An induced blood pressure rise does not alter upper airway resistance in sleeping humans

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An induced blood pressure rise does not alter upper airway resistance in sleeping humans. J. Appl. Physiol. 84(1): 269–276, 1998.—Sleep apnea is associated with episodic increases in systemic blood pressure. We investigated whether transient increases in arterial pressure altered upper airway resistance and/or breathing pattern in nine sleeping humans (snorers and nonsnorers). A pressure-tipped catheter was placed below the base of the tongue, and flow was measured from a nose or face mask. During non-rapid-eye-movement sleep, we injected 40- to 200-µg iv boluses of phenylephrine. Parasympathetic blockade was used if bradycardia was excessive. Mean arterial pressure (MAP) rose by 20 ± 5 (mean ± SD) mm Hg (range 12–37 mm Hg) within 12 s and remained elevated for 205 s. There were no significant changes in inspiratory or expiratory pharyngeal resistance (measured at peak flow, peak pressure, 0.2 l/s or by evaluating the dynamic pressure-flow relationship). At peak MAP, end-tidal CO2 pressure fell by 1.5 Torr and remained low for 20–25 s. At 26 s after peak MAP, tidal volume fell by 19%, consistent with hypocapnic ventilatory inhibition. We conclude that transient increases in MAP of a magnitude commonly observed during non-rapid-eye-movement sleep-disordered breathing do not increase upper airway resistance and, therefore, will not perpetuate subsequent obstructive events.

baroreceptor; phenylephrine; respiration; sleep apnea

Many reports have emphasized the inhibitory effects of increasing blood pressure (BP) on upper airway muscle electromyographic (EMG) activity (11, 18, 27, 31) and that this inhibition exceeds that of the diaphragm (11, 31). Accordingly, it has been postulated that an increase in BP may increase upper airway collapsibility and cause obstructive sleep apnea (11, 21). Furthermore, very large sustained increases in systemic BP in anesthetized cats do increase the collapsibility of the upper airway (21). In sleeping humans, sudden and often substantial increases in systemic BP occur most often immediately after apneic and hypoapneic events (5, 17, 25) and, if the effect of increased BP is to enhance upper airway collapsibility, this selective BP effect may contribute significantly to subsequent obstructive apneas and the perpetuation of sleep-disordered breathing. Our previous studies (20) in sleeping dogs failed to show a deleterious effect of even very large transient increases in pressure in the isolated carotid sinus on upper airway resistance (UAR). However, these negative findings in dogs may not apply to humans. Indeed, in many humans, significant inspiratory flow limitation occurs during sleep, and the upper airway becomes highly susceptible to closure in response to oscillating and reduced chemical ventilatory stimuli (30).

The purpose of this study was to determine whether transient increases in BP altered UAR and breathing pattern in sleeping humans. We tested this hypothesis by imposing pharmacologically induced transient increases in systemic BP during constant states of non-rapid-eye-movement (NREM) sleep in subjects who displayed a wide range of levels of UAR and, presumably, in upper airway collapsibility.

 Methods

Subjects

Three nonsnorers (2 men, 1 woman; 21–22 yr old) and six snoring subjects (5 men, 1 woman; 20–37 yr old) with no history of respiratory or cardiovascular disease were studied during NREM sleep. Snoring was detected by microphone during a screening sleep study. This study was approved by the Human Studies Committee at the University of Wisconsin Center for Health Sciences, Madison, and informed consent was obtained from all subjects.

Protocol

Subjects were instrumented with electrodes to record central and occipital electroencephalogram (EEG; C3/A2, C4/A1, O1/A2, O2/A1), chin electromyogram (EMG), and eye electrooculogram (EOG) activity (right and left EOG) and electrocardiogram (ECG). An intravenous line was placed in the right antecubital vein for bolus delivery of phenylephrine and the control vehicle (5% dextrose). After local lidocaine anesthesia was applied, an arterial catheter was inserted into the left radial artery for the direct measurement of BP (Hewlett-Packard transducer model HP1290A). A pressure-tipped catheter (model TC-500XG; Millar) was used to monitor pharyngeal pressure (Pph). After the nasopharynx was sprayed with Xylocaine (10%), a catheter was threaded through a nose mask, passed into one nostril, and placed so that, as judged by visualization, the tip of the catheter was ∼2 cm below the base of the tongue. Tincture of benzoin was applied to the nose, and the catheter position was secured by taping the catheter to the nose.

Subjects wore a nose mask (continuous positive air pressure mask; Respironics) sealed with theatrical glue and putty, and the mouth was taped closed. Leaks were detected by comparing inspiratory and expiratory tidal volume (VT) values. In one snoring subject, persistent leaks necessitated the use of a full face mask that had been modified to minimize dead space. The mask was attached to a differential pressure transducer (±0.8 cm H2O; Validyne) to measure bidirectional airflow. Ports in the nose mask allowed the measurement of mask pressure (Pm; ±56 cm H2O; Validyne) and the percentage of CO2 in the expirate (CD-3A; Ametek). In addition, subjects wore an ear oximetry probe (Biox 3740; Ohmeda).
An ultrasonic nebulizer was used to deliver a long-acting vasoconstricting medication (0.05% oxymetazoline hydrochloride) into the nasopharynx periodically during the night. A Y-shaped connector was attached to the mask, and corrugated tubing from the ultrasonic nebulizer was attached to the second side of the Y-shaped connector. This tubing was clamped when the nebulizer was not in use.

Subjects underwent a sleep study after a night of sleep deprivation (<2 h sleep). We applied aerosolized oxymetazoline hydrochloride to the nasopharynx to minimize vasoconstriction of nasopharyngeal vessels during phenylephrine injection. The vasoconstricting agent was delivered immediately before the subject was allowed to sleep (3–4 sprays of oxymetazoline delivered into each nostril). In addition, aerosolized oxymetazoline was delivered periodically throughout the study through the mask by using an ultrasonic nebulizer. The average time lag between delivery of the aerosolized vasoconstricting medication and a phenylephrine trial was 84 ± 21 min. When this approach is used, potential changes in UAR during phenylephrine-induced high BP should not be caused by changes in nasopharyngeal blood flow.

In 22 subjects, phenylephrine (0.3–0.4 µg/kg) and glycopyrrolate (0.5–1.5 µg/kg) were used in subsequent studies to maintain elevated BP by blocking the excessive baroreflex-mediated bradycardia. Therefore, glycopyrrolate (200–400 µg) was used in subsequent studies to induce and maintain NREM sleep (stages II-IV) for at least 15 min. In pilot studies in three subjects, phenylephrine injection (1.3–4.3 µg/kg) caused a double peak in BP and excessive bradycardia. Therefore, glycopyrrolate (200–400 µg) was used in subsequent studies to maintain elevated BP by blocking the excessive baroreflex-mediated bradycardia. Randomized injections of either phenylephrine (0.5–1.5 µg/kg) or the control vehicle (5% dextrose) were administered, followed by a 10-ml flush of 5% dextrose. Phenylephrine boluses were repeated when the subject's heart rate (HR) and systolic and diastolic BP (SBP and DBP, respectively) had returned to baseline values. We report 18 trials using glycopyrrolate and phenylephrine where no change in sleep state occurred (6 trials in subject 1, 4 trials in each of 2 subjects, and 1 trial in each of 2 subjects). In addition, during the pilot studies, 10 trials were obtained in three subjects without glycopyrrolate.

Data Analysis

Data were recorded on videotape for subsequent computer acquisition and analysis with the use of software programs developed in our laboratory. Data for two subjects were analyzed by hand because of technical problems.

Analysis of sleep signals. Sleep stage was determined by visual analysis of the central and occipital EEG, chin EMG, and EOG signals. Phenylephrine injections were given only when the subject was in sleep stages II-IV. After the study, trials were carefully analyzed for the presence of arousals (≥1 s of alpha activity (26), and all trials containing arousals were deleted from the analysis. Fast Fourier transform analysis was subsequently performed on the EEG signals (sampled at 128 Hz, low-pass filtered at 30 Hz, 1-s view window) for all analyzed trials to confirm the absence of arousals and to detect sleep stage changes by using the frequency distribution and centroid frequency of the EEG signal.

We assessed the effect of phenylephrine injection on cortical arousal in nine subjects with and without glycopyrrolate premedication. In total, 50 technically acceptable trials were performed in these nine subjects. We are not sure whether these arousals were caused by baroreceptor input or by the influence of nonspecific sensory stimuli caused by skin flushing, for instance.

Ventilatory and cardiovascular measurements. Baseline measurements were made of 13–20 consecutive breaths preceding each phenylephrine or control injection and of all breaths after the injection until HR and BP values returned to baseline levels. Breathing pattern was assessed by using VT, breathing frequency (f), instantaneous minute ventilation (Ve), inspiratory (Ti) and expiratory (Te) times, and mean inspiratory flow rate (VT/Ti). Inspiratory and expiratory resistance (RI, RE) values were calculated by using the difference between pharyngeal and mask pressures (Pph – Pm) at several points in the airflow signal: at peak flow (RI and RE peak flow), at peak pressure (RI and RE peak pressure), and at 0.2 L/s flow rate (RI and RE 0.2 L/s). In addition, pressure-flow plots over the entire breath were analyzed for each trial. Beat-by-beat measurements of SBP and DBP, mean arterial pressure (MAP), and HR were done throughout each trial.

Comparison of data across subjects. To assess the time course of the response, data from each trial were binned in 5-s intervals and aligned at the peak MAP achieved after phenylephrine injection. The cardiovascular, ventilatory, and UAR group mean responses to phenylephrine injection were then quantified by averaging over three breaths the data obtained at peak MAP and at the nadir VT after phenylephrine injection. These values were compared with baseline eupneic breathing values preceding the injection of phenylephrine or dextrose. All phenylephrine trials for each subject were averaged to obtain a representative trial for that subject; these representative trials were then averaged.

Statistical analysis. Group mean measurements made at peak MAP and nadir VT after phenylephrine injection were compared with baseline measurements during eupnea by using a one-way analysis of variance and post hoc t-tests comparisons (Table 1). Repeated-measures analysis of variance was used to compare changes from baseline in the binned data after phenylephrine injection; post hoc analysis was made by using the Bonferroni correction

RESULTS

Figure 1 is a representative example of a sleep trial in a snoring subject during phenylephrine injection with parasympathetic blockade. After the phenylephrine bolus injection, BP rises and gradually returns to baseline BP. There is no evidence of EEG arousal, there is a small fall in end-tidal CO2 pressure (PEtCO2) as BP rises, and there is a diminution of flow rate, VT, and pharyngeal pressure after the peak increase in BP. Injection of the control vehicle caused no change in BP, HR, UAR, or breathing pattern in any of the trials.

Time Course of Changes in Breathing Pattern and Resistance

Figure 2 shows mean values of data that were binned in 5-s intervals for the six subjects with parasympathetic blockade (18 trials). For these same trials, Table 1 shows the mean values of unbinned data that were measured at three specific points during each trial (baseline, peak BP, and nadir VT). Analysis of binned data (Fig. 2) showed that MAP increased by 20 mmHg and gradually returned to within 10% of baseline values over 105 ± 45 s. The increase in MAP was accompanied by an initial fall in HR (P < 0.05) and gradual recovery toward baseline that paralleled the recovery in MAP. There was no change in UAR (represented in Fig. 2 by R1 measured at peak pressure) or respiratory frequency (Table 1). VT began a downward trend as MAP rose, reaching significance 26 s after the occurrence of peak MAP (VT = 81 ± 12% of baseline, P < 0.05). At this time, Ve and mean inspiratory flow
Table 1. Respiratory and cardiovascular measurements at baseline and after PE bolus injection at peak MAP and nadir VT in subjects with parasympathetic blockade.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Baseline</th>
<th>At Peak MAP</th>
<th>At Nadir VT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time lag from PE bolus, s</td>
<td>43 ± 4.9</td>
<td>69 ± 7.3</td>
<td></td>
</tr>
<tr>
<td>MAP, mmHg</td>
<td>81.1 ± 5.9</td>
<td>101.2 ± 7.8</td>
<td>94.9 ± 9.6</td>
</tr>
<tr>
<td>Systolic BP, mmHg</td>
<td>115.5 ± 4.4</td>
<td>139.6 ± 11.5</td>
<td>132.4 ± 14.0</td>
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<tr>
<td>Diastolic BP, mmHg</td>
<td>63.7 ± 9.1</td>
<td>82.0 ± 9.8</td>
<td>76.2 ± 10.3</td>
</tr>
<tr>
<td>HR, beats/min</td>
<td>69.3 ± 15.7</td>
<td>13.5 ± 13.5</td>
<td>56.0 ± 11.5</td>
</tr>
<tr>
<td>VT, liters</td>
<td>0.47 ± 0.05</td>
<td>0.44 ± 0.05</td>
<td>0.38 ± 0.05</td>
</tr>
<tr>
<td>f, breaths/min</td>
<td>14.7 ± 1.0</td>
<td>14.6 ± 1.0</td>
<td>14.7 ± 1.0</td>
</tr>
<tr>
<td>VE, l/min</td>
<td>6.9 ± 0.7</td>
<td>6.4 ± 1.2</td>
<td>5.6 ± 1.0</td>
</tr>
<tr>
<td>Ti, s</td>
<td>1.8 ± 0.2</td>
<td>1.8 ± 0.2</td>
<td>1.8 ± 0.2</td>
</tr>
<tr>
<td>Te, s</td>
<td>2.3 ± 0.07</td>
<td>2.3 ± 0.15</td>
<td>2.3 ± 0.17</td>
</tr>
<tr>
<td>Ti/Ttot</td>
<td>0.44 ± 0.05</td>
<td>0.43 ± 0.05</td>
<td>0.44 ± 0.05</td>
</tr>
<tr>
<td>VT/Ti, l/s</td>
<td>0.27 ± 0.05</td>
<td>0.25 ± 0.07</td>
<td>0.22 ± 0.05</td>
</tr>
<tr>
<td>PETCO2, Torr</td>
<td>45.2 ± 2.0</td>
<td>43.7 ± 2.41</td>
<td>43.9 ± 2.9</td>
</tr>
<tr>
<td>SaO2, %</td>
<td>96.9 ± 1.2</td>
<td>96.8 ± 1.0</td>
<td>97.1 ± 1.5</td>
</tr>
<tr>
<td>Peak inspiratory flow, l/s</td>
<td>0.38 ± 0.07</td>
<td>0.36 ± 0.10</td>
<td>0.32 ± 0.02</td>
</tr>
<tr>
<td>Peak expiratory flow, l/s</td>
<td>0.41 ± 0.12</td>
<td>0.40 ± 0.15</td>
<td>0.33 ± 0.05</td>
</tr>
<tr>
<td>Ri, cmH2O·l−1·s</td>
<td>19.8 ± 6.9</td>
<td>20.6 ± 8.8</td>
<td>24.3 ± 14.9</td>
</tr>
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<td>At peak flow</td>
<td>47.6 ± 20.6</td>
<td>54.3 ± 25.7</td>
<td>58.9 ± 30.9</td>
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<tr>
<td>At peak pressure</td>
<td>17.9 ± 18.9</td>
<td>23.4 ± 25.5</td>
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<tr>
<td>Re, cmH2O·l−1·s</td>
<td>10.0 ± 4.7</td>
<td>8.9 ± 4.4</td>
<td>10.6 ± 5.4</td>
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<tr>
<td>At peak flow (n = 5)</td>
<td>11.0 ± 5.1</td>
<td>10.1 ± 4.9</td>
<td>11.4 ± 5.4</td>
</tr>
<tr>
<td>At peak pressure</td>
<td>5.3 ± 1.5</td>
<td>5.9 ± 1.2</td>
<td>6.0 ± 1.2</td>
</tr>
<tr>
<td>(n = 5)</td>
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</tr>
</tbody>
</table>

Values are means ± SD of original (unbinned) data; n, 6 subjects, except Re, n = 5. PE, phenylephrine; MAP, mean arterial pressure; BP, blood pressure; HR, heart rate; VT, tidal volume; f, respiratory frequency; VE, expired minute ventilation; Ti, inspiratory time; Te, expiratory time; Ttot, total time; PETCO2, end-tidal CO2 pressure; SaO2, arterial O2 saturation; Ri, inspiratory resistance; Re, expiratory resistance. *P < 0.05 and †P < 0.01 compared with baseline values.

Magnitude of BP Change and Resistance

The increase in MAP varied from 13 to 32 mmHg, and the subsequent fall in VT ranged from −9 to −40% of baseline values in 16 of 18 trials. Figure 3 shows the peak increase for each trial in MAP plotted against the Ri (calculated at 0.2 l/s) at baseline and at nadir VT. Note the large variability among the sleeping subjects in UAR during eupneic breathing. At nadir VT after BP elevation, Ri increased by >25% from baseline in 4 of 18 trials and decreased slightly or remained unchanged from baseline in the remaining 14 trials. No consistent relationship was obtained between the change in UAR and the increase in MAP or the decrease in VT when the change in Ri was calculated at either peak pressure or peak inspiratory flow rate (not shown). Although some subjects with higher baseline inspiratory resistances...
did further increase resistance with elevated BP (4 trials in 2 subjects), there are also three trials in these same subjects in whom resistance was unchanged from either a much higher or similar baseline resistance.

Within-Breath Analysis of Resistance

We reasoned that changes in UAR that were sufficient to cause hypoventilation should be detectable at nadir Vt; yet we found no change in resistance measured at this time. However, within-breath pressure-flow relationships are rarely linear during sleep, and, therefore, resistance calculated at one point (e.g., peak pressure or a fixed flow rate) does not accurately represent the changing resistance throughout the entire breath. Accordingly, representative pressure-flow plots are presented in Fig. 4 for each of the six subjects who were given the parasympathetic blocking agent. Significant inspiratory flow limitation was defined as a change in trans-pharyngeal pressure = 2 cmH2O with either no change or a decrease in flow rate. During baseline eupneic breaths, all snoring subjects showed highly significant truncation of flow rate, as 4–8 cmH2O pressure was developed during inspiration (subjects 2–6).

To determine whether the fall in Vt at high BP was associated with an increase in flow limitation, three breaths during nadir Vt are superimposed over the baseline pressure-flow plots (Fig. 4). Of the five subjects in whom significant inspiratory flow limitation was present at baseline, the pressure-flow relationship during nadir Vt breaths at high BP consistently showed slightly more flattening of the flow profile in two subjects (subjects 3 and 5) but was unchanged in the remaining three subjects. During three trials in the subject without flow limitation during eupneic breathing (subject 1, a nonsnorer), the nadir Vt breaths during elevated BP showed no inspiratory flow limitation.

The within-subject variability of the response to a phenylephrine-induced increase in MAP is shown...
demonstrated by showing three trials from one subject (Fig. 4B). In this subject, the pressure-flow profiles of the nadir \( V_T \) breaths at high MAP showed 1) an increase in flow limitation (trial 1); 2) a fall in the flow rate and pressure generated across the upper airway, but no change in the pressure-flow relationship (trial 2); and 3) no change in flow limitation, despite extreme flow limitation with falling flow rate during most of inspiration during baseline eupneic breathing (trial 3).

Complete flow limitation (i.e., obstruction) was not noted during increased BP in any of the trials, even in those subjects who had baseline \( R_I \) of \( >60 \text{ cmH}_2\text{O} \cdot \text{L}^{-1} \cdot \text{s} \) and showed declining flow rates over much of inspiration.
DISCUSSION

Effects of Increased BP on the Upper Airway

We had hypothesized that transient increases in BP in sleeping humans would increase UAR and perhaps cause airway obstruction in susceptible subjects. Our findings showed that this was not the case because, with very few exceptions, airflow resistance (determined at selected points within inspiration or evaluated from trans-pharyngeal pressure-flow plots) remained unchanged during trials with elevated BP.

There are several potential explanations for why we did not observe any increase in UAR despite previous documentation in sleeping or anesthetized animals of the highly selective inhibitory effects of increased BP on upper airway vs. chest wall muscle electrical activity (11, 31).

First, we cannot attribute the absence of increased airway resistance to the use of phenylephrine as a means of causing the vasoconstrictor-mediated increase in BP. 1) Phenylephrine infusion causes an inhibitory effect on the EMG of upper airway muscles in sleeping cats, anesthetized dogs, and awake humans (3, 11, 27) that is similar to the marked reductions in hypoglossal nerve activity caused by mechanical means of increasing carotid sinus pressure (31). 2) Any central nervous system effects of phenylephrine were minimized by using bolus injections (7). 3) The effect of nasopharyngeal vasoconstriction during phenylephrine injection on our measurement of UAR (32) was minimized by administering a long-acting aerosolized vasoconstricting agent at the beginning of each study period and every 1–2 h during the night. We believe this strategy was effective because, for each trial, UAR was unchanged between the baseline before phenylephrine injection and the period after the BP had returned to baseline (Fig. 2).

A second possible limitation in our study was that our imposed increase in BP was insufficient to exert a physiological effect on the upper airway. Our goal was to mimic the transient increase in systemic BP commonly observed after sleep-disordered breathing events (5, 17, 25). Accordingly, we were able to increase systemic BP an average of 20 mmHg (range, 12–37 mmHg; SBP, 24 mmHg; and DBP, 18 mmHg) within a 12-s period, and BP remained greater than control for ~2 min. The degree of baroreceptor stimulation elicited by these increases in BP must have been substantial, as noted by the immediate 14–19 beats/min reduction in HR observed in the absence of parasympathetic blockade. Furthermore, these levels of increased BP were previously shown to reduce genioglossus EMG in awake humans (3). Finally, in sleeping dogs, transient increases in carotid sinus pressure, which were two to three times the largest increases we found in systemic BP, also had no significant effect on UAR (20).

Third, although most healthy humans are resistant to airway closure in sleep, we chose several subjects with very high baseline airway resistance and clear evidence of severe inspiratory-flow limitation (including negative pressure-flow dependence). Similar types of subjects are highly susceptible to complete airway closure during sleep, when oscillations in chemostimulation and respiratory motor output are superimposed (1, 16, 30).

Based on these considerations, we believe our experimental design was appropriate to test the effects of physiological increases in systemic BP on UAR in sleeping humans. Given our negative findings, we conclude that the critical closing pressure of the human upper airway during increases in BP, although probably compromised, must have been more negative than the intrathoracic pressures generated by inspiratory muscle effort. We have two potential explanations why our sleeping subjects did not experience more flow limitation or airway obstruction during transient increases in BP.

First, perhaps the (presumed) reduction in upper airway muscle tone and increased airflow compliance with increased BP were counterbalanced by a reduction in collapsing pressure generated by the inspiratory muscles. The transient hypopnea that accompanied the elevation in BP in our trials is consistent with a reduced inspiratory muscle effort. However, a case has also been made that a reduced neural drive to inspiration, if sufficient, might actually enhance airway collapsibility (1, 16, 30). One proposed means of linking inspiratory drive to upper airway patency is via the caudal traction exerted on the trachea by cervical strap muscles (28). Our own correlative data speak against a protective role for reduced ventilatory drive, because Vt was only beginning to fall when BP had reached its peak. Presumably, changes in respiratory motor output would have had only a minimal, if any, independent effect on upper airway diameter at the time that the increase in BP was greatest and exerting its major effect on upper airway muscle tone.

A second possibility is that the well-established effect of increased BP on tonic upper airway muscle electrical activity may have only a relatively small influence on upper airway collapsibility, at least during eupneic breathing. Other investigators have observed that skeletal muscle paralysis in anesthetized animals did not increase upper airway closing pressure, nor did it abolish the augmentation by hypercapnia of the upper airway’s resistance to collapse (15). Accordingly, non-muscular mechanical properties of the upper airway, such as connective tissue, blood vessels, and mucosa, may be important in resisting collapse. On the other hand, a sustained, 2.5-fold increase in MAP causes the critical closing pressure to fall to about one-third of baseline in the anesthetized cat (21). Thus a mechanical effect on airway collapsibility is certainly demonstrable when BP increases are very large and sustained.

Consequently, we propose that the mechanical effect of increased BP on the airway remains small relative to the stabilizing influence of other muscular and nonmuscular factors when acute increases in BP are within the physiological range relevant to sleep apnea.
Finally, we caution that our findings apply only to transient increases in BP in healthy sleeping humans. Recent clinical studies have suggested that sleep-disordered breathing in hypertensive patients is exacerbated by chronic elevations in BP (12). Perhaps a sustained elevation in systemic BP exerts a more substantial influence on upper airway caliber during sleep-disordered breathing events.

Ventilatory Effects of Transient Increases in BP

We observed that the phenylephrine-induced increase in BP caused a maximum 19 ± 12% reduction in VT and Ve. This reduction in VT appeared to begin as BP was increasing, and VT continued to decrease to a nadir at 26 s after the peak in BP, when BP had returned only one-third of the way back to baseline levels. In our experiments, many mechanisms may have contributed to these changes, and it is difficult to determine precisely which factors were primarily responsible for the reduction in VT.

We are certain that an increase in UAR was not responsible for the reduction in VT. In addition, chemoreceptor inhibition via phenylephrine infusion seems unlikely as shown by the slight increase in the electrical activity of the carotid sinus nerve with phenylephrine infusion (at 10-fold the dose used in the present study) in the anesthetized cat (10).

Barostimulation from transient increases in BP per se has been shown to cause ventilatory and/or phrenic nerve inhibition in anesthetized (6), awake, and sleeping animals (11, 19, 27). In sleeping dogs instrumented with an isolated carotid sinus, Sauer et al. (19) reported that a 35- to 75-mmHg stepwise increase in carotid sinus pressure caused VT to fall by 15–40% over a 10-s period. Increased carotid sinus pressure >75 mmHg caused no further inhibition of VT. The lower range of these changes in BP is similar to the pressures used in our human study, and the effect on VT is also similar. Furthermore, the downward trend in VT in the present study began as BP was rising and continued well beyond the occurrence of peak BP. On the other hand, the previous findings that used square-wave increases in BP would predict an abrupt fall in VT, indicating, in the present study, either an effect of the longer, ramp-like onset and slower return of BP to baseline and/or the influence of other inhibitory factors coincident with the increase in BP.

Transient, mild hypocapnia (PETCO2, −1.3 to −1.6 Torr) probably played a significant inhibitory role in the reduction in VT. We observed that PETCO2 fell just before the peak in BP and remained less than baseline levels for 20–25 s as VT decreased. It is not clear whether this small reduction in arterial CO2 pressure (Paco2) would have an inhibitory influence on Ve, because the brief duration (<30 s) of hypocapnia indicates a primary influence on carotid (rather than medullary) chemoreceptors. However, the ventilatory inhibition achieved during hypocapnic mechanical ventilation in humans has been shown to be enhanced during NREM sleep (22). In sleeping dogs, hypocapnia applied only at the isolated perfused carotid chemoreceptor caused a progressive reduction in VT below eupneic VT (23).

The reason for this transient fall in PaCO2 with phenylephrine-induced increases in BP is not clear. It is probably caused by a transient decrease in the rate of blood flow and, therefore, CO2 delivered to the lungs caused by a fall in HR and cardiac output and/or the systemic vasoconstriction (8). We also think it likely that this transient hypocapnia might be in response to normally occurring transient vasoconstriction-induced increases in BP, as described in Application of Findings to Sleep-Disordered Breathing.

In summary, on the basis of the time course of change in BP and PaCO2, we propose that both baroreceptor stimulation and reduced carotid chemoreceptor stimulation mediate the moderate reduction in VE in response to vasoconstrictor-mediated transient increases in systemic BP.

Application of Findings to Sleep-Disordered Breathing

We believe our findings pertain to the control of UAR and Ve in the human in response to vasoconstrictor-mediated increases in systemic BP. However, whether these data are pertinent to the effects of the transient increases in BP that occur during sleep-disordered breathing depends on how well our model of increased BP mimics the events occurring with sleep apnea. Increased sympathetic outflow to skeletal muscle (24) and to the renal vasculature (14) has been reported to be a consistent response to apnea in sleeping humans and dogs; the coincident increases in BP is prevented via ganglionic blockade in humans and dogs (9, 13). Therefore it is likely that systemic vasoconstriction contributes significantly to the increase in BP. Changes in cardiac output are less well defined in sleeping humans, primarily because of the difficulty in obtaining accurate continuous measurements of cardiac output. Reductions in stroke volume and cardiac output during and immediately after obstructive apneas have been observed by using radionuclide imaging (4) and pulmonary arterial blood-velocity sensing (2). However, the HR and therefore cardiac output response during recovery from apnea may be highly variable, especially if transient arousals occur (2).

1 This small increase in carotid sinus nerve activity with phenylephrine may have included changes in baroreceptor as well as chemoreceptor activity (29). Preliminary data in the whole carotid sinus nerve preparation in the anesthetized rat showed no effect of infused phenylephrine bolus in a baroreceptor-denervated rat preparation (E. Vidruk, personal communication).

2 To verify that this decrease in PETCO2 also reflected dynamic alterations in PaCO2, we performed four phenylephrine bolus injections and obtained sequential arterial blood samples in a chloralose-anesthetized dog that was mechanically ventilated at constant VT and breathing frequency. PETCO2 and PaCO2 fell similarly (1.3–2.5 Torr) after each phenylephrine injection. 2.9 ± 1.7 s after peak MAP was reached (unpublished observations).
Our experimental model uses a transient increase in BP and, therefore, baroreceptor stimulation, systemic vasoconstriction, and, probably, reduced cardiac output. All these are present in many normally occurring sleep-disordered breathing events. Thus, on the basis of our findings, we would predict that these normally occurring, transient cardiovascular sequelae would not cause increased airflow resistance. The tendency we observed for VT to fall at peak BP might slightly dampen the ventilatory overshoot that normally occurs for VT to fall at peak BP might slightly dampen the ventilatory overshoot that normally occurs during the recovery period, we would predict less ventilatory inhibition after the hypopneas, because the increase in cardiac output would limit the amount of hypocapnia that occurred as a result of the hypopnea. In either case, we conclude that it is unlikely that the transient increases in BP after sleep-disordered breathing events are important in perpetuating subsequent events.

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REFERENCES