Hemodynamic effects of pressures applied to the upper airway during sleep

P. R. EASTWOOD, A. K. CURRAN, C. A. SMITH, AND J. A. DEMPSEY

The John Rankin Laboratory of Pulmonary Medicine, University of Wisconsin Medical School, Madison, Wisconsin 53705

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Eastwood, P. R., A. K. Curran, C. A. Smith, and J. A. Dempsey. Hemodynamic effects of pressures applied to the upper airway during sleep. J Appl Physiol 89: 537–548, 2000.—The increase in systemic blood pressure after an obstructive apnea is due, in part, to sympathetically mediated vasoconstriction. We questioned whether upper airway (UA) receptors could contribute reflexly to this vasoconstriction. Four unanesthetized dogs were studied during wakefulness and non-rapid-eye-movement (NREM) sleep. The dogs breathed via a fenestrated tracheostomy tube sealed around the tracheal stoma. The snout was sealed with an airtight mask, thereby isolating the UA when the fenestration was closed and exposing the UA to negative inspiratory intrathoracic pressure when it was open. The blood pressure response to three UA perturbations was studied: 1) square-wave negative pressures sufficient to cause UA collapse with the fenestration closed during a mechanical hyperventilation-induced central apnea; 2) tracheal occlusion with the fenestration open vs. closed; and 3) high-frequency pressure oscillations (HFPO) with the fenestration closed. During NREM sleep, 1) blood pressure response to tracheal occlusion was similar with the fenestration open or closed; 2) collapsing the UA with negative pressures failed to alter blood pressure during a central apnea; and 3) application of HFPO to the UA during eupnea and resistive-loaded breaths increased heart rate and blood pressure. However, these changes were likely to be secondary to the effects of HFPO-induced reflex changes on prolonging expiratory time. These findings suggest that activation of UA pressure-sensitive receptors does not contribute directly to the pressor response associated with sleep-disordered breathing events.

dog; fenestrated tracheostomy tube; upper airway reflexes; high-frequency oscillating pressure; sleep apnea

Obstructive sleep apnea (OSA) is characterized by repetitive nocturnal oscillations in blood pressure. These oscillations are usually multiphasic in nature with a decrease in blood pressure occurring during the initial part of the apneic period, a gradual increase as the apnea proceeds, and a marked increase immediately after the apnea (13, 23, 26, 27). The mechanisms responsible for these blood pressure changes are still under investigation; however, recent studies indicate a major role for hypoxic chemoreceptor stimulation causing increasing sympathetic tone to the peripheral vasculature, together with other potential modulatory inputs that may include hypercapnia, arterial baroreceptors, lung stretch receptors, humoral factors, sleep stage, and arousal. In addition to these factors, we hypothesize that reflexes originating in the upper airway (UA) may also play an as-yet-undefined role in the acute cardiovascular changes that accompany OSA.

Support for the idea that UA reflexes may contribute to these hemodynamic changes is based on studies using mechanical stimulation of the larynx in paralyzed and/or decerebrate anesthetized cats (29, 35). In these preparations, laryngeal stimulation caused excitation of sympathetic preganglionic neurons of the cervical sympathetic trunk and/or an increase in systemic arterial pressure (29, 35). The afferent limb of this response appears to be the superior laryngeal nerve (SLN), because its section abolishes the response (29). Other studies using electrical stimulation of the SLN at low voltages caused systemic vasodilation, probably because of stimulation of aortic baroreceptor afferents (12), whereas electrical stimulation at intensities greater than those required for suppression of phrenic activity caused sympathoexcitation and increased blood pressure (3), possibly because of stimulation of chemoreceptor fibers or unmyelinated afferents from muscle receptors. Although these findings point to an important effect of laryngeal receptors in the autonomic control of sympathetic efferent activity, whether these are the same receptors and pathways that are activated by the naturally occurring pressures developed by the inspiratory muscles or by distortion of the UA that accompanies its collapse or narrowing is unknown. An additional critical factor is that the anesthesia or decerebration used in all of these studies does not simulate the effects of naturally occurring sleep on the gain of these reflexes or their integration.

The present study used a chronically instrumented, waking and sleeping dog model with an isolated UA to investigate the effect of stimulation of UA receptors by intraluminal pressure changes on the regulation of systemic blood pressure. Our experiments in this model were intended to simulate the effects on the UA
of naturally occurring airway obstruction, high inspiratory resistance, and snoring, i.e., high-frequency, low-amplitude pressure oscillations.

METHODS

General

Studies were performed on four unanesthetized female mixed-breed dogs (20–25 kg) during wakefulness and sleep. The dogs were trained to sleep in an air-conditioned sound-attenuated chamber. Throughout all experiments, the dogs’ behavior was monitored by an investigator seated within the chamber and also by closed-circuit television. The surgical and experimental protocols for this study were approved by the Animal Care and Use Committee of The University of Wisconsin.

Animal Preparation

Sterile surgical techniques were used to create a permanent tracheostomy via a midline cervical incision and removal of the ventral aspect of four to five cartilaginous rings. A microurethane catheter was introduced into the left femoral artery and advanced rostrally to the thoracic aorta for measurement of systemic blood pressure. Bipolar Teflon-coated multistrand stainless steel wire electrodes were sewn into the crural diaphragm and genioglossus muscles for measurement of electromyogram (EMG) activity. Five wire electrodes were implanted subcutaneously for staging of sleep state, consisting of an electroencephalogram (EEG), two electrooculograms, a common reference, and a ground electrode. The blood pressure catheter and EMG electrodes were tunneled subcutaneously to the cephalad portion of the dog’s back, where they were exteriorized.

The dogs were premedicated with acepromazine (0.5 mg/kg sc), anesthetized with thiopental sodium (20 mg/kg iv), and maintained on a mechanical ventilator with 1% halothane in O2. Analgesics (butorphanol, 0.3 mg/kg sc), anesthetic with thiopental sodium (20 mg/kg iv), and antibiotics (enrofloxacin, 2.2 mg/kg po, or trimethoprim sulfa, 24 mg/kg po) were administered postoperatively as required. At least 2 mo were allowed for recovery from surgery before any experiments were performed.

Experimental Setup and Measurements

The dogs breathed via a fenestrated cuffed tracheostomy tube (10.0 mm OD; Shiley, Irvine, CA), which was inserted into the permanent tracheostomy and then sealed around the stoma (Fig. 1). A removable inner sleeve allowed the fenestration to be closed or open. Airflow was measured via a thermostated (37°C) pneumotachograph system (model 3700, Hans Rudolph, Kansas City, MO; model MP-45-14-871, Validyne, Northbridge, CA) connected to the tracheostomy tube, which was calibrated before each study with five known flows.

A lightweight polyethylene mask with polymer gel inserts (Silipos, Niagara Falls, NY) was placed over the dogs snout to form an airtight seal around the mouth and nose. Therefore, when the fenestration was open, the UA was exposed to respiratory-related intrathoracic pressure changes in the absence of UA flow or temperature changes. In contrast, when the fenestration was closed, the UA was effectively isolated from all intrathoracic pressure changes (9).

Airway pressure changes were simultaneously measured at three sites: mask pressure (Pm) was measured with a catheter passed through the mask near the nares, sublaryngeal pressure (Psl) was measured via a catheter affixed to the outer sleeve of tracheostomy tube and positioned ~0.5 cm above the fenestration, and tracheal pressure (Ptr) was measured from a catheter passed into the tracheostomy tube. Each catheter was connected to a pressure transducer (model MP-45-14-871, Validyne) and was calibrated before each study by applying eight known pressures.

All signals were collected on a 12-channel polygraph (Gould ES 2000, Rolling Meadows, IL) and were passed via an analog-to-digital converter and stored on the hard disk of a microcomputer for subsequent analysis.

Experimental Protocol

On several separate days, measurements were obtained of the blood pressure response to three different perturbations of the UA: 1) square-wave negative or positive pressures applied to the isolated UA (n = 4), 2) graded negative intrathoracic pressures generated during spontaneous respiratory efforts against a tracheal occlusion that were isolated from (fenestration closed) or transmitted to the UA (fenestration open) (n = 4), or 3) high-frequency pressure oscillations (HFPO) applied to the isolated UA (n = 3). Multiple measurements were obtained during wakefulness and non-rapid-eye-movement (NREM) sleep.

Square-wave pressure changes in the UA. During these studies, the dogs breathed a hyperoxic gas mixture (0.7–0.9 inspired O2 fraction) via the cuffed tracheostomy tube with the fenestration closed. Connected to the tracheostomy tube was a valve system that allowed rapid switching from spontaneous breathing to volume-cycled mechanical ventilation (model 613 respirator pump, Harvard Apparatus, South Natick, MA).

Once a stable breathing pattern and sleep state were observed, the dog was mechanically hyperventilated for 5–10 breaths, after which the ventilator was shut off. During the
ensuing central apnea, a square-wave negative or positive pressure was applied to the isolated UA by using a syringe connected to either the sublaryngeal or mask catheter. This square-wave pressure was maintained until evidence of diaphragm EMG activity appeared, at which time the pressure was released. Multiple measurements were performed during wakefulness and NREM sleep. At least 2 min was allowed for recovery between trials.

**Graded negative pressure changes in the UA.** Once stable NREM sleep was observed, the tracheostomy tube was occluded during end expiration (zero flow). The occlusion was maintained for three successive efforts and was released during late expiration of the third effort. This technique ensured that all inspiratory efforts against the occlusion and all unloaded recovery breaths were initiated at the dog’s normal functional residual capacity. Multiple measurements were obtained with the UA isolated from (fenestration closed) or exposed to (fenestration open) the negative intrathoracic pressures generated during each inspiratory effort against the occluded airway. At least 2 min were allowed for recovery between trials.

**HFPO in the UA.** Trials were performed on each dog in stable NREM sleep. A single trial consisted of the application of HFPO to the isolated UA (∆±2 to ±4 cmH2O at 30 Hz) for a single respiratory effort, during inspiration or expiration, while the tracheostomy tube remained unloaded, or was inspiratory resistive loaded (80 cmH2O·l−1·s at 0.2 l/s). Time of application (inspiratory vs. expiratory), mode of breathing (unloaded or loaded), and direction of application of HFPO (via sublaryngeal or mask catheters) were randomized.

HFPO was applied to the UA in one of two ways: 1) HFPO was initiated during expiration and maintained throughout the following inspiratory effort against no load (eupnea) or against a resistance (e+iHFPO), or 2) HFPO was initiated during inspiration and maintained until the beginning of the subsequent expiration (iHFPO). Time of initiation of HFPO during expiration and inspiration was varied.

**Data Collection and Analysis**

**Sleep staging.** Sleep staging was determined from the paper record of each study by using previously described criteria (31). NREM sleep was defined as a synchronized low-frequency EEG associated with an absence of rapid eye movements. Any trials in which the dog changed sleep state before or during the application of square-wave pressure, graded pressure, or oscillating pressure were excluded from analysis.

**Respiratory timing, EMGs, and blood pressure.** Timing of all respiratory events was based on the moving-time-averaged EMG activity of the diaphragm. Once inspiratory time (T1) was defined, an in-house software package determined ventilatory variables, including expiratory time (T2); tidal volume (Vt); peak negative Pm, Psl, and Ptr; and beat-by-beat heart rate and systolic, diastolic, and mean arterial blood pressure (MAP).

**Statistical analyses.** During each experiment, beat-by-beat hemodynamic values were averaged over the duration of each central apnea for UA square-wave trials, for each respiratory effort during graded negative pressure trials, and for each respiratory cycle for HFPO trials. Data were compared by using the means obtained via multiple trials within a single dog and the means obtained for all dogs (one-way ANOVA with Bonferroni correction for multiple comparisons). Significance was inferred when $P < 0.05$.

**RESULTS**

**Square-Wave UA Pressure Effects on Blood Pressure During Central Apnea**

Representative polygraph recordings for one dog in NREM sleep are shown in Fig. 2. The beat-by-beat changes in MAP during control breaths and the mechanical ventilation-induced central apnea for each of the four dogs are shown in Fig. 3.

During eupnea, heart rate and MAP increased during inspiration and decreased in expiration (Figs. 2 and 3, control breaths). Positive pressure mechanical ventilation reduced Pco2 by 14 ± 3 Torr during wakefulness and by 15 ± 3 Torr during NREM sleep, abolished EMG activity of the diaphragm, and decreased the magnitude of these phasic respiration-linked hemodynamic changes. On cessation of mechanical ventilation, the inspiratory-related sinus arrhythmia was reduced during the ensuing central apnea (Fig. 2A), thereby allowing application of pressure to the isolated UA on a more stable background of blood pressure change (Fig. 2B). At the onset of apnea, MAP was less than that during eupnea (71 ± 16 vs. 81 ± 14 mmHg, $P < 0.05$ for each dog). Over the course of the apnea (mean duration: awake, 11.6 ± 2.1 s; NREM sleep, 11.3 ± 2.5 s), blood pressure gradually increased and reached a peak after the initial spontaneous inspiratory effort. Application of square-wave negative pressure of sufficient magnitude to collapse the UA did not augment the blood pressure or heart rate changes observed during the central apnea (Fig. 2B). This lack of effect of UA pressure changes on blood pressure (Fig. 3) and heart rate was seen in each dog, whether the dog was awake or asleep, whether pressure was applied from the sublaryngeal or mask catheter, and whether negative pressures (range −4.5 to −42.0 cmH2O) or positive pressures (range 7.1−27.0 cmH2O) were applied to the isolated UA ($P$ values from 0.072 to 0.96).

**Negative Pressure UA Effects on Blood Pressure During Tracheal Occlusion**

Figure 4 shows representative polygraphs for one dog during NREM sleep of the responses to three unloaded eupneic control breaths, three respiratory efforts against a tracheal occlusion, and three unloaded recovery breaths. The mean changes in MAP and PTr for each dog before, during, and after the tracheal occlusions are shown in Fig. 5.

Successive inspiratory efforts against the occluded airway generated a progressively more negative peak PTr, indicating increased inspiratory effort (Figs. 4 and 5). Blood pressure and heart rate progressively increased with successive efforts, reaching a maximum during the third occluded breath or the first or second breath after removal of the occlusion (Figs. 4 and 5). EEG evidence of arousal was noted after the third occluded effort or during or after the first recovery breath in ∼82% of trials with the fenestration closed and ∼57% of trials with the fenestration open. The presence of arousal did not significantly alter the mag-
plitude of change of MAP during any occluded effort or during the first recovery breath. During tracheal occlusions with the fenestration closed, Ptr changes were not transmitted to either the mask or sublaryngeal catheters, indicating that the UA was effectively isolated (Fig. 4A).

When the fenestration was open Ptr was transmitted to the UA and similar pressure changes were usually observed in the tracheal, sublaryngeal, and mask catheters, indicating that the UA was effectively isolated (Fig. 4A).

In all dogs, the peakPtr generated in response to tracheal occlusions was significantly less negative when the fenestration was open and the UA was exposed to intrathoracic pressure changes (Fig. 5). The duration of occlusion was significantly increased in three dogs when the fenestration was open vs. closed (22.9 ± 8.4 vs. 17.7 ± 6.3 s, mean of three dogs, P < 0.001 in each dog). Although MAP tended to be slightly greater during trials with the fenestration closed, this difference was not statistically significant (Fig. 5). On the first breath immediately after release of the occlusion, MAP was significantly increased (by 14.3 mmHg) with fenestration open vs. closed only in dog 2 (P < 0.05). This general lack of effect of negative UA pressure was also seen in measurements of heart rate, diastolic pressure, and systolic blood pressure.

**Blood Pressure Responses to HFPO in the UA**

Figure 6 shows representative polygraphs for one dog during NREM sleep of the responses to HFPO...
applied to the isolated UA. In this example, inspiration is against a resistance, and HFPO was applied during expiration and maintained throughout the subsequent inspiration. Relative to a control effort against a resistance (Fig. 6A), e+iHFPO prolonged the expiration during which it was applied and increased heart rate and diastolic and systolic blood pressure during the inspiration over which it was maintained (Fig. 6B).

Table 1 quantifies the cardiorespiratory responses to HFPO in each of the three dogs. Similar changes were seen regardless of whether HFPO was applied from the sublaryngeal or mask catheter. e+iHFPO delayed the onset of the subsequent inspiration (prolonged Tₑ), prolonged T₁, and increased Vₜ in all dogs. Prolongation of T₁ was also seen when HFPO was applied during inspiration alone. Heart rate, systolic blood pressure, diastolic blood pressure, and MAP increased when e+iHFPO or iHFPO was applied. These cardiovascular responses to HFPO were seen most consistently during eupneic breathing but were also present during inspiration against a resistance.

**DISCUSSION**

We used a sleeping dog model with an isolated UA to test the role of airway pressure-sensitive reflexes on the acute cardiovascular responses that normally accompany sleep-disordered breathing events. We found that imposition of UA collapsing pressures throughout central apnea, adding negative UA pressures during tracheal occlusion, and simulating the effects of snoring by applying HFPO to the UA all had significant effects on the control of breath timing but were of little or no additional consequence to the heart rate and/or
Comparison to Other Findings

Our mainly negative findings, as summarized above, differ from the sympathoexcitatory and pressor responses reported with mechanical stimulation of the larynx (see the introduction). It is difficult to say exactly how the different types of pressure changes and changes in airway caliber that we instigated in the UA may have differed from those using more direct mechanical probing of the laryngeal mucosa, although both perturbations are known to produce similar feedback effects on phrenic (inhibitory) and hypoglossal (excitatory) motor outputs (4, 9, 10, 18–20, 36). We also need to reemphasize that these laryngeal stimuli were applied on a background of muscle paralysis, anesthesia, or decerebration, all of which are known to significantly influence responsiveness to airway receptor stimulation (20). Our negative findings also differ from the significant vasomotor effects (dilation or constriction) attending varying intensities of SLN electrical stimulation. As explained in the introduction, the intensity and frequency of electrical stimulation will determine the type of fibers to be recruited in the SLN. We can only conclude, then, that our changes in pressure in the UA did not stimulate the same fibers or combination of fibers in the SLN as did different levels of electrical stimulation, although our effects on breath timing were similar to the inhibition of phrenic nerve activity obtained with low-intensity stimulation of the SLN (15). Finally, we note that our findings do not speak against the amply documented systemic

Fig. 4. Polygraph records from 1 dog during NREM sleep of the responses to 3 unloaded eupneic control breaths, 3 respiratory efforts against a tracheal occlusion, and 3 unloaded recovery breaths. During tracheal occlusions with the fenestration closed (A), the negative intrathoracic pressures (Ptr) developed with each inspiratory effort were not transmitted to either the mask or sublaryngeal catheters, indicating that the UA was effectively isolated. In contrast, during inspiratory efforts with the fenestration open (B), pressure changes were observed in both the sublaryngeal and mask catheters, indicating that the entire UA was exposed to intrathoracic pressures. Blood pressure is given in mmHg.
pressor response obtainable via stimulation of the nasal, pharyngeal, and/or laryngeal mucosa by direct mechanical stimuli or by noxious gases (1, 8, 22, 25).

In summary, we believe our dog model studied during sleep, with isolated UA and with the different types of pressure application, provides a realistic simulation of the airway mechanics normally experienced during obstructive apnea and high airway resistance during sleep, and therefore we can attribute little or none of the associated pressor response to reflexes from the UA.

**Cardiovascular Effects of UA Negative and Positive Pressure During Central Apnea**

A mechanical hyperventilation-induced central apnea permitted negative and positive square-wave pressures to be applied to the UA on a background of stable and normal blood pressure and in the absence of breathing-related hemodynamic fluctuations (see Fig. 2A). Over the course of the apnea, blood pressure gradually increased, reaching a peak after the initial spontaneous inspiratory effort. Increased sympathetic
activation by chemoreflex stimulation is the most probable explanation for these changes (23), even though the contribution of peripheral chemoreceptors was minimized by the administration of a hyperoxic gas mixture.

The pattern of change of MAP during the central apnea was unaltered by the application of square-wave positive or negative pressures to the UA, implying a lack of effect of stimulation of UA mechanoreceptors on cardiovascular inputs. The negative pressures, when applied from either the snout or sublarynx, were of sufficient magnitude to collapse the isolated UA. In the presence of a collapsed UA, more cranial or caudal mechanoreceptor fields would be activated depending on whether the pressure was applied from the mask or sublarynx, respectively. Yet, regardless of the direction of application of pressure, similar changes in respiratory timing have been observed (6, 18), implicating laryngeal as well as pharyngeal and nasal receptors in this reflex response (21, 36). The finding in the present study that blood pressure is unchanged by negative pressure, regardless of the direction of application, suggests that neither laryngeal nor extralaryngeal pressure-sensitive mechanoreceptors play a role in the acute cardiovascular changes that accompany an obstructive apnea.

**Cardiovascular Effects of UA Negative Pressure During Obstructed Apnea**

The use of a fenestrated tracheostomy tube allowed us to approximate the conditions in which the UA is normally exposed to negative pressure, that is, during inspiration, with the timing and magnitude of UA negative pressure being spontaneously generated in proportion to inspiratory drive (9). During efforts against tracheal occlusions, blood pressure changed similarly with the fenestration closed or open, implying...
a minor, if any, role for mechanoreceptor afferents in the UA in the cardiovascular changes that occur during an obstructive apnea. Under both conditions, blood pressure tended to increase gradually during the apnea and to reach a maximum on the first or second breath after the release of the occlusion. This pattern of pressor response to an obstructed apnea has been documented previously in sleeping dogs (30) and is consistent with the changes seen in humans during an obstructive event (26, 27). The transient elevation in blood pressure after the apnea is hypothesized to represent a complex interaction of the effects of arousal and chemoreceptor stimuli (16, 27). Arousal, which was often observed after the third occluded effort, may have contributed to the postapnea increases in blood pressure (30), but the magnitude of blood pressure change was similar whether an EEG arousal response was observed or not observed.

Inspiratory efforts against the tracheal occlusion with the fenestration open were associated with the development of less negative intrathoracic pressure changes relative to efforts with the fenestration closed and also with slightly longer periods of tracheal occlusion. We have previously documented these effects, which are principally a consequence of reflex inhibition of inspiratory drive by UA mechanoreceptors sensitive to negative pressure changes (9). The observation that blood pressure responses to the obstructive apneas were similar with and without the UA exposed to negative pressures implies that the magnitude of respiratory motor output and intrathoracic pressure change also had little effect in modulating sympathetic efferent activity and/or blood pressure during the obstructive apneas, a finding consistent with recent studies in intact animals (30) and humans (23, 28, 34).

Cardiovascular Effects of HFPO Applied to the UA

Application of HFPO during eupnea and during inspiratory efforts against a resistance increased heart rate, systolic and diastolic blood pressure, and MAP during inspiration in each of the three dogs.

Table 1. HFPO during NREM sleep: hemodynamic effects

<table>
<thead>
<tr>
<th>Dog</th>
<th>Control</th>
<th>iHFPO</th>
<th>e+iHFPO</th>
<th>Control</th>
<th>iHFPO</th>
<th>e+iHFPO</th>
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<td>56</td>
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<td></td>
<td>Heart rate, bpm</td>
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<td>73 ± 9</td>
<td>80 ± 8*</td>
<td>74 ± 6</td>
<td>82 ± 6*</td>
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<td>Blood pressure, mmHg</td>
<td>Diastolic</td>
<td>64 ± 4</td>
<td>66 ± 4</td>
<td>68 ± 4*</td>
<td>64 ± 5</td>
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<tr>
<td></td>
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<td>Systolic</td>
<td>158 ± 8</td>
<td>158 ± 6</td>
<td>155 ± 9*</td>
<td>152 ± 6</td>
</tr>
<tr>
<td></td>
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<td>97 ± 4</td>
<td>97 ± 5*</td>
<td>93 ± 5</td>
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<td></td>
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<tr>
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<td>Ti, s</td>
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<td>2.0 ± 0.2</td>
<td>2.1 ± 0.4*</td>
<td>2.1 ± 0.2</td>
<td>2.6 ± 0.4*</td>
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<tr>
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<td>Te, s</td>
<td>2.8 ± 0.5</td>
<td>3.7 ± 1.6</td>
<td>3.8 ± 1.0*</td>
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<td></td>
<td>Vt, ml</td>
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<td>390 ± 79</td>
<td>440 ± 98*</td>
<td>175 ± 46</td>
<td>262 ± 65*</td>
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<td>Heart rate, bpm</td>
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<td>92 ± 5*</td>
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<td>67 ± 1</td>
<td>68 ± 2*</td>
<td>69 ± 2*</td>
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<td>137 ± 3*</td>
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<td>-0.8 ± 0.5</td>
<td>-0.7 ± 0.3</td>
<td>-12.0 ± 1.7</td>
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<td>Heart rate, bpm</td>
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<td>81 ± 4*</td>
<td>80 ± 7*</td>
<td>73 ± 8</td>
<td>76 ± 9</td>
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<tr>
<td></td>
<td>Blood pressure, mmHg</td>
<td>Diastolic</td>
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<td>62 ± 4</td>
<td>69 ± 4*</td>
<td>62 ± 4</td>
</tr>
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<td>Systolic</td>
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<td>147 ± 2</td>
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<td>147 ± 7</td>
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<tr>
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<td>Peak Ptr, cmH2O</td>
<td>-0.9 ± 0.2</td>
<td>-0.7 ± 0.3*</td>
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<tr>
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<td>Ti, s</td>
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<td>2.6 ± 0.4*</td>
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<tr>
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<tr>
<td></td>
<td>Vt, ml</td>
<td>351 ± 42</td>
<td>390 ± 42*</td>
<td>388 ± 69*</td>
<td>155 ± 23</td>
<td>190 ± 21</td>
</tr>
</tbody>
</table>

Values are means ± SD when high-frequency pressure oscillation (HFPO) was applied during inspiration only (iHFPO) or during expiration and inspiration (e+iHFPO) during eupnea and during efforts against an inspiratory resistance. Data for iHFPO when breathing against a resistance were obtained in 2 dogs only. NREM, non-rapid-eye-movement; bpm, beats per minute; Ptr, tracheal pressure; Ti, inspiratory time; Te, expiratory time; Vt, tidal volume. *Significantly different from control, P < 0.05.
These findings contrast with those obtained during application of square-wave negative pressure to the UA or with spontaneously generated negative pressure during tracheal occlusions, when cardiovascular effects were not observed. Although such findings lend support for a role of HFPO-sensitive mechanoreceptors in the UA on cardiovascular function, it is difficult to define the precise mechanism underlying the hemodynamic changes. HFPO-sensitive pharyngeal afferents may directly augment sympathetic activity. Alternatively, activation of the sympathetic nervous system and increased blood pressure may be secondary to the reflex changes in respiratory timing induced by HFPO.

High-frequency oscillating pressures applied to the UA at a similar frequency (30 Hz) as seen during snoring (24, 33) have been shown to cause reflex stimulation of UA muscles (4, 19, 32) and inhibition of inspiratory motor output (10, 32). The UA mechanoreceptors mediating these reflexes appear to be more sensitive to these oscillating pressures than to static or graded pressure changes (10, 38). Similarly, we found that prolongations of T_i and T_e with HFPO were more than double those obtained during the tracheal occlusion with open fenestration, even though the magnitude of pressure oscillations in the UA during HFPO were <10% of those during occlusion. Furthermore, HFPO applied to the UA over a single respiratory cycle augmented blood pressure, whereas negative pressure transmitted to the UA during multiple efforts against a tracheal occlusion did not. It is possible that, over a single respiratory cycle, a longer T_i and T_e with HFPO resulted in hypercapnia and hypoxia, leading to increased sympathetic activation (23).

Application of HFPO during eupnea or during inspiratory efforts against a resistance also augmented V_t changes. Such changes in lung volume can reflexly increase heart rate (2) but depress sympathetic nerve activity (14) with resultant vasodilation (7). Lung inflation also renders baroreceptor stimulation less effective in increasing sympathetic nerve efferent activity (11). These effects may be particularly important in the dog, in which lung inflation-related reflexes are more powerful than in humans (7, 17, 37).

Thus interpretation of the HFPO findings is made difficult because of the confounding influences of associated respiratory changes. However, Fig. 7 shows that during the initial few beats (before inspiration) after the onset of HFPO (applied during expiration) there were no changes in MAP or heart rate beyond those predicted by the effect of a prolonged T_e. This analysis removes the confounding influence of differences in lung volume and magnitude of chemostimulation and implies a minor, if any, effect of direct stimulation of HFPO-sensitive pharyngeal afferents on blood pressure.

In summary, HFPO applied to the UA augments blood pressure; however, we cannot be sure whether this is a direct effect of HFPO or is secondary to

![Figure 7](http://jap.physiology.org/Downloadedfrom/10.220.33.1.on.November.10.2017)
changes in respiratory timing and \( V_t \). Negative UA pressure during obstructive apneas did not augment blood pressure; however, these results are confounded in part by reductions in central respiratory motor output and in pleural pressure. The most definitive and least confounded experimental evidence against a role for UA negative pressure effects on blood pressure were with the application of negative pressure to the UA during central apnea. In these studies, blood pressure was stable throughout almost all of the prolonged apnea. The findings clearly showed that very large negative pressures applied to the UA sufficient to cause airway closure did not augment blood pressure during any phase of the apneic period, including the later stages in which blood pressure was rising, presumably because of accumulating chemoreceptor stimuli. We conclude that activation of UA negative pressure-sensitive receptors do not contribute directly to the pressor response associated with sleep-disordered breathing events. Any cardiovascular effects of UA pressure are more likely to be expressed indirectly through their effects on breath timing.

Finally, the findings of this study are also relevant to experimental animal models used to study cardiovascular consequences of OSA, in which breathing occurs via a tracheostomy and the UA is bypassed (5). Occlusion of the tracheostomy, as used in these models, does not simulate the “collapsing” effect of negative intrathoracic pressures acting on the UA that occurs in normal obstructive events, nor does this tracheal site of airflow occlusion produce any reflex effects of negative pressures in the UA on breath timing or \( V_t \) (9, 18, 20, 36). Nevertheless, our data indicate that the independent effect of UA negative pressure directly on cardiovascular inputs is negligible.

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REFERENCES


