Systemic and myocardial hemodynamics during periodic obstructive apneas in sedated pigs

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Systemic and myocardial hemodynamics during periodic obstructive apneas in sedated pigs. J. Appl. Physiol. 84(4): 1289–1298, 1998.—The effects of periodic obstructive apneas on systemic and myocardial hemodynamics were studied in nine preinstrumented sedated pigs under four conditions: breathing room air (RA), breathing 100% O2, breathing RA after critical coronary stenosis (CS) of the left anterior descending coronary artery, and breathing RA after autonomic blockade with hexamethonium (Hex). Apneas with RA increased mean arterial pressure (MAP; from baseline 103.0 ± 3.5 to late apnea 123.6 ± 7.0 Torr, P < 0.001) and coronary blood flow (CBF; late apnea 193.9 ± 22.9% of baseline, P < 0.001) but decreased cardiac output (CO; from baseline 2.9 ± 0.15 to late apnea 2.39 ± 0.19 l/min, P < 0.001). Apneas with O2 increased MAP (from baseline 105.1 ± 4.6 to late apnea 110.7 ± 4.8 Torr, P < 0.001). Apneas with CS produced similar increases in MAP as apneas with RA but greater decreases in CO (from baseline 3.03 ± 0.19 to late apnea 2.1 ± 0.15 l/min, P < 0.001). In LAD-perfused myocardium, there was decreased segmental shortening (baseline 11.0 ± 1.5 to late apnea 7.6 ± 2.0%, P < 0.01) and regional intramyocardial pH (baseline 7.05 ± 0.03 to late apnea 6.72 ± 0.11, P < 0.001) during apneas with CS but under no other conditions. Apneas with Hex increased to the same extent as apneas with RA. Myocardial O2 demand remained unchanged during apnea relative to baseline. We conclude that obstructive apnea-induced changes in left ventricular afterload and CO are secondary to autonomic-mediated responses to hypoxemia. Increased CBF during apneas is related to regional metabolic effects of hypoxia and not to autonomic factors. In the presence of limited coronary flow reserve, decreased O2 supply during apneas can lead to myocardial ischemia, which in turn adversely affects left ventricular function.

obstructive apnea; coronary blood flow; myocardial oxygen demand; hypoxemia; hexamethonium

ACUTE AND CHRONIC cardiovascular disturbances are the most serious complications of obstructive sleep apnea (3, 21). These complications include elevations in blood pressure and left ventricular (LV) afterload, decreases in cardiac output (CO) and stroke volume (SV), oscillations in heart rate (HR), and pulmonary hypertension. In addition, myocardial ischemic disease including infarction can occur in patients with sleep apnea who also have coronary heart disease (21). Theoretically, increased LV afterload due to elevated blood pressure and increasingly negative swings in intrathoracic pressure, sympathoadrenal stimulation during apneas, and postapneic tachycardia should act synergistically to increase myocardial O2 demand (MVO2). On the other hand, apnea-associated bradycardia could decrease MVO2. By decreasing arterial O2 content, hypoxemia would act to decrease O2 content of blood perfusing the myocardium, thereby decreasing myocardial O2 supply. Hence there is a tendency toward the development of an imbalance between myocardial O2 supply and MVO2 in patients with obstructive sleep apnea.

Normally, there is tight coupling between coronary blood flow (CBF) and MVO2 (25). Because myocardial O2 extraction is normally large, the working myocardium generally meets the challenges of hypoxemia and increases in MVO2 by increasing blood flow (25). Therefore myocardial vasodilatory reserve is high. Under apneic conditions, CBF could be increased by regional metabolism, metabolic production of regional vasodilators, and/or β-adrenergic stimulation to the myocardium related to the overall sympathoadrenal response associated with apneas. On the other hand, α-adrenergic stimulation associated with the sympathoadrenal response to apneas could restrict the degree to which coronary vasodilation occurs during apneas (17). It is difficult to measure the relationships among MVO2, CBF, and regional ischemia in patients with sleep apnea. Hence animal models have been developed to examine these factors (11, 19). In one study on anesthetized animals, regional myocardial ischemia was observed during apneas when coronary vasodilatory reserve was limited (19). However, the cardiovascular response in the anesthetized animals was different from that in sleep-apnea patients. Specifically, blood pressure decreased in the anesthetized animals during apneas, and anesthesia blunts the sympathoadrenal response to apneas and the degree to which intrathoracic pressure decreases during apneas.

We (5) have developed a preparation using sedated animals in which the hypertensive response during apnea is mimicked and swings in intrathoracic pressure during apneas are in the clinical range. We used this preparation to examine the relationships among arterial hypoxemia, CBF, MVO2, myocardial ischemia, and sympathoadrenal stimulation during apneas. We tested the following hypotheses: 1) during obstructive apneas (OAs), there is a substantial increase in both MVO2 and CBF; 2) CBF increase is due to metabolic factors (e.g., hypoxemia and hypercapnia) rather than increased sympathetic tone; and 3) regional ischemia can develop during apneas if coronary vasodilator reserve is limited.

METHODS

All methods, protocols, anesthesia, and sedation were approved by the local Institutional Animal Care and Use Committee in accordance with National Institutes of Health guidelines. Studies were carried out in two phases: instrumentation and data collection.

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Instrumentation phase. Nine conditioned female Yorkshire farm pigs (Sus scrofa) weighing 16–22 kg were anesthetized with ketamine (4 mg/kg) and xylazine (2 mg/kg), intubated, and placed on mechanical ventilation with tidal volume of 12 ml/kg and respiratory rate of 15 breaths/min. Anesthesia was maintained using halothane (0.5–0.75%) in an O2-enriched ml/kg and respiratory rate of 15 breaths/min. Anesthesia was and placed on mechanical ventilation with tidal volume of 12

If collateral venous connections to the great cardiac vein and reserve (see below).

For measurement of the pH of myocardium perfused by the proximal to the flow probe, which served for precise control of the LAD lumen diameter using a threaded air-filled locking syringe attached to the balloon occluder.

By use of two pairs of sonomicrometer crystals (Crystal Biotech), regional LV myocardial shortening was measured in myocardium perfused by both the LAD and left circumflex (CFX) coronary arteries. LAD- or CFX-perfused myocardium was delimited by observation of coronary artery distribution and myocardial cyanosis secondary to 10-s occlusion of the LAD or CFX artery. The crystals in each pair were placed into the midmyocardium in the orientation of the superficial fibers, at a depth of 0.5 cm and a distance of 1.5–2.5 cm, and stabilized by suturing of an overlying mesh of 6–0 nylon. Regional myocardial ischemia leads to a severe decrease in percent regional shortening or even regional systolic lengthening (systolic bulging or negative shortening) (1). The position of all crystals and probes was confirmed at autopsy after the experiments.

In this study, a Khuri tissue monitor system (Vascular Technologies, North Chelmsford, MA) was used to measure regional intramyocardial (extracellular) pH, which has been shown to correlate with histochemical markers of ischemia (8). With use of this system, preliminary studies in our laboratory have shown that the drift was ≤0.1 pH unit over 6 h, and the 95% response time to a step change was 15 s (18). For measurement of the pH of myocardium perfused by the LAD and CFX arteries, pH and temperature probes were inserted into and secured to myocardium perfused by these vessels, respectively, close to the sonomicrometer crystal pairs. Regional CFX-perfused myocardial pH and contraction served as controls for LAD-perfused myocardium during experiments on regional restriction of coronary vasodilator reserve (see below).

The coronary sinus and great cardiac vein were identified. If collateral venous connections to the great cardiac vein and coronary sinus from the hemiazygous vein were identified, these venous connections were ligated. For measurement of blood-gas tensions of the coronary sinus, by use of a Seldinger technique, a small heparin-filled catheter sealed with a plastic plug, guided with a bent 16-gauge needle, was tunneled through the myocardium into one branch of the great cardiac vein and advanced into the coronary sinus approximately at the junction of the coronary sinus and the great cardiac vein. Blood-gas samples were taken from the catheter and the right atrium to verify the position of the catheter. The catheter was secured by suture.

A heparin-filled plastic catheter sealed with a plastic plug was inserted into the left atrial appendage and secured by purse-string suture. At the data-collection phase (see below), this catheter served for injection for thermodilution CO measurement and insertion of an LV catheter. For continuous measurement of CO, the ascending aorta was separated from the pulmonary artery, and a sterile square-wave electromagnetic flow probe (Biotronix Manufacturing) was placed around the ascending aorta (size 14–18 mm depending on aortic diameter).

A 2-cm-long latex balloon, on the end of multihole polyethylene PE-100 tubing, was placed along the lateral surface of the left lung for measurements of intrathoracic pressure. This balloon system has been used and validated previously in this laboratory (18, 19). A volume of air put into the balloon was the least volume on the flat portion of the pressure-volume curve of the balloon.

The wires and catheters were wrapped in plastic, brought through the chest wall, and placed in a subcutaneous pocket. A chest tube was placed percutaneously. The thoracotomy was closed in layers. The chest was then evacuated by using positive pressure, and the chest tube was removed. The animal was allowed to awaken and was placed in an individual pen. Antibiotic prophylaxis with penicillin (24,000 U/kg im) and dihydrostreptomycin (30 mg/kg im) was administered at surgery and on the following day. Morphine sulfate (5 mg im) was given every 6 h during the first 24 h for pain control.

Data collection phase. Five to seven days after initial surgery, the animals were anesthetized with an injection of ketamine (2 mg/kg im) and were monitored with a pulse oximeter. This included 30–40 min of surgical anesthesia. Animals were intubated and mechanically ventilated. Tidal volume was set to 10 ml/kg, and respiratory frequency was adjusted to maintain arterial PCO₂ in the physiological range.

With the pig under local anesthesia with 2% lidocaine, a large-bore catheter was placed via cutdown into the right femoral vein for administration of fluids and medications. A 7-F thermistor-tipped catheter was inserted into the femoral artery and advanced into the ascending aorta for measurement of mean arterial pressure (MAP), measurement of CO by thermodilution, and blood-gas sampling.

The subcutaneous pocket was opened under local anesthesia, and the wires and catheters were exposed. The end of the left atrial catheter was exposed, and the plastic plug was replaced with a plastic head with a one-way valve and sidearm, which served for insertion of a 5-F micrometer-tipped catheter (Millar Instrument, Houston, TX) into the LV for high-fidelity recording of LV pressure. The aortic flow probe was calibrated against simultaneous measurements by thermodilution, in which 5 ml of iced saline were injected into the left atrium via the sidearm of the left atrial catheter and blood temperature was sampled via the femoral arterial catheter.

The cutdowns were closed, and the animal was placed on its right side. A continuous intravenous drip with a mixture of 0.9% alfaxalone and 0.3% alfadolone (Saffan, Pittman-Moore,
Oxbridge, Middlesex, UK; 3 mg·kg$^{-1}$·h$^{-1}$ total steroid) was instituted. This served to maintain a constant level of sedation once the animals came out of the surgical plane of anesthesia.

Experimental protocols. OAs were caused by occluding the endotracheal tube for 30 s at end expiration (apnea phase) and then releasing the occlusion to allow spontaneous breathing for 30 s (interapnea interval). An apneic-interapneic cycle was thus defined as the 1 min that it took to allow apneic phase and interapneic interval. Eight cycles were repeated for each specified condition before data were collected.

We tested the effects of OA under the following four conditions: 1) room air breathing (RA); 2) 100% O$_2$ administered to the endotracheal tube (O$_2$); 3) RA after CS of the LAD artery (CS); and 4) RA after hexamethonium (Hex; 5 mg/kg). Preliminary studies demonstrated that the dose of Hex used here was enough to produce maximal autonomic blockade in these studies. CS was produced as follows. First, vasodilatory flow reserve in the LAD artery was confirmed by observing a vigorous hyperemic response after 10 s of complete LAD coronary occlusion produced by using the balloon occluder. Once LAD flow had returned to baseline, the 10-s complete occlusion was repeated. At the end of this time, air was slowly withdrawn from the pneumatic occluder until LAD flow returned to a level no greater than the preocclusion level. Thus critical CS was defined functionally as stenosis sufficient to abolish the LAD flow reserve but to keep the flow within 15% of its preocclusion level. The meaning of the word “critical” is that vasodilatory reserve is lost, since the coronary bed distal to the stenotic segment is already maximally dilated, but CBF is maintained. A consequence of the technique is that normal coronary autoregulation is abolished.

Data collection and analysis. Data, including arterial and coronary sinus blood gases, intrathoracic pressure, arterial and coronary sinus blood gases, intrathoracic pressure, aortic blood pressure, CO, LAD flow, regional myocardial pH, and coronary vascular resistance (CVR) of the myocardial region perfused by the LAD artery was estimated as the difference between MAP and mean right atrial pressure divided by LAD flow. For each pair of crystals (in LAD and CFX area), we measured regional myocardial lengths at end diastole (EDL) and end systole (ESL). Percent fiber shortening was calculated as [(EDL – ESL)/EDL] × 100. End diastole was defined as the point of rapid upstroke of the LV pressure tracing. End systole was defined as the zero crossing of the aortic flow after ejection.

Data were compiled and expressed as means ± SE. LAD flow, CVR, and MVO$_2$ were normalized to baseline values. For each condition, statistical significance was tested using one-way ANOVA for repeated measures. If significance was found, a Newman-Keuls procedure was used to analyze the differences between each pair of values. Two-way ANOVA was used to assess statistical significance of differences between conditions. The null hypothesis was rejected at the 5% level.

RESULTS

There were no significant differences between baseline and recovery in any respiratory or hemodynamic variables for any conditions. Thus the preparation demonstrated no time-related deterioration.

Intrathoracic pressure and arterial blood-gas tensions. Table 1 demonstrates the changes in maximal intrathoracic pressure swings and blood-gas tensions. During apnea, all conditions were associated with similarly exagger-

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<th>Table 1. Intrathoracic pressure and arterial blood-gas tensions in sedated pigs with periodic obstructive apnea</th>
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Values are means ± SE. RA, room air breathing; O$_2$, breathing 100% O$_2$; CS, breathing room air after critical coronary stenosis; Hex, breathing room air after hexamethonium; ITP, maximal intrathoracic pressure. ITP was measured during late apnea of 8th apneic-interapneic cycle. Arterial blood-gas samples were taken during 10-s period from late apnea to early interapnea of 8th apneic-interapneic cycle. $^*P < 0.01$, compared with baseline.
ated inspiratory swings in intrathoracic pressure (31–36 Torr) and a similar degree of hypercapnia and decreases in pH. In the three conditions with room air (RA, CS, and Hex), OAs led to moderate hypoxemia. However, there was no hypoxemia during apneas with O2 supplementation (O2).

Systemic hemodynamics and global cardiac function. MAP (Fig. 1) increased significantly relative to baseline at all points of the apneic-interapneic cycle with RA, CS, and O2 (both \( P < 0.001 \) but not with Hex. MAP was significantly higher with RA than with O2 (\( P < 0.05 \)) and significantly lower with Hex than in the other three conditions (\( P < 0.001 \), respectively). Relative to baseline, HR (Fig. 2) increased significantly with RA at late interapnea (\( P < 0.05 \)) and with Hex at all points of the cycle (\( P < 0.001 \)) but remained unchanged relative to baseline with O2 and CS. Over the cycle, there were significant differences in HR between late apnea (lowest) and late interapnea (highest) in all the conditions (\( P < 0.05 \), respectively) except CS. With Hex, baseline HR was significantly greater than in the other three conditions (\( P < 0.01 \), respectively). Both CO (Fig. 3) and SV (Fig. 4) decreased significantly relative to baseline at late apnea and early interapnea with RA (both \( P < 0.001 \)) and at all points over the apneic-interapneic cycle with CS (both \( P < 0.001 \)). The changes in CO (\( P < 0.05 \)) and SV (\( P < 0.01 \)) were greater with CS than with RA. CO and SV remained unchanged during the cycle relative to baseline with O2 or Hex, although Hex was associated with higher CO at baseline than in the other three conditions (\( P < 0.001 \), respectively). Relative to baseline, SVR (Fig. 5) increased significantly at all points in the apnea-interapnea cycle and under all conditions except Hex. With Hex, baseline SVR was decreased compared with the other conditions (\( P < 0.001 \)), and there was no change in SVR with apneas.

LAD flow and CVR. Normalized LAD flow (Fig. 6) increased significantly at all the points of the apneic-interapneic cycle with both RA and Hex relative to baseline (both \( P < 0.001 \)) except at early apnea with RA. There were no significant differences between RA and Hex. There was no significant change in LAD flow relative to baseline with O2 or Hex. With Hex, baseline HR was significantly greater than in the other three conditions (\( P < 0.01 \), respectively). Relative to baseline, SVR (Fig. 5) increased significantly at all points in the apnea-interapnea cycle and under all conditions except Hex. With Hex, baseline SVR was decreased compared with the other conditions (\( P < 0.001 \)), and there was no change in SVR with apneas.

**Significance compared with baseline, \( P < 0.01 \). Note that some SE bars were not shown to avoid overlapping.

![Fig. 1. Effects of periodic obstructive apneas on mean arterial pressure. RA, room air breathing; O2, breathing O2; CS, breathing room air after critical coronary stenosis; Hex, breathing room air after hexamethonium; Base, baseline; EAP, early apnea; LAP, late apnea; EIA, early interapnea; LIA, late interapnea; Recov, recovery. Data are means ± SE; each datum point represents 5 s of data. **Significance compared with baseline, \( P < 0.01 \). Note that some SE bars were not shown to avoid overlapping.](http://jap.physiology.org/)

![Fig. 2. Effects of periodic obstructive apneas on heart rate. See Fig. 1 legend for further details. Significance compared with baseline: \*\( P < 0.05 \); **\( P < 0.01 \). ††Significance of baseline values compared with Hex, \( P < 0.01 \).](http://jap.physiology.org/)

![Fig. 3. Effects of periodic obstructive apneas on cardiac output. See Fig. 1 legend for further details. See Fig. 2 legend for explanation of symbols.](http://jap.physiology.org/)
over the apneic-interapneic cycle with O₂ and CS. As noted above, with CS, LAD flow cannot reflect changes in global CBF, and we cannot calculate CVR and MVO₂ with CS. Normalized CVR (Fig. 7) decreased significantly at all points of the apneic-interapneic cycle with Hex (P < 0.001) and at late apnea and early interapnea with RA (P < 0.001). There were no significant differences between RA and Hex in maximal CVR change, although, with Hex, the maximal decrease in CVR occurred in late apnea and, with RA, the maximal change occurred in early interapnea. CVR remained unchanged during the apneas with O₂.

MVO₂. In six pigs, we successfully obtained blood samples from the coronary sinus. Figure 8 shows that there was no significant change in MVO₂ during apnea relative to baseline in the three experimental conditions in which this could be calculated (RA, O₂, and Hex).

Fig. 4. Effects of periodic obstructive apneas on stroke volume. See Fig. 1 legend for further details.

Fig. 5. Effects of periodic obstructive apneas on systemic vascular resistance. See Fig. 1 legend for further details. See Fig. 2 legend for explanation of symbols.

Fig. 6. Effects of periodic obstructive apneas on left anterior descending coronary (LAD) artery flow (normalized as baseline, n = 5). Apneas, period from late apnea, and early interapnea, in which arterial and coronary sinus blood-gas samples, were collected. See Fig. 1 legend for further details.

Fig. 7. Effects of periodic obstructive apneas on coronary vascular resistance (normalized as baseline). See Fig. 1 legend for further details.
Regional function. Figure 9 shows regional myocardial contractile function expressed as segmental shortening for LAD- and CFX-perfused myocardium. Segmental shortening significantly decreased during apneas only in LAD-perfused myocardium with CS (P < 0.01). With RA, O₂, and Hex, there were no significant changes in either region, and there were no changes in regional shortening in CFX-perfused myocardium with CS of the LAD artery.

Regional intramyocardial pH. Regional intramyocardial pH is presented in Fig. 10. In CFX-perfused myocardium, there were no significant changes under any conditions. During apneas, regional pH decreased significantly only in LAD-perfused myocardium with CS.

**DISCUSSION**

There are four major findings of the present study: 1) CO decreased and LV afterload increased during OA with RA and CS, a response that was abolished with O₂ and Hex; 2) during apneas, LAD flow increased and CVR decreased with RA and Hex but were unchanged with O₂; 3) during apneas, MVO₂ remained unchanged even though LV afterload increased; and 4) with CS, OAs caused regional myocardial ischemia, as indicated by decreased intramyocardial pH and segmental shortening of LAD-perfused myocardium. The ensuing discussion considers these points in the light of the limits of the experimental preparation and currently available literature.

Experimental preparation. The present model allowed us to continuously measure CBF and global and regional LV functional responses to OAs on a beat-to-beat basis. It demonstrated good stability over time, as shown by the fact that there were no differences in any cardiorespiratory parameters between baseline and recovery.

Because the model utilized preinstrumented sedated pigs, cardiorespiratory depression caused by anesthesia and major surgery was minimized. Thus swings in intrathoracic pressure with OA were greater than those seen in the anesthetized dog model (19) and were comparable to those seen in sleep-apnea patients (13). Compared with some other sedative-anesthetics, alfaxalone-alfadoline produces less suppression of baroreceptor and chemoreceptor function (2). In the doses used here, there is preservation of corneal reflexes, spontaneous ventilation, and responses to very loud noises and severely painful stimuli. In our previous study (5), we also doubled the dose of alfaxalone-alfadoline in several animals and observed the same response in MAP and HR to apneas, suggesting that the changes seen were not due to a nonspecific response to pain or...
discomfort or being inadequately sedated. However, although the present model reproduces many of the features of human OA (large swings in intrathoracic pressure, periodic hypoxemia, increased LV afterload, and decreased CO), in our previous study, electroencephalograph (EEG) monitoring suggested that there was no postapneic arousal phase, and changes due to changing sleep state are not observed (4). Thus changes in MVO2 and CBF related to these factors are not seen in the present model and should be considered an additional strain on the myocardium in human disease.

Systemic hemodynamics and global cardiac function. Here we discuss the global changes seen with RA, O2, and Hex. Apnea-induced changes under the CS conditions are discussed below.

As demonstrated in our previous study (5), OA during RA was associated with a marked increase in LV afterload as indicated by MAP and SVR and an ~20% decrease in CO and SV at late apnea compared with baseline. Eliminating hypoxemia (O2) and autonomic blockade (Hex) resulted in the diminution of the increase in LV afterload and blunting of the CO and SV response. These findings indicate that the mechanism responsible for decreased CO and SV was the increase in LV afterload expressed as MAP and/or SVR. Although detailed studies of contractility were not done, absence of a change in segmental shortening during apneas is consistent with absence of change in myocardial contractility as a cause of decreased SV. As in the present study, many previous clinical and experimental studies have observed an inverse correlation between oxyhemoglobin saturation and MAP during apneas (3). Thus our results are consistent with data demonstrating that the primary stimulus to increased MAP during apneas is hypoxemia.

As in our previous study using paralyzed pigs (5), the present study also showed that, with O2, there was a small residual increase in MAP during apneas, suggesting that factors besides hypoxemia can play a role in the hypertensive response to apneas. The stimulus for the hypertensive response during hypoxic apneas is not clear. There was no sign of arousal observed in this model by monitoring the EEG (our unpublished data). Although hypercapnia can lead to increased MAP, it also leads to increased HR, decreased SVR, decreased myocardial dimensions, and increased CO (4). Because none of these secondary findings were present during apneas with O2, it is unlikely that hypercapnia is the hypertensive stimulus during apneas in this model. However, alterations in thoracic mechanoreceptor or central circulatory reflexes could possibly have influenced MAP during apneas in our model.

Slowing of HR during late apnea compared with the early part of apnea of end interapnea is well known in OA patients (7, 13, 24, 27) and animal models (6). This slowing is related to enhanced vagal tone related at least in part to hypoxemia (22). The responses that we observed are consistent with these studies in that, during the apneic-interapneic cycle, minimal HR was immediately before resumption of ventilation (late apnea). Zwillich et al. (27) suggested that the bradycardia of OA was correlated to the severity of hypoxemia. In the present study, the difference in HR between late interapnea and late apnea was not significant with O2, results consistent with the postulate of Zwillich et al. (27). Hypoxia could lead to HR slowing through secondary baroreceptor responses as well as primary vagal stimulation via the carotid chemoreceptors (22).

After autonomic blockade with Hex, we observed a rise in baseline HR and a further rise in HR during apneas. The rise in baseline HR could have been due to withdrawal of vagal tone because of autonomic ganglionic blockade. The reasons for the secondary increase in HR during apneas with Hex are not as clear. Hex has been shown to prevent ganglionic neurotransmission by interfering with the postsynaptic action of acetylcholine either through nicotinic receptors or through ionic channels (26). However, Hex does not antagonize post-ganglionic muscarinic receptors that may mediate a slow excitatory postsynaptic potential (26). It has been postulated that, in the presence of ganglionic blocking drugs, postganglionic muscarinic receptors may take...
over the functional role of ganglionic neurotransmission normally carried out by the nicotinic receptor (26). These may possibly have cardiovascular effects. Furthermore, we have previously observed systemic catecholamine release during apneas even after Hex (6), although the site of release is unknown. Additionally, there may be a local metabolic release of catecholamines from myocardium independent of central sympathetic activation (20). Finally, there may be release of catecholamines from autonomic ganglia. This is because Hex does not antagonize the muscarinic receptors on small, intensely fluorescent cells in autonomic ganglia and such cells release catecholamines as their neurotransmitter (26). Thus increased HR during apneas with Hex could relate to catecholamine release at any of a number of sites unopposed by vagal tone.

Clinical studies have suggested increased activity of the sympathetic nervous system in obstructive sleep-apnea patients (3, 9, 23). Furthermore, relatively brief periods of asphyxia (i.e., Mueller maneuver and breath hold) also substantially increase sympathetic activity (14). Data suggest that increased sympathoadrenal activity is a cause of hypertension (3) and thus may be a cause of high cardiovascular morbidity and mortality in these patients. Treatment with continuous positive airway pressure is associated with decreased muscular sympathetic activity (23) and plasma catecholamine levels (9). The present study also demonstrates the primary sympathoadrenal response during OA, since Hex eliminated OA-induced changes in MAP, SVR, CO, and SV. Thus sympathetic activation is the major mechanism mediating the cardiovascular responses to OA. These include increased LV afterload (MAP), which leads to decreased CO and SV.

LAD flow and CVR. With RA, LAD flow rose 86% and calculated CVR fell 43% at early interapnea relative to baseline. Because both the responses were completely eliminated with O2 supplementation, LAD flow response during OAs is primarily determined by hypoxemia. Furthermore, because the changes in CVR and CBF during apneas with Hex were the same as those with RA, there appears to be little role for sympathetic stimulation in the determination of CBF during apneas. Thus the changes in CBF and CVR during apneas are mediated by hypoxia, probably through production of vasoactive mediators or direct effects of hypoxia. In a study on inspiratory loading from this laboratory, small increases in CBF were observed during exaggerated inspiratory efforts in the absence of hypoxemia (10). In that previous study, however, increased coronary flow was attributed to hypercapnia, which was considerably greater (60–66 Torr) than observed in the present study. Thus the absence of coronary vasodilation during hyperoxic apneas (O2) is not inconsistent with these previous results. Possibly, had hyperoxic apneas been associated with greater hypercapnia, some coronary vasodilation would have been observed. In sleeping pigs, Pinto et al. (16) reported no significant change in LAD flow during brief periods (10 s) of upper airway occlusion. Although these data appear contradictory to the present study, O2 saturation was not assessed in the Pinto study. Furthermore, the authors themselves stated that “it is unlikely that...pigs developed hypoxemia during the...induced occlusion.” Thus it is unlikely that the pigs in the Pinto study were hypoxic enough to lead to changes in CBF.

It has been suggested that shifts in β-adrenergic tone during sleep can be responsible for sleep stage-related changes in CBF (11, 12). Indeed, CBF increases during arousal from apnea can be eliminated with β-adrenoceptor blockade (12). In the latter study (12), there was no marked desaturation during apnea, suggesting that sympathoadrenal tone determines CBF during sleep stage shifts. As already stated, our model does not permit assessment of this aspect of sleep apnea. However, sleep stage-related shifts in CBF were far smaller (13–22% increase in CBF) than hypoxemia-related changes in CBF observed in the present study. Thus the major changes in CBF during human sleep apnea are most likely related to local myocardial effects of hypoxemia.

MVO2. We found no significant change in MVO2 during apnea relative to baseline. Theoretically, MVO2 should be a function of HR and afterload (25). Under all conditions in which MVO2 could be measured (RA, O2, and Hex), there were increases in one or both of these factors during apneas. Furthermore, increases in LV afterload related to large negative swings in intrathoracic pressure during apneas might also have been expected to increase MVO2 (15). Thus it is unexpected that we failed to find increased MVO2 during apneas in our study.

First, with regard to the effect of negative swings in intrathoracic pressure during apneas, our data are consistent with previous data in anesthetized animals during inspiratory resistive loading (10). In those previous studies, failure to find increased MVO2 was attributed to the fact that overall mean intrathoracic pressure changed little despite exaggerated inspiratory swings. It is possible that similar factors were operative here. Even though there were exaggerated decreases in intrathoracic pressure during apneas, overall inspiratory time was usually less than one-third of the total cycle time and mean intrathoracic pressure probably changed little. Another factor influencing the measurement of MVO2 could have been the fact that myocardial venous blood was withdrawn over only part of the apneic-interapneic cycle. In some of experiments, however, coronary sinus blood was also withdrawn over the entire apnea cycle, with no change in the calculated MVO2. During hypoxemia, there may be an increase in the efficiency of myocardial O2 utilization so that a given work load may be accomplished at lower MVO2 (25). Thus increased myocardial work during RA apneas, when changes in MAP were the greatest, may not have been associated with increased MVO2. Changes in MAP and HR during O2 and Hex conditions were relatively small as a percentage of baseline and might not have been expected to produce large changes in MVO2. Finally, decreased SV can lead to decreased MVO2 (25). This may have counterbalanced the tendency for MVO2 to increase during RA apneas.
CS. During apneas under CS conditions, there were clear signs of regional myocardial ischemia. These were decreased regional myocardial pH and shortening in myocardium perfused by the stenotic coronary artery (LAD) and not in the control region perfused by the CFX coronary artery. With CS, during apneas, there were greater decreases in CO and SV than with RA apneas, despite the fact that both RA and CS were matched for blood-gas changes and systemic hemodynamic changes during apneas. Most likely, the greater falls in CO and SV with CS apneas were due to the effects of regional ischemia on global LV function; i.e., with part of the myocardium ischemic, the overall pumping ability of the LV was diminished.

The most likely cause of regional ischemia with CS was imbalance of myocardial O2 supply-demand balance due to decreased O2 supply secondary to decreased O2 content of arterial blood. With CS, decreased arterial O2 content could not be compensated for by an increase in CBF with CS, a situation leading to ischemia. In the previous paper from this laboratory demonstrating myocardial ischemia during apneas (19), it was speculated that increased MVO2 played a role in the genesis of ischemia during CS. However, MVO2 was not measured in that previous study. We are unaware of other studies measuring MVO2 during apneas. Although we could not measure MVO2 during CS conditions, there is no reason to believe that it would have changed. During RA conditions, changes in arterial blood gases, HR, and afterload were similar to those during CS conditions. In the ischemic area, if anything, MVO2 would have been decreased. Thus increased MVO2 in LAD-perfused myocardium is unlikely to be a factor upsetting the O2 supply-demand balance and leading to ischemia.

In the presence of CS, even though there was an increase in MAP, there was no change in CBF. Thus CBF in LAD-perfused myocardium remained fixed during CS, even though perfusion pressure increased. Although decreases in perfusion pressure during apneas were associated with decreased CBF during CS in anesthetized dogs (19), the converse was not true in the present study. Possibly the presence of orifice blood flow with CS limited the degree to which CBF could increase during CS with increases in coronary perfusion pressure. Hence, increased perfusion pressure during apneas could not compensate for limited myocardial vasodilatory reserve during apneas (CS).

Ischemia occurred within 8 min (8 cycles) of the onset of apneas in CS conditions. Given the changes in pH associated with apneas, saturation would have decreased to ~78% in our animals. We did not assess the effects of more modest changes in O2 saturation on regional ischemia. Scharf et al. (19) noted the development of some ischemia in their anesthetized dogs even while receiving O2. However, these changes were associated with pulsus paradoxus-induced decreases in MAP, which were not observed in the sedated pigs of the present study. This difference in blood pressure response probably reflects a difference between general anesthesia and sedation as well as possible species differences. Clearly, the limits of O2 desaturation tolerated in the presence of CS should be determined, and this is an important clinical question. Furthermore, it is not known whether ischemia induced by apneas with CS would lead to myocardial infarction.

Conclusions. We examined the changes in LV myocardial circulation, metabolism, and contractile function during periodic OA in previously instrumented sedated pigs. Apneas were associated with increases in LV afterload, increased CBF, and decreased CO and SV. Most of this response was related to the hypoxic stimulus and was mediated via the autonomic nervous system. Increases in CBF during apneas were primarily determined by the local effects of hypoxemia and were independent of changes in coronary perfusion pressure or autonomic activity. LV MVO2 during apnea remained unchanged despite changes in loading conditions. In the presence of limited coronary flow reserve, decreased O2 supply during OAs led to acute myocardial ischemia.

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