Systemic and pulmonary hemodynamic responses
to normal and obstructed breathing during sleep

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Schneider, H., C. D. Schaub, K. A. Andreoni, A. R. Schwartz, R. L. Smith, J. L. Robotham, and C. P. O’Donnell. Systemic and pulmonary hemodynamic responses to normal and obstructed breathing during sleep. J. Appl. Physiol. 83(5): 1671–1680, 1997.—We examined the hemodynamic responses to normal breathing and induced upper airway obstructions during sleep in a canine model of obstructive sleep apnea. During normal breathing, cardiac output decreased (12.9 ± 3.5%, P < 0.025) from wakefulness to non-rapid-eye-movement sleep (NREM) but did not change from NREM to rapid-eye-movement (REM) sleep. There was a decrease (P < 0.05) in systemic (7.2 ± 2.1 mmHg) and pulmonary (2.0 ± 0.6 mmHg) arterial pressures from wakefulness to NREM sleep. In contrast, systemic (8.1 ± 1.0 mmHg, P < 0.025), but not pulmonary, arterial pressures decreased from NREM to REM sleep. During repetitive airway obstructions (56.0 ± 4.7 events/h) in NREM sleep, cardiac output (17.9 ± 3.1%) and heart rate (16.2 ± 2.5%) increased (P < 0.05), without a change in stroke volume, compared with normal breathing during NREM sleep. During single obstructive events, left (7.8 ± 3.0%, P < 0.05) and right (7.1 ± 0.7%, P < 0.01) ventricular outputs decreased during the apneic period. However, left (20.7 ± 1.6%, P < 0.01) and right (24.0 ± 4.2%, P < 0.05) ventricular outputs increased in the post-apneic period because of an increase in heart rate. Thus 1) the systemic, but not the pulmonary, circulation vasodilates during REM sleep with normal breathing; 2) heart rate, rather than stroke volume, is the dominant factor modulating ventricular output in response to apnea; and 3) left and right ventricular outputs oscillate markedly and in phase throughout the apnea cycle.

cardiac output; non-rapid-eye-movement sleep; obstructive sleep apnea; rapid-eye-movement sleep

It is well known that, during normal breathing, changes in sleep/wake state produce significant alterations in systemic hemodynamics. In particular, cardiac output (12, 16) and systemic arterial pressure (4, 5, 12, 16) decrease from wakefulness to non-rapid-eye-movement (NREM) sleep. In rapid-eye-movement (REM) sleep, systemic arterial pressure has been shown to decrease (10, 16, 23, 37) or exhibit no consistent change (4, 5, 12, 13, 31) compared with NREM sleep. The effect of sleep state on systemic hemodynamics has been largely attributed to changes in autonomic neural output (10, 14, 37). However, data show differences in sympathetic neural control of the systemic and pulmonary circulations, such that an increase in sympathetic neural activity may vasoconstrict the systemic vessels and vasodilate the pulmonary vessels (19). Thus it is possible that the pulmonary and systemic circulations may respond differently with respect to sleep/wake state.

Recurrent upper airway obstructions in obstructive sleep apnea (OSA) severely disrupt the stable systemic and pulmonary arterial pressures during sleep with normal breathing. Patients with OSA exhibit sinusoidal fluctuations in systemic and pulmonary arterial pressures that correspond to the periodicity of apnea (6, 18, 33). There may also be transient cardiac output changes in relation to the apnea periodicity (11). Although many studies agree that OSA causes periodic hemodynamic fluctuations, it is unclear whether cardiac output and systemic and pulmonary arterial pressures are elevated during sleep with obstructed breathing compared with sleep with normal breathing.

Several studies have described the sinusoidal fluctuations in systemic and pulmonary arterial pressures that occur with upper airway obstruction during sleep (6, 17, 24, 30, 33). However, changes in ventricular output that occur during each apneic and interapneic period (i.e., apnea cycle) are not well understood. Studies of left (8, 11, 32, 34) and right (3) ventricular output in patients with OSA have employed a variety of indirect techniques. These studies have failed to yield a consensus about the changes in ventricular output, particularly in the interapneic phase (36), when changes in lung volume and body movement may produce significant artifacts. To control for such artifacts, it will be necessary to make direct measurements of ventricular output in relation to the apnea cycle.

The respiratory efforts that occur within an obstructive apnea cycle may have opposing influences on left and right ventricular output. Large negative pleural pressure swings decrease left ventricular output (27, 29) and increase right ventricular output in anesthetized animals (26, 29). Studies in OSA patients using indirect techniques also suggest that, during obstructed inspiratory efforts, left ventricular output decreases (34) and right ventricular output increases (3). If such changes in left and right ventricular output during obstructed inspirations are not counterbalanced during the subsequent “expiratory” period, left ventricular output will fall relative to right ventricular output over the duration of an apnea. Measurements of left and right ventricular output throughout the apnea cycle are necessary to address whether such an imbalance exists between left and right ventricular outputs.

The purpose of this study was to examine the acute systemic and pulmonary hemodynamic changes associated with normal and obstructed breathing during sleep. We used a canine model of OSA in which the
upper airway could be maintained patent during sleep or the upper airway could be intermittently obstructed to simulate OSA. This model demonstrates acute respiratory and systemic blood pressure responses quantitatively similar to human OSA (20–22). In this model, we directly measured beat-to-beat left and right ventricular outputs and systemic and pulmonary arterial pressures to specifically ask the following questions: 1) What is the effect of sleep/wake state on cardiac output and systemic and pulmonary arterial pressures during normal breathing? 2) What is the effect of upper airway obstruction during sleep on cardiac output and systemic and pulmonary arterial pressures compared with sleep with normal, unobstructed breathing? 3) What is the effect of upper airway obstruction during sleep on left and right ventricular outputs within an apnea cycle?

METHODS

Surgical Procedures

Experiments were performed in seven mongrel dogs (3 males and 4 females) weighing 23.9 ± 1.0 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). A chronic tracheal stoma was created. 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 (4th interspace) was performed in the presence of assisted ventilation, and electromagnetic flow probes were placed around the ascending aorta (22–26 mm ID; Zepeda Instruments, Seattle, WA) in two animals and around the pulmonary artery (18–22 mm ID; Zepeda Instruments) in two animals and the ascending aorta and pulmonary artery in three animals. The size of each circular flow probe was chosen to closely match the external diameter of the pulmonary artery or ascending aorta. In addition, a minimum of 2 wk was allowed for the vessel to fibrose to the flow probe (confirmed at autopsy) before data collection to ensure 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. A balloon catheter was anchored to the inside of the chest wall to estimate pleural pressure. 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 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. The vascular catheters were filled with a mixture of heparin (1,000 U/ml) and penicillin G potassium (20,000 U/ml) to maintain their patency and sterility. All catheters were flushed, and the dead space fluid was replaced at least 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 (trimethoprim-sulfadiazine, 30 mg·kg⁻¹·day⁻¹), beginning at the time of surgery and continuing for 7–10 days postoperatively. The study was approved by the Johns 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 hemoglobin saturation (averaged every 1 s; minimum detectable change of 1%), and allow sampling of end-tidal carbon dioxide and measurement of tracheal pressure from side ports (20–22). The resistance of the endotracheal tube and the time constants for obstructing and restoring airway patency have been previously described (22). 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 short-wave closed-circuit television. The flexible tube containing the recording wires and catheters exited through a hole in the top of the sleep box and passed under a communicating door and attached to the recording equipment in the adjacent room. Intravascular and airway pressures were measured with pressure transducers (Cobe, Lakewood, CO) zeroed 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, systemic arterial pressure, pulmonary arterial pressure, left atrial pressure, pleural pressure, and tracheal pressure traces. Left and right ventricular stroke volume were measured with an electromagnetic flowmeter (model SWF-5RD, Zepeda Instruments). A Nellcor N-200 pulse oximeter (Haywood, CA) measured arterial hemoglobin 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 and 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 trace from the electromagnetic flow signal was digitally integrated to determine stroke volume. Transmural pulmonary arterial pressure (pulmonary arterial pressure − pleural pressure) and transmural systemic arterial pressure (systemic arterial pressure − pleural pressure) were derived digitally for analysis during periods of obstructive apnea.

Experimental Protocol

Two separate experiments were performed at least 7 days apart. In experiment A the endotracheal tube was maintained continuously patent over a 4-h period, and each animal was allowed to cycle through normal sleep. Experiment B consisted of three parts: 1) a 1-h control period, in which the endotracheal tube was maintained continuously patent and the animal cycled through sleep/wake states; 2) 1 h of intermittent upper airway obstruction, as previously described (20–22); and 3) a 1-h recovery period, in which the endotracheal tube was maintained continuously patent and the animal cycled through sleep/wake states. Each animal was sleep deprived for 24 h, as previously described (21, 22), before each experiment. The sleep deprivation ensured sufficient hypersomnolence to allow for several REM cycles in experiment A and to permit high rates of airway obstruction in experiment B.
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Data Analysis

We defined cardiac output as steady-state measurements of ≥3 min and ventricular output as an average of stroke volume over discrete periods of time that could not be considered steady state (i.e., within an apnea cycle). Cardiac output and left and right ventricular outputs were calculated as stroke volume × heart rate. Systemic vascular resistance was calculated as systemic arterial pressure/cardiac output, and pulmonary vascular resistance was calculated as (pulmonary arterial pressure − left atrial pressure)/cardiac output. Vascular resistances were not calculated within a single apnea cycle, since neither ventricular outputs nor vascular pressures were in a steady state.

During airway obstruction, pleural pressure was used to define a respiratory cycle. A respiratory cycle consisted of an obstructed inspiratory effort and an expiratory period, defined as the period between successive obstructed inspiratory efforts.

Sleep/wake states were characterized as 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 wakefulness), and REM sleep (low-amplitude and high-frequency central EEG activity, similar to wakefulness, and reduced nuchal EMG activity compared with wakefulness and NREM sleep), as previously described for the canine model (22).

Experiment A. Data were averaged in each animal (Table 1) for periods of quiet wakefulness, NREM sleep, and REM sleep. Within each sleep cycle, a minimum of 3 min of continuous data, without movement during wakefulness and without arousal during NREM and REM sleep, were necessary for inclusion in the pooled data. These averaged data were then pooled across animals for subsequent analysis.

Experiment B. In the control and recovery periods, bracketing the period of airway obstruction, data were averaged during continuous periods of normal breathing during NREM sleep without arousal. In the period of induced airway obstruction, data were averaged across the longest consecutive period of intermittent upper airway obstructions during NREM sleep in which there was a maximum of 180 s between any two consecutive periods of obstruction. This allowed data from stable periods of NREM sleep in the control and recovery periods to be compared with data from continuous periods of intermittent upper airway obstruction during NREM sleep. These averaged data were then pooled across animals (Table 1) for subsequent analysis.

A subanalysis was performed from the data collected from the five animals in experiment B (Figs. 2 and 3) and a sixth animal, which did not meet the criteria for inclusion in the pooled data. These averaged data were then pooled across animals for subsequent analysis.

The effects of maximal swings in pleural pressure on left and right ventricular stroke volume were analyzed using the data collected from the subanalysis of experiment B. The stroke volume from the final cardiac cycle of the obstructive period and that from the final cardiac cycle of the obstructed inspiratory effort were averaged for the last two respiratory cycles at end apnea. These data were then averaged across the five periods of apnea in each animal and pooled across animals.

Data were analyzed using Crunch 4 (Crunch Software, Oakland, CA) and are reported as means ± SE. Paired t-tests were used to compare percent changes in cardiac output, ventricular outputs, stroke volumes, vascular resistances, and heart rate. Within-subject one-way analysis of variance with repeated measures was used to detect significant differences in systemic and pulmonary vascular pressures. If the analysis of variance was significant for a factor, a Newman-Keuls test was used to identify which means were significantly different. Differences were considered significant if P < 0.05.

RESULTS

Systemic and Pulmonary Hemodynamics During Sleep With Normal Breathing

In experiment A, pulmonary and systemic hemodynamics were examined during wakefulness and NREM and REM sleep. There were an average of 6.0 ± 0.9 REM cycles throughout the 240-min protocol. Figure 1 shows a trace of an animal cycling through NREM and REM sleep. The transition from NREM to REM sleep was accompanied by a fall in systemic arterial pressure that was sustained until an arousal or the resumption of NREM sleep. Pulmonary arterial pressure remained constant throughout NREM and REM sleep.

Pooled data comparing hemodynamic responses during wakefulness and NREM and REM sleep are shown in Fig. 2. Cardiac output decreased 12.9 ± 3.5% (P < 0.025) between wakefulness and NREM sleep because of a decrease in heart rate of 16.4 ± 3.6% (P < 0.025) in the presence of an unchanged stroke volume (Fig. 2). Cardiac output, heart rate, and stroke volume did not change between NREM and REM sleep. Mean systemic arterial pressure decreased 7.2 ± 2.1 mmHg (P < 0.025) between wakefulness and NREM sleep and decreased an additional 8.1 ± 1.0 mmHg (P < 0.025) between NREM and REM sleep (Fig. 3). Mean pulmonary arterial pressure decreased 2.0 ± 0.6 mmHg (P < 0.05).
0.05) between wakefulness and NREM sleep. In contrast to mean systemic arterial pressure, mean pulmonary arterial pressure did not change between NREM and REM sleep (Fig. 3). Mean left atrial pressure did not change among wakefulness (4.0 ± 0.8 mmHg), NREM sleep (3.9 ± 0.8 mmHg), and REM sleep (3.6 ± 0.6 mmHg). There was no change in systemic or pulmonary vascular resistance between wakefulness and NREM sleep. In contrast, systemic vascular resistance decreased 7.4 ± 2.0% (P < 0.025) between NREM and REM sleep, while pulmonary vascular resistance remained unchanged.

Systemic and Pulmonary Hemodynamic Responses to Airway Obstruction in NREM Sleep

Sustained period of repetitive apneas. In experiment B, cardiac output and systemic and pulmonary arterial pressure responses to a period of induced repetitive airway obstruction were compared with normal, unobstructed breathing during NREM sleep in control and recovery periods. Data were analyzed over an average period of 37.4 ± 8.8 min of repetitive airway obstruction (56.0 ± 4.7 apneas/h).

Figure 4 shows the effect of repetitive upper airway obstruction on cardiac output, heart rate, and stroke volume. The cardiac output during the period of upper airway obstruction increased by 17.9 ± 3.1% (P < 0.05) compared with normal breathing during sleep in the control and recovery periods. The pattern for heart rate response was similar to that for cardiac output (Fig. 4). Thus changes in cardiac output associated with airway obstruction were entirely mediated by heart rate, since mean stroke volume remained constant throughout the control, airway obstruction, and recovery periods (Fig. 4).

Mean systemic and pulmonary arterial pressures increased from the control to the airway obstruction period (Fig. 5). The increase in mean pulmonary arterial pressure was not attributable to an increase in mean left atrial pressure, which averaged 5.5 ± 0.8 mmHg.
mmHg in the control period, 4.8 ± 0.8 mmHg in the airway obstruction period, and 5.0 ± 1.1 mmHg in the recovery period. There was no change in systemic or pulmonary vascular resistance between the airway obstruction period and either the control or recovery period.

Single period of apnea. For each animal the five longest periods of induced airway obstruction were analyzed in detail. The period of airway obstruction averaged 24.8 ± 4.3 s and included 6.7 ± 0.9 inspiratory efforts. Hemodynamic data were collected at preapnea, end apnea, and postapnea. The time delay between the apnea used for analysis and the immediately preceding apnea averaged 51.1 ± 9.1 s and ensured that pre- and postapneic periods did not overlap. The arterial O₂ saturation decreased on average 6.4 ± 1.1% from preapnea to the nadir in the postapneic period.

Pleural pressure and stroke volume. The effect of a maximal change in pleural pressure on left and right ventricular stroke volumes during obstructed inspiratory efforts was examined at end apnea. Figure 6 shows the changes in left and right ventricular stroke volume that occurred during the last two obstructed inspiratory efforts at end apnea in one animal. The horizontal marks span the last two obstructed inspiratory efforts and demonstrate that left ventricular stroke volume decreases and right ventricular stroke volume increases as pleural pressure falls. The pooled data presented in Fig. 7 show that the negative pleural pressure swings during obstructed inspiration decreased left ventricular stroke volume by a maximum of 33.8 ± 1.0% while increasing right ventricular stroke volume by a maximum of 14.2 ± 6.0%.

Left and right ventricular output. Stroke volumes were averaged over the last two respiratory cycles at end apnea and the first three respiratory cycles at postapnea. This analysis was used to determine whether the opposing effects of pleural pressure on left and right ventricular outputs during obstructed inspiratory efforts were counterbalanced during the subsequent expiratory period. Figure 8 shows the left and right ventricular stroke volumes and outputs at preapnea, end apnea, and postapnea. Left and right ventricular stroke volumes fell (P < 0.05) from preapnea to postapnea by 6.7 ± 1.8 and 6.5 ± 1.5%, respectively. There was also a fall in left and right ventricular outputs from preapnea to end apnea of 7.8 ± 3.0% (P < 0.05) and 7.1 ± 0.7% (P < 0.01), respectively. In contrast, left and right ventricular outputs increased from end apnea to

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**Fig. 2.** Cardiac output (n = 3 aortic flow; n = 3 pulmonary flow), heart rate, and stroke volume during wakefulness and NREM and REM sleep with normal breathing. Values are means ± SE. †P < 0.025 (paired t-test).

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**Fig. 3.** Mean systemic arterial pressure (n = 6) and mean pulmonary arterial pressure (n = 4) during wakefulness and NREM and REM sleep with normal breathing. Values are means ± SE. *P < 0.05; ††P < 0.025 (1-way analysis of variance).
postapnea by 20.7 ± 1.6% (P < 0.01) and 24.0 ± 4.2%
(P < 0.05), respectively, because of an increase in heart
rate.

DISCUSSION

The results of this study provide a quantitative
framework for assessing the acute systemic and pulmo-
nary hemodynamic responses to normal and obstructed
breathing during sleep. The data provide a number
of new findings. First, during sleep with normal breath-
ing the systemic arterial pressure, but not the pulmo-
nary arterial pressure, decreases from NREM to REM
sleep (Figs. 1 and 3). A decrease in systemic vascular
resistance accounts for the fall in systemic arterial
pressure in REM sleep, since cardiac output did not
change. Thus, in the dog, this effect of REM sleep may
reflect a state-dependent difference in neural control of
systemic and pulmonary vessels. Second, a sustained
period of repetitive airway obstruction caused in-
creases in cardiac output and systemic and pulmonary
arterial pressures compared with normal breathing
during NREM sleep (Figs. 4 and 5). Such a simulta-
neous elevation of cardiac output and peripheral vascu-
lar pressures may represent a significant cardiovascu-
lar stress if present chronically in OSA patients. Third,
left and right ventricular stroke volumes fell through-
out the apnea cycle, whereas left and right ventricular
outputs increased during the postapneic period (Fig. 8).
Thus direct, beat-to-beat measurements demonstrate
that right and left ventricular outputs oscillate mark-
edly, and in phase, throughout the apnea cycle. This
study examines the acute hemodynamic responses of
both sides of the heart to normal and obstructed
breathing during sleep and may have implications for
OSA if comparable hemodynamic changes occur in
response to chronic repetitive airway obstruction.

The use of an animal model offers unique advantages
for studies related to sleep/wake state and upper
airway obstruction. Important cardiovascular param-
eters can be measured invasively in response to revers-
able periods of upper airway obstruction. The chronic
implantation of electromagnetic flow probes around the
pulmonary artery and the ascending aorta avoids the
potential problems of noninvasive measurements of
stroke volume. In addition, the canine model is devoid
of comorbid features, particularly with respect to cardio-

![Fig. 4. Cardiac output (n = 3 aortic
flow; n = 2 pulmonary flow), heart rate,
and stroke volume during a control
(Cont) and a recovery (Recov) period, in
which upper airway was maintained
patent during NREM sleep, and during
a period of intermittent airway obstruc-
tion (AO) during NREM sleep. Values
are means ± SE. Differences were deter-
mained by paired t-test.](http://jap.physiology.org/)

![Fig. 5. Mean systemic arterial pressure
(n = 4) and mean pulmonary arterial
pressure (n = 4) during a control and a
recovery period, in which upper airway
was maintained patent during NREM
sleep, and during a period of intermittent
airway obstruction during NREM sleep.
Values are means ± SE. Differences were
determined by 1-way analysis of variance.](http://jap.physiology.org/)
vascular pathology, which could complicate quantitative determination of pulmonary and systemic hemodynamic responses to normal and obstructed breathing during sleep.

Hemodynamic Responses During Sleep With Normal Breathing

There are reports of variable changes in systemic arterial pressure related to sleep/wake state. In particular, some studies have been unable to demonstrate any consistent change in systemic arterial blood pressure between NREM and REM sleep (4, 5, 12, 13, 31). In our study, however, the tracheostomized dog showed distinct changes in systemic hemodynamics related to sleep/wake state. Cardiac output, systemic arterial pressure, and heart rate showed the expected decrease from quiet wakefulness to NREM sleep. Systemic arterial pressure continued to fall from NREM to REM sleep, whereas cardiac output and heart rate remained constant. Thus REM sleep caused a decrease in systemic vascular resistance. A similar pattern of hemodynamic response in REM sleep has been noted in the pig (23, 37) and cat (9). The decrease in systemic arterial pressure in these two species during REM sleep may be mediated by the autonomic nervous system. The pig displays an α-adrenergic-mediated decrease in systemic arterial pressure in REM sleep (37), and the cat decreases systemic arterial pressure (9, 10, 14) and renal nerve activity from NREM to REM sleep (2). Although the present study did not examine mecha-
nisms, it is likely that the REM-related decrease in systemic arterial pressure in our study is also mediated by a decrease in sympathetic neural output.

The pulmonary arterial pressure and cardiac output did not decrease in REM compared with NREM sleep (Figs. 1 and 3). Thus pulmonary vascular resistance in the dog remains constant in NREM and REM sleep. This implies that any decrease in neural sympathetic output related to the change from NREM to REM sleep (2, 37) has little or no influence on the pulmonary vasculature. In fact, previous literature in awake, chronically instrumented dogs suggests that the pulmonary vessels may actually vasoconstrict in response to combined α- and β-adrenergic blockade (19). Thus the changes in vascular resistance of the pulmonary and systemic vascular beds may reflect a differential response to sleep state-related changes in sympathetic nerve activity.

**Hemodynamic Responses During Sleep With Airway Obstruction**

The effect of a sustained period of repetitive airway obstruction was to increase cardiac output and systemic and pulmonary arterial pressures compared with normal breathing during sleep (Figs. 4 and 5). Our data indicate that airway obstruction can significantly and simultaneously elevate cardiac output and systemic and pulmonary arterial pressures. Given the quantitative similarity of respiratory and hemodynamic responses in the canine model and human OSA, these results suggest that comparable stresses to the heart and peripheral vasculature would be manifest with upper airway obstruction in OSA patients.

Repetitive airway obstruction increased overall cardiac output (Fig. 4) and produced marked fluctuations in left and right ventricular output within each apnea cycle (Fig. 8). Studies in OSA patients show a trend for left and right ventricular stroke volume and ventricular output to decrease throughout the apneic period (3, 8, 11, 34). Data from our canine model (Fig. 8) are consistent with these changes in left and right ventricular stroke volume and output reported in OSA patients. In OSA patients, ventricular output immediately after apnea has been reported to decrease (3, 8), increase (11), or exhibit no change (32). The data from the canine model indicate that ventricular output increases in the immediate postapneic period when accompanied by a tachycardia. Thus the variability in the human data may reflect technical differences between studies or differences between subjects in the heart rate response associated with arousal in the postapneic period.

The left and right ventricular stroke volumes fell over the course of an apnea cycle, despite large and opposite fluctuations in left and right ventricular stroke volume during inspiratory efforts (Figs. 7 and 8). We observed a decrease in left ventricular stroke volume and an increase in right ventricular stroke volume during obstructed inspiratory efforts. However, when we averaged the stroke volumes over a complete respiratory cycle, left and right ventricular outputs were similar. Thus the opposing effects of pleural pressure on left and right ventricular stroke volumes during obstructed inspiratory efforts (Figs. 6 and 7) were counterbalanced during the expiratory period.

The findings of our study may have some important clinical implications. First, the absence of a state-dependent decrease in pulmonary arterial pressure during REM sleep (Fig. 3) may represent a risk factor in patients with underlying lung disease. In patients with lung disease, structural damage to the pulmonary circulation and the development of hypoxemia (7) may act to significantly elevate pulmonary pressures during REM sleep. Second, changes in cardiac output during sleep with obstructed breathing depend on changes in heart rate, not stroke volume (Fig. 4). Thus our data suggest that the normal heart is able to adjust its rate to meet the demands imposed by periods of obstructed breathing during sleep. In OSA patients with conduction abnormalities (35), however, such adjustments in heart rate may not be possible and may potentially lead to increases in inotropic stress on the heart. Third, in a normal heart, obstructed inspiratory efforts cause substantial decreases in left ventricular stroke volume of >30%, with rebound compensation during the succeeding expiratory period (Figs. 6–8). In OSA patients with impaired cardiac function [e.g., congestive heart failure]...
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or coronary artery disease (15, 28), decreases in left ventricular stroke volume during obstructed inspiratory efforts may not be compensated in the succeeding expiratory period. Thus left ventricular stroke volume and ventricular output may fall considerably during the apneic period, increasing the risk of ischemic cardiovascular events.

In summary, we have demonstrated that, during normal breathing, sleep state differentially affects the systemic and pulmonary circulations. Furthermore, an acute period of repetitive airway obstruction during sleep significantly elevates cardiac output and systemic and pulmonary arterial pressures compared with normal breathing during sleep. Finally, left and right ventricular outputs oscillate markedly, and in phase, throughout the apneic cycle.

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