Effects of arousal and sleep state on systemic and pulmonary hemodynamics in obstructive apnea


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Effects of arousal and sleep state on systemic and pulmonary hemodynamics in obstructive apnea. J. Appl. Physiol. 88: 1084–1092, 2000.—During obstructive sleep apnea (OSA), systemic (Psa) and pulmonary (Ppa) arterial pressures acutely increase after apnea termination, whereas left and right ventricular stroke volumes (SV) reach a nadir. In a canine model (n = 6), we examined the effects of arousal, parasympathetic blockade (atropine 1 mg/kg iv), and sleep state on cardiovascular responses to OSA. In the absence of arousal, SV remained constant after apnea termination, compared with a 4.4 ± 1.7% decrease after apnea with arousal (P < 0.025). The rise in transmural Ppa was independent of arousal (4.5 ± 1.0 vs. 4.1 ± 1.2 mmHg with and without arousal, respectively), whereas Psa increased more after apnea termination in apneas with arousal compared with apneas without arousal. Parasympathetic blockade abolished the arousal-induced increase in Psa, indicating that arousal is associated with a vagal withdrawal of the parasympathetic tone to the heart. Rapid-eye-movement (REM) sleep blunted the increase in Psa (pre- to end-apnea: 5.6 ± 2.3 mmHg vs. 10.3 ± 1.6 mmHg, REM vs. non-REM, respectively, P < 0.025), but not transmural Ppa, during an obstructive apnea. We conclude that arousal and sleep state both have differential effects on the systemic and pulmonary circulation in OSA, indicating that, in patients with underlying cardiovascular disease, the hemodynamic consequences of OSA may be different for the right or the left side of the circulation.

airway obstruction; arterial pressure; canine; heart rate; hypoxia; non-rapid-eye-movement sleep; rapid-eye-movement sleep; stroke volume

Surgical Procedures

Experiments were performed on six mongrel dogs (3 male and 3 female) in the weight range of 20–25 kg. The animals were pretreated with fentanyl (0.4 mg im) and droperidol (20 mg im) and anesthetized with pentobarbital sodium (30 mg/kg iv), and mechanical ventilation was initiated. A chronic tracheal stoma was created by removing the ventral portion of five tracheal rings. Tygon catheters (0.05 in. ID, 0.09 in. OD) were introduced into the right femoral artery and vein and advanced rostrally to the thoracic aorta and inferior vena cava, respectively. A left thoracotomy (fourth interspace) was performed, and electromagnetic flow probes (Zepeda Instruments, Seattle, WA) were placed around the ascending aorta in two dogs, around the pulmonary artery in two dogs, and around both the ascending aorta and the pulmonary artery in two dogs as previously described (21). The size of each circular flow probe was chosen to closely match the external

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diameter of the vessel. A minimum of 2 wk was allowed for local fibrosis to occur (confirmed at autopsy) before data collection, assuring that all flow measurements occurred through a constant cross-sectional area. In those animals with pulmonary artery flow probes, Tygon catheters (0.05 in. ID, 0.09 in. OD) were also placed in the pulmonary artery and left atrium to monitor Ppa and left atrial pressure (Pla), respectively. A balloon catheter was anchored to the inside of the chest wall at the level of the fourth interspace on the right side of the chest to estimate pleural pressure (Ppl) as previously reported (21). The chest was then closed, and negative intrapleural pressure was established with a chest tube to completely reinflate the lungs. The chest tube was removed, and spontaneous ventilation was allowed to resume. All catheters and electrical leads were tunneled subcutaneously and exteriorized between the scapulae and were protected in the pocket of a jacket. Polysomnographic leads for measurement of electroencephalographic (EEG) and nuchal electromyographic (EMG) activity were attached with needle electrodes only during data collection periods. Patency and sterility of the vascular catheters were maintained by filling them with a mixture of heparin (1,000 U/ml) and penicillin G potassium (20,000 U/ml). All catheters were flushed and had the dead space fluid replaced at a minimum of every 72 h. The animals were allowed at least 2 wk to recover from surgery, during which time they were monitored daily and acclimated to the laboratory environment. All animals were treated with a broad-spectrum antibiotic (30 mg·kg−1·day−1 of trimethoprim/sulfadiazine), beginning at the time of surgery and continuing for 7–10 days postoperatively. The study was approved by the Iohns Hopkins University Animal Use and Care Committee and complied with the American Physiological Society guidelines.

Apparatus and Methods of Measurement

A custom-designed endotracheal tube was used to control airway patency, measure arterial Hb saturation (averaged every 1 s; minimum detectable change of 1%), and allow sampling of end-tidal carbon dioxide and measurement of tracheal pressure (Ptr) from side ports (16). After atropine administration, dilation of the trachea precluded reliable contact of the oximeter probe with the mucosal lining and prevented measurement of arterial Hb saturation, as previously discussed (14). The resistance of the endotracheal tube and the time constants for obstructing and restoring airway patency have been previously described (16). The connections from the endotracheal tube, the polysomnographic extension leads, and the vascular lines were placed in a 40-in.-long flexible tube that attached to the back of the animal’s jacket.

The animals slept in a specially constructed box with a clear Plexiglas front panel that could be monitored from an adjacent room with a shortwave closed-circuit television. The flexible tube containing the recording wires and catheters exited through a hole in the top of the sleep box, passed under a communicating door, and attached to the recording equipment in the adjacent room. Intravascular and airway pressures measurements were made with pressure transducers (Cobe, Lakewood, CO) referenced to zero at midthoracic level with the animal lying prone. Calibrations were checked at 30-min intervals throughout experiments. A pen recorder (Grass Instruments, Quincy, MA) was used to record EEG and EMG activity and Psa, Ppa, Pla, Ppl, and Ptr traces. The SV of the left and right ventricles were measured with a model SWF-5RD electromagnetic flowmeter (Zepeda Instruments). A Nellcor N-200 pulse oximeter (Haywood, CA) measured arterial Hb saturation, and a Beckman analyzer (Anaheim, CA) sampled end-tidal carbon dioxide. Both instruments were connected to the pen recorder. Data from the pen recorder were sampled at 300 Hz, converted to digital format (DI-200 data acquisition board; Dataq Instruments, Akron, OH), and acquired to optical disk for storage with Windaq/200 acquisition software (Dataq Instruments). The velocity signal from the electromagnetic flow probe was digitally integrated to determine SV. Transmural pulmonary arterial pressure (Ppa – Ppl; Ppa,tm) and transmural left atrial pressure (Pla – Ppl; Pla,tm) were derived digitally for analysis during periods of obstructive apnea.

Experimental Protocol

We performed two separate experiments at least 1 wk apart in each animal. Before each experiment, the animals were sleep deprived for a period of 24 h as previously described (14, 15, 21). Experiments were conducted between 1400 and 2000. In the first experiment, a series of apneas was induced in six animals during both NREM and REM sleep. The duration of airway obstruction was controlled such that restoration of airway patency was associated with either the absence or the presence of an EEG arousal (as previously described; Ref. 14). In the second experiment, a series of airway obstructions with arousal was induced in six animals during NREM sleep before (control) and after pharmacological blockade of the parasympathetic nervous system with atropine (intravenous infusion of 1 mg/kg). The efficacy of the blockade was verified by bolus administration of ACh (40 µg/kg iv) and by the marked increase in heart rate (HR) from 72 ± 3 to 164 ± 9 beats/min (bpm). All data in the second experiment were collected within 60 min before and 60 min after atropine administration.

Data Analyses

Sleep/wake states were characterized as either awake (low-amplitude and high-frequency central EEG activity and high-frequency nuchal EMG activity), NREM sleep (high-amplitude and low-frequency central EEG activity and decreased nuchal EMG activity compared with awake), and REM sleep (low-amplitude and high-frequency central EEG activity, similar to awake, and reduced nuchal EMG activity compared with awake and NREM sleep), as previously described for the canine model (16). Arousal was classified by the changes in EEG and EMG activity at apnea termination according to American Sleep Disorders Association criteria (1).

Apnea duration was defined as the time from onset of an apnea to the nadir of the last inspiratory effort during the apnea. For each apnea, the number of respiratory efforts, the duration, and the concomitant oxyhemoglobin saturation were determined. In each animal, apneas with and without arousal were matched for length by selecting the five longest apneas without arousal and comparing them to five apneas of equal duration with arousal. In this way, the duration, number of respiratory efforts, and degree of oxygen desaturation were matched in apneas that were terminated either with or without arousal. Ventricular output was calculated as SV×HR. There were no differences between left and right ventricular SV as previously described (21), so data were then pooled to provide a single value for ventricular SV.

The following definitions and criteria were used in the measurement of preapnea, end-apnea, and postapnea values for Psa, Ppa,tm, Pla,tm, and HR: preapnea is the three respiratory cycles immediately before apnea, end-apnea is the last two “inspiratory and expiratory cycles” of the apnea, and postapnea is the first three respiratory cycles after the restoration of airway patency.
Before data analyses, the vascular pressure signals were filtered digitally (Windaq, filter factor 100, Dataq Instruments) to provide a mean pressure. The filtered traces were then used to assess the mean vascular pressures at various points throughout the apnea cycle. At preapnea, vascular pressures were calculated as the maximum expiratory level averaged for the three respiratory cycles during this period. At end-apnea and postapnea, vascular pressures were calculated as the maximum expiratory value during each period. The HR was measured from the pulsatile arterial blood pressure trace by counting the number of systolic peaks over each period. Summaries of the apnea characteristics and dogs used for each analysis are presented in Tables 1–3. For each animal, the values for pre-, end-, and postapnea were averaged over three to five apneas. The averaged data from each animal were then pooled across all the animals and analyzed by paired t-test. Differences were considered significant if P < 0.05. Data were analyzed using Crunch 4 (Crunch Software, Oakland, CA) and are reported as means ± SE.

**RESULTS**

Effect of Apnea-Induced Arousal

The SV, HR, Psa, and Ppa,tm were examined during apneas that were terminated either with or without an arousal during NREM sleep. Respiratory characteristics of the apneas are presented in Table 1. Figure 1 shows a trace from one animal during an apnea with an arousal (A) and without an arousal (B). In both apneas, Psa, Ppa,tm, and left ventricular SV at

| Table 1. Duration of apnea, arterial oxygen desaturation, number of respiratory efforts, and number of apneas analyzed per dog comparing obstructive apneas that terminate either with or without arousal |
|----------------------------------|-----------------|-----------------|
|                                  | Arousal          | No Arousal       | P     |
| Duration, s                     | 28.2±2.9         | 27.5±3.8         | NS    |
| Oxygen desaturation, %          | 5.9±0.6          | 5.6±0.6          | NS    |
| Number of efforts               | 6.4±0.9          | 6.2±0.9          | NS    |
| Number of apneas per dog        | 5.0±0.4          | 5.0±0.0          | NS    |

Values are means ± SE; n = 6 dogs. NS, not significant. P, differences between no arousal and arousal conditions determined by paired t-test (two-tailed).

Fig. 1. Computer-generated sample traces from one animal during an obstructive apnea with arousal (A) and an obstructive apnea without arousal (B) showing electroencephalographic (EEG) and nuchal electromyographic (EMG) activity, expired CO₂, tracheal pressure (Ptr), arterial Hb saturation (SaO₂), systolic arterial pressure (Psa), transmural pulmonary arterial pressure (Ppa,tm), and left ventricular stroke volume (LVSV) during non-rapid-eye-movement (NREM) sleep. Note that, in comparison to apnea without arousal, apnea with arousal is associated with a greater end- to postapnea increase in heart rate (HR) and in Psa but not in Ppa,tm.
pre- and end-apnea were comparable. In contrast, from end-apnea to postapnea the Psa and HR increased more and the SV decreased more in the apnea that was terminated by arousal compared with the apnea without arousal.

The pooled data (n = 6) comparing cardiovascular responses to obstructive apneas with and without arousal are shown in Fig. 2. From end-apnea to postapnea, HR increased 20.7 ± 2.6 bpm with arousal but only 4.6 ± 2.1 bpm without arousal (P < 0.004). Similarly, ventricular output increased 21.4 ± 2.6% with arousal compared with 6.0 ± 3.0% without arousal from end-apnea to postapnea (P < 0.002). The SV decreased from end-apnea to postapnea by 4.4 ± 1.7% with arousal (P < 0.025) and remained constant without arousal. Thus apneas with arousal produced an increase in HR and ventricular output but a decrease in SV compared with apneas without arousal.

Psa and Ppa. Pooled data comparing Psa and Ppa,tm responses to apneas with and without arousal during NREM are shown in Fig. 3. From end-apnea to postapnea, mean Psa increased 10.9 ± 2.8 mmHg with arousal compared with 3.3 ± 1.4 mmHg without arousal (P < 0.025). In contrast, the presence of arousal did not affect the increase in the Ppa,tm from end-apnea to postapnea (Fig. 3). In the three animals in which Pla was measured, comparable changes in Pla,tm occurred from preapnea to postapnea between the arousal (0.3 ± 0.1 mmHg) and no arousal (0.6 ± 0.3 mmHg) conditions. Thus arousal increased the systemic, but not the pulmonary, arterial pressure responses to an obstructive apnea.

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**Fig. 2.** HR (A), ventricular output (VO; B), and stroke volume (SV; C) responses (mean ± SE; n = 6) to obstructive apneas with arousal (●) and without arousal (■) during NREM sleep. Pre, 3 respiratory cycles immediately before apnea; End, last 2 "inspiratory and expiratory cycles" of apnea; Post, first 3 respiratory cycles after restoration of airway patency; bpm, beats per minute. Differences from end-apnea to postapnea between the arousal and nonarousal condition were determined by paired t-test (two-tailed).

**Fig. 3.** Psa (n = 6) (A) and Ppa,tm (n = 4) (B) responses (mean ± SE) to obstructive apneas with arousal (●) and without arousal (■) during NREM sleep. Differences from end-apnea to postapnea between the arousal and nonarousal condition were determined by paired t-test (two-tailed).
Effect of Parasympathetic Blockade

Atropine administration increased the baseline, or preapnea, HR (192 ± 6 7.7 bpm) and Psa (116.8 ± 6 2.0 mmHg) and decreased the SV (238.5 ± 6 4.2%). Therefore, the cardiovascular responses to apnea and arousal were compared between the control and atropine conditions as a percent change from preapnea. The respiratory characteristics of the obstructive apneas are presented in Table 2. The effect of parasympathetic blockade on HR, Psa, and ventricular output responses to obstructive apneas with arousal is shown in Fig. 4. Compared with control, the effect of parasympathetic blockade was to abolish the HR and Psa increase from end- to postapnea. During parasympathetic blockade, SV (Fig. 4) and also ventricular output remained constant between end- and postapnea. In four of the six animals, the Ppa,tm response to obstructive apnea was measured. Before atropine administration, the Ppa,tm was 10.1 ± 6 0.5 mmHg at preapnea, 11.6 ± 6 0.8 mmHg at end-apnea, and 16.2 ± 6 1.7 mmHg at postapnea. The comparable values after atropine administration were 11.2 ± 6 1.6, 12.9 ± 6 2.2, and 14.6 ± 6 2.1 mmHg, respectively, and these were not different from the control response.

Effect of Sleep State

The respiratory characteristics for obstructive apneas with arousal during NREM and REM sleep are shown in Table 3. Sleep state did not affect the changes from preapnea to end-apnea and end-apnea to postapnea for HR, SV, ventricular output, or Ppa,tm (Table 4). In contrast, the response of the Psa to an obstructive apnea with arousal was different between the sleep states. Figure 5 shows a sample trace from one dog demonstrating that during REM sleep the Ppa,tm, but not the Psa, increased from preapnea to end-apnea. The pooled data in Table 4 show that the increase in Psa from preapnea to end-apnea was reduced in REM sleep compared with NREM sleep. Conversely, from end-apnea to postapnea, Psa increased more in REM than NREM sleep, such that the absolute Psa at end-apnea was not different between REM (129.4 ± 6 2.9 mmHg) and NREM (132.8 ± 6 3.3 mmHg) sleep.

**DISCUSSION**

This study investigated the influences of arousal and sleep state on cardiovascular responses to OSA in a canine model. We present several new findings from

**Table 2. Duration of apnea, number of respiratory efforts, and number of obstructive apneas analyzed per dog before (control) and after parasympathetic blockade (1 mg/kg atropine)**

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>Atropine</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duration, s</td>
<td>28.2 ± 6 2.9</td>
<td>26.3 ± 6 2.4</td>
<td>NS</td>
</tr>
<tr>
<td>Number of efforts</td>
<td>6.4 ± 6 0.9</td>
<td>6.8 ± 6 1.6</td>
<td>NS</td>
</tr>
<tr>
<td>Number of apneas per dog</td>
<td>5.0 ± 6 0.4</td>
<td>3.3 ± 6 0.3</td>
<td>&lt; 0.05</td>
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</table>

Values are means ± SE; n = 6 dogs. After atropine administration, we were unable to record arterial Hb saturation from the mucosal lining of the trachea for reasons previously described (14). P, differences between control and atropine conditions determined by paired t-test (two-tailed).

**Table 3. Duration of apnea, arterial oxygen desaturation, number of respiratory efforts, and number of apneas analyzed per dog during obstructive apneas in NREM and REM sleep**

<table>
<thead>
<tr>
<th></th>
<th>NREM</th>
<th>REM</th>
<th>P</th>
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<tbody>
<tr>
<td>Duration, s</td>
<td>25.8 ± 6 1.1</td>
<td>27.9 ± 6 3.0</td>
<td>NS</td>
</tr>
<tr>
<td>Oxygen desaturation, %</td>
<td>6.4 ± 6 0.8</td>
<td>9.0 ± 6 0.7</td>
<td>&lt; 0.05</td>
</tr>
<tr>
<td>Number of efforts</td>
<td>6.9 ± 6 1.3</td>
<td>6.1 ± 6 1.0</td>
<td>NS</td>
</tr>
<tr>
<td>Number of apneas per dog</td>
<td>5.0 ± 6 0.5</td>
<td>3.0 ± 6 0.5</td>
<td>&lt; 0.05</td>
</tr>
</tbody>
</table>

Values are means ± SE; n = 4 dogs. P, differences between non-rapid-eye-movement (NREM) and rapid-eye-movement (REM) conditions determined by paired t-test (two-tailed).

**Fig. 4.** HR (A), Psa (B), and SV (C) responses (mean ± SE; n = 6) to obstructive apneas before (control; C) and after (■) parasympathetic blockade (1 mg/kg atropine) during NREM sleep. Comparisons of cardiovascular parameters between control and atropine were performed as a percentage of values at preapnea. Differences from end-apnea to postapnea between control and atropine conditions were determined by paired t-test (two-tailed).
end-apnea (with arousal).

Table 4. Effect of sleep state on changes in heart rate, stroke volume, ventricular output, transmural pulmonary arterial pressure, and systemic arterial pressure from preapnea to end-apnea and from end-apnea to postapnea (with arousal)

<table>
<thead>
<tr>
<th>Sleep State</th>
<th>Change from Pre-to End-Apnea</th>
<th>Change from End-to Postapnea</th>
</tr>
</thead>
<tbody>
<tr>
<td>HR, bpm</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NREM</td>
<td>-3.6 ± 1.9</td>
<td>23.2 ± 2.8</td>
</tr>
<tr>
<td>REM</td>
<td>-20.2 ± 2.5</td>
<td>20.0 ± 1.7</td>
</tr>
<tr>
<td>SV, %</td>
<td></td>
<td></td>
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<tr>
<td>NREM</td>
<td>-4.2 ± 1.0</td>
<td>-6.8 ± 1.2</td>
</tr>
<tr>
<td>REM</td>
<td>-2.8 ± 1.2</td>
<td>-7.8 ± 1.7</td>
</tr>
<tr>
<td>Ventricular output, %</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NREM</td>
<td>-8.7 ± 3.3</td>
<td>20.7 ± 2.8</td>
</tr>
<tr>
<td>REM</td>
<td>-5.7 ± 2.6</td>
<td>17.1 ± 3.2</td>
</tr>
<tr>
<td>Psa, mmHg</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NREM</td>
<td>10.3 ± 1.6</td>
<td>13.9 ± 3.3</td>
</tr>
<tr>
<td>REM</td>
<td>5.6 ± 2.3</td>
<td>19.5 ± 2.7</td>
</tr>
</tbody>
</table>

Values are means ± SE; n = 4 dogs. HR, heart rate; SV, stroke volume; Ppa,tm, transpulmonary arterial pressure; Psa, systemic arterial pressure. P, differences between NREM and REM conditions determined by paired t-test (two-tailed).

In this study, we confirmed our previous finding that Psa due to arousal from an obstructive apnea is dependent on a tachycardia mediated by vagal withdrawal of parasympathetic tone to the heart (Fig. 4). Second, we demonstrate that a consequence of the arousal-mediated tachycardia is a decrease in ventricular SV immediately after termination of the obstructive apnea (Fig. 2). Third, we show that arousal from apnea does not contribute to any of the increase in Ppa after apnea termination (Fig. 3). This absence of an effect of arousal on the pulmonary circulation is in contrast to the systemic circulation in which arousal is the dominant factor increasing Psa after apnea (Figs. 1 and 3; see Ref. 14). Finally, we show that, in REM sleep, the increase in Psa that occurs during an obstructive apnea is blunted compared with the response in NREM sleep (Figs. 5 and Table 4). In contrast, the pulmonary circulation exhibited no such effect of sleep state in response to obstructive apnea. Thus both sleep state and arousal have differential effects on the systemic and pulmonary circulations in obstructive apnea. In the discussion that follows, we examine in more detail the relationship of arousal and sleep state to changes in the systemic and pulmonary circulation that occur in OSA.

Systemic Circulation

In this study, we confirmed our previous finding that arousal from NREM sleep increases HR and contributes to the acute systemic hypertension immediately after apnea termination (14). These increases in HR and Psa with arousal were blocked after atropine administration. These data indicate that the cardiovascular effects of apnea-induced arousal are predominantly due to withdrawal of the parasympathetic tone to the heart. These data are consistent with those of Horner et al. (11), who showed that spontaneous arousal from NREM sleep also increased HR through withdrawal of parasympathetic tone. It is possible that arousal may also affect sympathetic tone to the systemic vasculature, but our data suggest that such a response is not necessary to explain the increases in Psa due to arousal. Thus the effects of arousal from obstructive apnea on the systemic circulation are predominantly dependent on the heart.

The surge in Psa at arousal from an obstructive apnea was associated with a decrease in SV (Fig. 2). A fall in SV in response to obstructive apnea has been demonstrated in both humans (2, 6, 9, 22, 28) and animals (21, 30). In this study, we show that the arousal response is an important factor contributing to the fall in SV immediately after an apnea. This fall in SV is due to a tachycardia because the presence of a constant HR during arousal from obstructive apneas following atropine administration eliminated the fall in SV after apnea termination (Fig. 4). The increase in HR and decrease in SV with arousal are consistent with a transient decrease in the preload of the left ventricle, although direct measurements of ventricular volume would be necessary to confirm changes in preload. Nevertheless, in the absence of arousal, SV progressively decreased over the course of an obstructive apnea (Fig. 4; preapnea to end-apnea), suggesting that other mechanisms contribute to the fall in SV preceding arousal. In the accompanying study (21a), we demonstrate that this fall in SV during an obstructive apnea is produced by an increase in left ventricular afterload. Thus, in OSA, two different mechanisms account for the decrease in SV that occurs before and after arousal.

In the present study, we report that Psa increases less during an obstructive apnea in REM sleep than in NREM sleep (Fig. 5 and Table 4). Given that hypoxic stimulation of the chemoreceptors is the dominant factor increasing sympathetic nerve activity during apnea (10, 12, 17), the attenuated systemic blood pressure response to apnea during REM sleep suggests that sleep state can inhibit the chemoreceptor-sympathetic nerve activity reflex arc (8, 13). It is known from human and animal studies that respiratory responses to chemoreceptor stimulation are blunted during REM sleep compared with NREM sleep (4, 29). The present data suggest that a comparable situation may exist with respect to the cardiovascular system; namely, the chemoreceptor stimulus associated with an obstructive apnea is less effective in raising Psa during REM than during NREM sleep.

Despite a differential effect of sleep state on the Psa response to apnea, the maximal blood pressure response at arousal was independent of the previous sleep state. That is, the maximal Psa reached at arousal was the same whether or not apneas occurred during NREM sleep or REM sleep. In contrast, the only comparable study conducted in humans with OSA indicated that systemic blood pressure surged to higher levels in REM sleep compared with NREM sleep (7). However, it was unclear whether this was due to a more acute increase in blood pressure at arousal from REM sleep, which would be consistent with our current data,
or to the fact that baseline blood pressure was higher in REM sleep than in NREM sleep before apnea.

Pulmonary Circulation

In the present study, the magnitude of the Ppa response to an obstructive apnea was independent of sleep state (Table 4). Such a result builds on our previous demonstration that during normal, unobstructed breathing the Ppa is the same during NREM and REM sleep (21). This absence of a sleep state effect on the pulmonary circulation is in contrast to the effect on the systemic circulation, as discussed above. The vascular resistance in the pulmonary circulation, therefore, is much less dependent on the autonomic nervous system (ANS) than is the vascular resistance in the systemic circulation. Further support for such a hypothesis is provided in the accompanying study (21a), which demonstrates that the increase in Ppa during apnea is dependent on hypoxic pulmonary vasoconstriction and is independent of the ANS. Thus several lines of evidence suggest that the pulmonary circulation both has minimal neural regulation and is unresponsive to changes in sleep state.

In addition to sleep state, the pulmonary circulation was also unaffected by the arousal response (Figs. 1 and 3). This finding is in contrast to that regarding the systemic circulation, in which the tachycardia associated with arousal produced a significant increase in Psa (14) (Fig. 3). One possible explanation for the absence of a change in Ppa with arousal may be that the pressure gradient from the pulmonary artery to the left atrium was higher in the arousal than the nonarousal condition. However, in the three animals in which Pla was measured, the pressure changes over the apnea cycle were the same for the arousal and nonarousal conditions. Thus the pressure gradient
across the pulmonary circulation was the same with and without arousal. A second possible explanation may be that, as argued above, the systemic circulation is much more responsive to the ANS than is the pulmonary circulation. Therefore, if arousal increased vascular resistance through the ANS, then Psa would be expected to increase more with arousal than does the Ppa. However, we have shown that it is the tachycardia of arousal rather than a vascular response that can account for the increase in systemic vascular pressure. As such, this tachycardia from arousal should also affect the pulmonary circulation. We did not observe any effect of the tachycardia from arousal on the pulmonary circulation, and we can only speculate that differences in compliance between the two circulations may play a role. Consider that the tachycardia associated with arousal is very transient and the vascular resistance of pulmonary circulation is particularly low (5, 25). Thus the very brief infusion of blood into the pulmonary circulation during the tachycardia may be accommodated without any measurable increase in Ppa.

The cardiovascular effects of arousal and sleep state that we have demonstrated in our canine model may have implications for OSA patients; namely, that the ANS has distinct effects on the heart and systemic circulation but not on the pulmonary circulation. Our results in animals with normal hearts demonstrate that obstructive apnea produces a neurally mediated stress that is specific to the left side of the circulation. This stress may be exacerbated in OSA patients with underlying left-sided heart disease such that arousal, for example, may cause significant reductions in SV at end-apnea and expose the heart or brain to increased risk of ischemia. Because such studies are extremely difficult to perform in OSA patients, particularly if significant comorbidity is present, the need exists to develop more sophisticated animal models of OSA that incorporate heart failure, coronary ischemia, hypertension, and other cardiovascular diseases.

In summary, we have demonstrated specific differences in the cardiovascular responses of the systemic and pulmonary circulations to arousal and sleep state in a canine model of OSA. Arousal from obstructive apnea caused an increase in Psa but not in Ppa. The effect of arousal on the systemic circulation was dependent on a tachycardia, and this tachycardia also contributed to a decrease in ventricular SV immediately after the apnea. The systemic arterial blood pressure response during an obstructive apnea was attenuated during REM sleep compared with during NREM sleep. In contrast, the pulmonary circulation, which is much less responsive to the ANS, showed similar blood pressure responses during NREM and REM sleep.

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