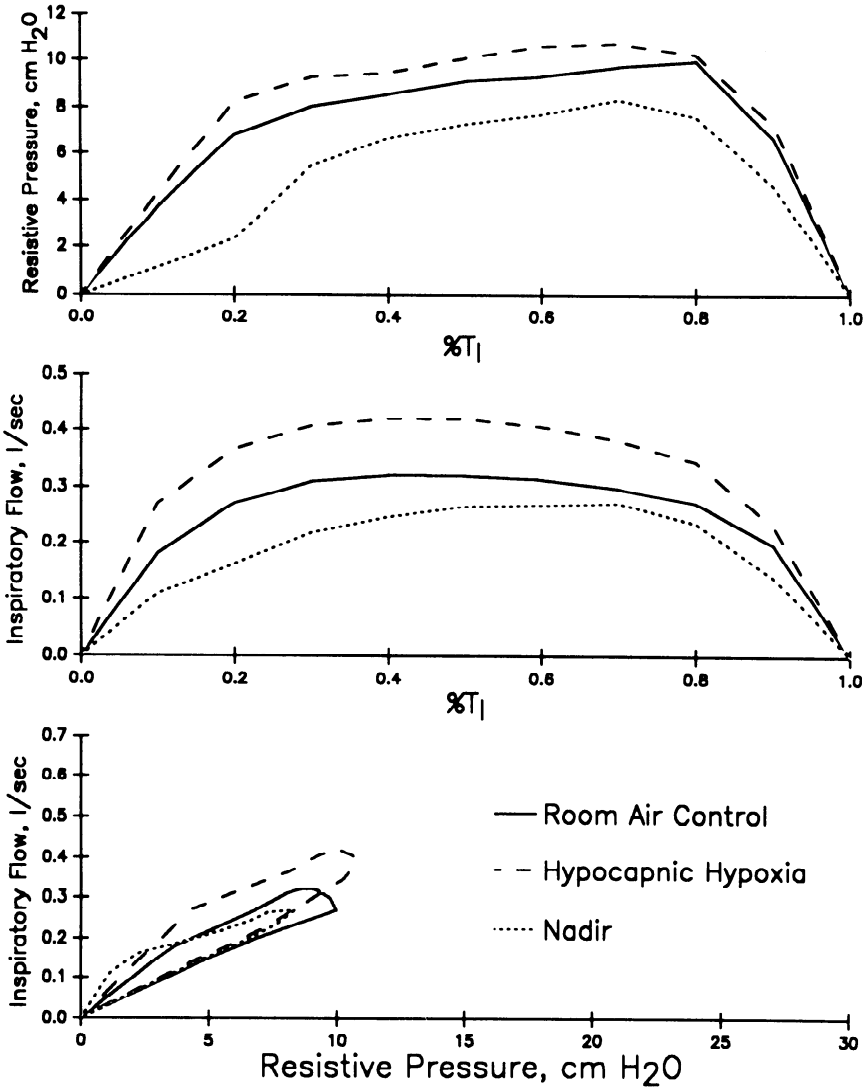

FIG. 6. Group effect of chemoreceptor inhibition on pulmonary mechanics. Resistive pressure (*top*) and inspiratory flow (*middle*) are displayed as %TI and are plotted against each other (*bottom*). Note increases in both resistive pressure and inspiratory flow during hypoxic stimulation and reductions with chemoreceptor inhibition. Pressure-flow relationship was not compromised during chemoreceptor inhibition.

DISCUSSION

The main findings of our study were that *1*) hypoxic chemoreceptor stimulation is associated with reduced RL in normal nonsnoring subjects (low baseline RL) or healthy snorers (high baseline RL) and *2*) mild hypocapnic chemoreceptor inhibition during the recovery from brief hypoxia does not compromise total pulmonary pressure-flow relationships.

Limitation of Methods

Several factors have to be considered for proper interpretation of our data. We measured RL as an index of Ruaw because most of our subjects tolerated an esophageal catheter better than a pharyngeal catheter. Furthermore, Pes measurement ensures that hypopharyngeal pressure changes are detected. We feel that the use of RL as an index of Ruaw is justified for the following reasons. *1*) Ruaw constitutes most of RL during NREM sleep (15). *2*) Hypoxia or hypocapnia may induce bronchoconstriction (18, 29) and hence tend to increase RL. A constant or reduced RL suggests that Ruaw is also constant or reduced, i.e., that upper airway patency is preserved. *3*) Previous work from our laboratory (5) has shown by direct fiber-optic visualization that changes in RL correlate with changes in pharyngeal cross-sectional area. *4*) Our present study shows that chemoreceptor stimulation or inhibition exerted similar effects on the resistive pressure-flow rate relationship compared with the supraglottic pressure-flow rate relationship. In conclusion, we believe that changes in RL in our present study are representative of changes in Ruaw and not intrathoracic airways.

Measurement of RL_{pf} (36) or RL_{ff} (17) is commonly used to express total pulmonary mechanics. Although RL_{pf} may be valuable in expressing baseline resistance, it often falls short under conditions of decreased inspiratory flow, as is the case during chemoreceptor inhibition. For example, in *subject AG*, RL_{pf} at the nadir breath was 72% of room air, whereas the resistive pressure-flow plot suggested a slight increase in RL throughout the nadir breath relative to room air (Fig. 7). To obviate the limitation of pressure-flow alinearity, RL could be measured at a fixed flow rate. Our data also illustrate the limitation of measuring RL at a single fixed inspiratory flow, especially when the slope of the pressure-flow plots is changing. For example, in *subject TW* (Fig. 7), the room air

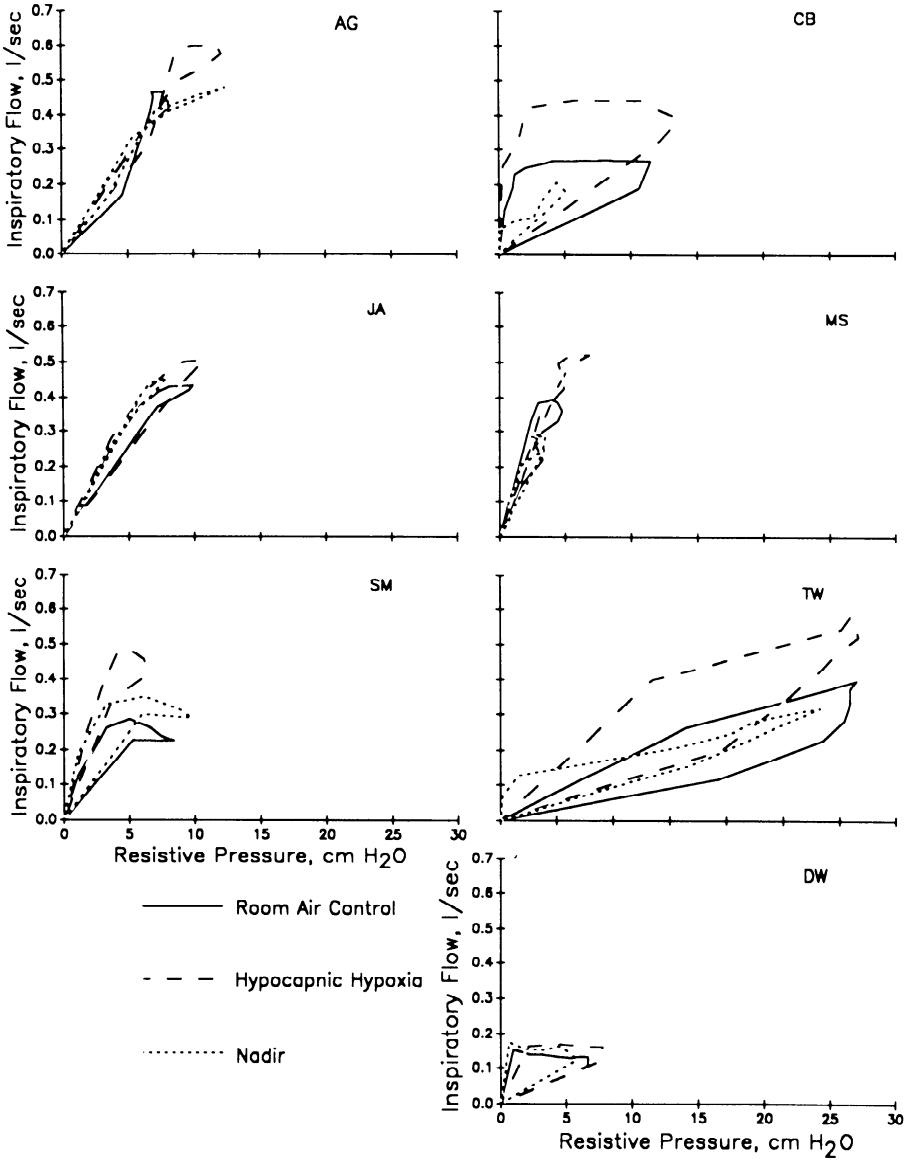

FIG. 7. Effect of chemoreceptor inhibition on pressure-flow relationship in each subject. Note stability of pressure-flow relationship at nadir of ventilatory drive in all subjects except *subject CB*.

pressure-flow curve crosses its nadir breath counterpart. Different conclusions could be reached about the effect of chemoreceptor inhibition on upper airway mechanics depending on the arbitrary "fixed flow" selected for measurement. In conclusion, we have demonstrated that measurement of RL at a single point within inspiration is not sufficient to characterize upper airway mechanics. Although our study was not designed as a systematic evaluation of different indexes of RL, these findings mandate caution in ascribing changes in a single index to changes in Ruaw throughout the breath.

Two potential hurdles must be overcome for interpretation of pressure-flow plots. First, quantification of pressure-flow loops and hence statistical analysis remain elusive. We attempted to apply several "best-fit" models to our data, including the one published by Hudgel et al. (14). Unfortunately, pressure-flow plots with extreme flow limitation (increased pressure with no corresponding increase in flow) could not be fitted without compromising accuracy; the hysteresis of the loop further complicated the best-fit application. Second, the relationship between resistance to airflow and upper airway cross-sectional area has not been determined systematically. The complex geometry of the upper airway coupled with turbulent flow confound the use of RL or pressure-flow plots as indexes of upper airway cross-sectional area. Studies with simultaneous measurement of upper airway cross-sectional area and Ruaw are needed.

Hypoxic Chemoreceptor Stimulation and Airway Mechanics

We have found that hypoxic chemoreceptor stimulation results in decreased RL because of reduced supraglottic or intrathoracic airway resistance. The latter is unlikely, since the magnitude of decreased RL (-12 $cmH_2O \cdot l^{-1} \cdot s$) exceeds the reported values of intrathoracic airway resistance (15). Furthermore, hypoxia is known to increase intrathoracic airway resistance (18). Thus, reduced RL is most likely due to decreased Ruaw. The salutary effect of hypoxic chemoreceptor stimulation is not due to changing sleep state or end-expiratory lung volume, since both remained constant. Hypoxia is also unlikely to exert its effects by changing vasomotor

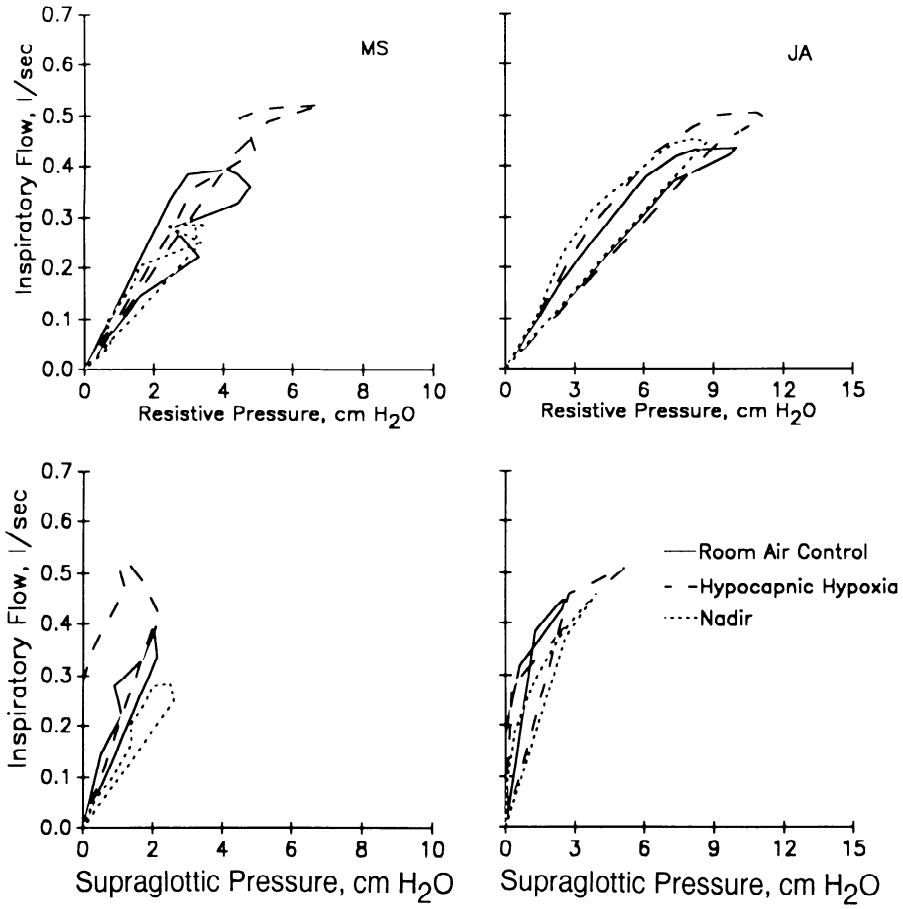

FIG. 8. Comparison of total pulmonary resistance vs. upper airway mechanics in *subjects MS* (*left*) and *JA* (*right*). *Top*: resistive pressure-inspiratory flow loops for each subject. *Bottom*: supraglottic pressure-inspiratory flow loops. Note similarity in response between resistive and supraglottic loops under hypoxic stimulation or at nadir breath.

tone because hypoxia is associated with vasodilatation, which may increase Ruaw (26). Augmented thoracic inspiratory activity may cause a proportional caudal traction on the upper airway, decreasing RL and maintaining upper airway patency despite augmented collapsing pressures (30). Finally, chemoreceptor stimulation may decrease Ruaw by increasing upper airway dilating muscle activity to offset the augmented collapsing pressure. Our data do not permit us to determine the relative contribution of increased upper airway dilating muscle recruitment vs. caudal traction in decreasing RL and preserving upper airway patency.

The relative effect of hypercapnic (central chemoreceptors) vs. hypoxic (peripheral chemoreceptors) stimulation on upper airway patency in sleeping humans has not been studied. We have previously shown that increasing $P_{ET_{CO_2}}$ by 6 Torr resulted in an increase in $\dot{V}E$ to 164% of room air and an average reduction of RL_{pf} to 65% of room air. By comparison, brief isocapnic hypoxia (n = 8) resulted in a 151% increase in $\dot{V}E$ and a reduction of RL_{pf} to 65% of room air. Thus, hypoxic chemoreceptor stimulation exerts similar effects on RL relative to hypercapnic central chemoreceptor stimulation. This conclusion is different from previous animal studies showing that peripheral chemoreceptor stimulation has a preferential effect on upper airway dilating muscle (7, 31). EMG studies, however, cannot predict the global behavior of the upper airway during sleep.

In summary, our data confirm and extend previous studies by demonstrating that hypoxic chemoreceptor stimulation during NREM sleep results in decreased RL, suggesting increased upper airway caliber. We conclude that chemoreceptor stimulation exerts salutary effects on upper airway patency regardless of its mechanism.

Effect of Chemoreceptor Inhibition on Airway Mechanics

We have shown that mild hypocapnic hyperoxic chemoreceptor inhibition is not associated with increased RL. The preservation of total pulmonary mechanics suggests that upper airway patency was not compromised during periods of low drive (see *Limitation of Methods*). However, our data do not allow us to ascertain whether upper airway cross-sectional area increased or remained constant. Our findings can be contrasted with those from previous studies suggesting that low ventilatory drive predisposes subjects to upper airway narrowing because of preferential recruitment of thoracic pump muscles relative to upper airway dilating muscles (6, 11, 12, 24, 35). However, EMG studies on individual muscle groups do not necessarily predict upper airway mechanics during sleep. Our findings can also be contrasted with observations from previous studies during hypoxia-induced periodic breathing (13, 21, 22, 33), including data from our own laboratory (33). In these studies, increasing and decreasing neural drive was associated with decreased and increased Ruaw, respectively. In fact, Warner et al. (33) demonstrated complete upper airway obstruction in heavy snorers at the nadir of ventilatory drive. The large fluctuation in RL during periodic breathing compared with in the present study could be explained by a greater reduction in ventilatory motor output. In turn, this may

be due to *1*) the longer duration of hypoxic exposure and hence hypoxic brain depression of ventilatory motor output, *2*) EEG arousal on termination of upper airway obstruction with resulting hyperpnea and further arterial hypocapnia, or *3*) a vagally mediated nonchemical neuromechanical inhibition of ventilatory motor output due to large recovery breaths. In contrast, we induced mild brief hypocapnic chemoreceptor inhibition (−3.5 Torr for 1 min), resulting in a 37% reduction of $\dot{V}_E$. It is possible that further reduction in ventilatory motor output may compromise the pulmonary pressure-flow relationship as demonstrated previously (13, 21, 22, 33). Likewise, subjects with breathing instability during sleep or sleep apnea may not preserve upper airway mechanics if ventilatory drive is reduced. Thus, our data are limited to mild inhibition in healthy subjects with no sleep-disordered breathing.

The preservation of upper airway patency during chemoreceptor inhibition cannot be explained by changing sleep state or end-expiratory lung volume. Instead, it suggests optimal coordination between upper airway dilating muscles and thoracic inspiratory pump muscles. The coordinated reduction in activity may be due to linked neural control or to afferent pathways originating from the airways, lung parenchyma, or chest wall. Alternatively, the activation of short-term poststimulus potentiation (afterdischarge) may maintain the activity of nerves supplying the upper airway despite hypocapnia (1, 9). Thus, upper airway mechanics would be preserved if the time constant and the magnitude of inhibition are similar between the two muscle groups. The role of short-term potentiation in preserving upper airway patency requires a comparison between hypocapnic inhibition induced passively (i.e., no short-term potentiation is present) and hypocapnic hypoventilation induced actively (i.e., short-term potentiation is present).

Implications

During NREM sleep, periods of transient hyperpnea may occur followed by hypocapnic hypopnea. Examples of such perturbations include *1*) fluctuating sleep state; *2*) transient hypoxia secondary to obesity, retention of secretions, or lung disease; and *3*) termination of apnea or hypopnea. Our data suggest an enhancement of upper airway patency without changes in sleep state during the hyperpneic phase. During the hypocapnic recovery, upper airway patency is preserved, even in subjects with a high propensity for collapse. This precise coordination of upper airway and thoracic pump muscles prevents upper airway obstruction or narrowing during periods of low ventilatory drive. The preservation of upper airway patency during fluctuating ventilatory drive may represent an important mechanism for sustaining rhythmic breathing in the face of transient perturbations.

In summary, we have shown that mild hyperoxic hypocapnic chemoreceptor inhibition does not compromise lung mechanics in sleeping humans, suggesting preservation of upper airway patency under conditions of mild reduction of ventilatory motor output.

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