Comparative hemodynamic effects of periodic obstructive and simulated central apneas in sedated pigs

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Comparison of hemodynamic effects of periodic obstructive and simulated central apneas in sedated pigs. J. Appl. Physiol. 83(2): 485–494, 1997.—It has been speculated that because of increased left ventricular (LV) afterload, decreased intrathoracic pressure (ITP) is responsible for decreased cardiac output (CO) in obstructive sleep apnea. If this were true, then obstructive apnea (OA) should have a greater effect on CO than would central apnea (CA). To assess the importance of decreased ITP during OA, we studied seven preinstrumented sedated pigs with OA and simulated CA that were matched for blood gases and apnea periodicities (with 15- or 30-s apnea duration). Compared with OA, CA with 30-s apnea duration produced comparable decreases in heart rate (from baseline to end apnea: OA, 106.6 ± 4.8 to 93.4 ± 4.4 beats/min, P < 0.01; and CA, 111.1 ± 6.2 to 94.0 ± 5.2 beats/min, P < 0.01) and comparable increases in LV end-diastolic pressure and LV end-diastolic myocardial segment length but greater increases in mean arterial pressure (97.1 ± 3.7 to 107.7 ± 4.3 Torr, P < 0.05; and 97.3 ± 4.8 to 119.3 ± 7.4 Torr, P < 0.01) and systemic vascular resistance (2,577 ± 224 to 3,346 ± 400 dyn·s·cm⁻², P < 0.01; and 2,738 ± 294 to 5,111 ± 1,181 dyn·s·cm⁻², P < 0.01) and greater decreases in CO (3.18 ± 0.31 to 2.74 ± 0.26 l/min, P < 0.05; and 3.07 ± 0.38 to 2.30 ± 0.36 l/min, P < 0.01) and stroke volume (32.2 ± 2.9 to 25.9 ± 2.4 ml, P < 0.05; and 31.5 ± 1.9 to 19.8 ± 3.1 ml, P < 0.01). Only CA increased LV end-systolic myocardial segment length. Since no increases were observed with 15-s apnea duration. We conclude that CA produced greater depression of CO and greater changes of afterload-related LV dysfunction than did OA. Therefore, decreased ITP was not the dominant factor determining LV function with apneas.

sleep apnea; left ventricular function; hypoxia

SLEEP APNEA, which has high prevalence and wide-ranging sequelae, is increasingly being recognized as a public health problem (14). Numerous investigations have explored various aspects of acute cardiovascular changes induced by sleep apnea. For example, the oscillation of heart rate (HR) and systemic arterial pressure during apneas has been well documented (2). However, the effects on left ventricular (LV) function are not well understood.

The interactions of several factors, including intrathoracic pressure (ITP), systemic hypoxemia, and disruption of sleep architecture, have been reported to be responsible for acute cardiovascular effects of obstructive sleep apnea (2). However, the relative importance of each factor remains unclear. Inspiratory ITP may decrease considerably during obstructive apneas (OAs) (10). This leads to increased right ventricular preload (venous return) and can produce substantial inspiratory increases in right ventricular end-diastolic pressure and stroke volume (SV) (17). In addition, it has been suggested that the large inspiratory swings in ITP that occur with OA lead to increased LV afterload and may contribute to decreased cardiac output (CO) during apneas (5, 25). When sustained decreases in ITP (Mueller maneuver) are associated with increased LV afterload (16, 18), the effects of phasic swings in ITP may be dominated by preload (27). Several recent reports suggest that mechanical factors play relatively minor roles in the oscillation of mean arterial pressure (MAP) during the apnea and the interapneic phase (12, 13, 27, 30). In this regard, apneas are associated with changes in sympathoadrenal tone due to hypoxia and arousal. It is possible that these reflex effects are more important than are changes in LV function due to mechanical effects (decreased ITP).

To evaluate the role of decreased ITP in influencing the cardiac effects of apneas, we used previously instrumented sedated pigs and studied the effects of two types of apneas matched for periodicity and blood-gas changes: OA (with decreased ITP) and simulated central apneas (CAs; without changes in ITP). We tested the hypothesis that because of decreasing ITP, which would act additively with blood-gas changes, the effects of OA on LV function would be more severe than those of CA.

METHODS

The study was carried out in two phases: sterile instrumentation and data collection. 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.

Instrumentation Phase

Seven conditioned female Yorkshire farm pigs weighing 16–22 kg were anesthetized with ketamine (20 mg/kg) and xylazine 2 (mg/kg), intubated, and placed on mechanical ventilation with tidal volume of 12–18 ml/kg and respiratory rate of 15 breaths/min. Anesthesia was maintained by using halothane (0.5–0.75%) in an enriched oxygen mixture (35–45%) throughout. HR and oxygen saturation were continuously monitored by using a pulse oximeter attached to the ear. The animals were turned into the right lateral decubitus position for left thoracotomy. Under sterile conditions, the chest was opened in the sixth left intercostal space, and the fifth rib was cut near the sternum. The pericardium was widely incised. Bretylium tosylate (100 mg) was administered intravenously to prevent arrhythmias while the pericardium and heart were manipulated. After the ascending aorta was separated from the pulmonary artery, a sterile square-wave electromagnetic flow probe (Biotronix) was placed around the ascending aorta (size 14–18 mm depending on the size of the aorta). To measure the change of LV myocardial segment length, one pair of sonomicrometer crystals (Crystal Biotech, Hopkinton, MA) was placed on the epicardium on the anterior...
LV free wall in the orientation of the superficial fibers. Crystals were placed ~3 cm apart, ~1 cm from the atrial-ventricular septum. The crystals were stabilized by suturing an overlying mesh of 5-0 nylon. A 2.5-mm-inner-diameter heparin-filled plastic catheter sealed with a plastic plug was inserted into the left atrial appendage and secured by purse-string suture. The wires and catheter 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, and the chest tube was removed. The animal was allowed to awaken and was placed in an individual pen. Antibiotic prophylaxis, penicillin (24,000 U/kg) and dihydrostreptomycin (30 mg/kg), was administered intramuscularly at surgery and on the following day. Morphine sulfate (5 mg) was given intramuscularly every 6 h during the first 24 h for pain control.

Data Collection Phase

Five days after the initial surgery, the animals were anesthetized with an intramuscular injection of ketamine (2 mg/kg). This induced 30–40 min of surgical anesthesia. Animals were intubated and breathed through an endotracheal tube for the duration of the studies. A large-bore catheter was inserted into the femoral artery via the sidearm of the left atrial catheter, and a plastic head with a one-way valve, a micrometer-tipped catheter (Millar Instrument, Houston, TX) and connected to a differential transducer (Validyne, Northridge, CA). The wires and catheter were calibrated at each baseline by using the thermodilution technique. SV, LV pressure, and myocardial segment length were measured as mean values from blood pressure tracing, and CO was measured from Qao. The flow probe signals were calibrated at baseline by using commercially available software (ACQ4600, Gould, Cleveland, OH). The following data were recorded: blood pressure, LV pressure, instantaneous Qao, SV, LV myocardial segment length, and airway pressure.

Data were analyzed off-line by using commercially available software (View II, Gould). Data during the fifth apnea-interapnea cycle were taken at specified times (Fig. 1) as follows: early apnea, late apnea, early interapnea, late interapnea, midapnea (for 30/30), and end interapnea (for 15/45). Each data point represented a 5-s period. HR and MAP were measured as mean values from blood pressure tracing, and CO was measured from Qao. The flow probe signals were calibrated at each baseline by using the thermodilution technique. SV, LV pressure, and myocardial segment length were measured in duplicate or triplicate on a beat-to-beat basis and at end expiration as seen on the airway pressure tracing. Both LV pressure and myocardial segment lengths were measured at end diastole (LVEDL) and end systole (LVESEL). End diastole was defined as the point of rapid upstroke of the LV tracing. End systole was defined as the zero crossing of the Qao after ejection. Systemic vascular resistance (SVR) was calculated as (MAP/CO)·79.9 (dyn·s·cm⁻²). For OA, we measured the largest difference between inspiratory and expiratory airway pressures during apnea. At constant lung volume, this is assumed equal to the maximum swing in ITP.

Statistical Analysis

Data were compiled and expressed as means ± SE. Differences between baseline and recovery, as well as between OA and CA at baseline and recovery, were assessed by using Student’s t-test for paired variates. One-way analysis of variance for repeated measures was used to test for significant differences between baseline and all points during the apnea-interapnea cycle, as well as to test changes within the apnea-interapnea cycle for each condition. Separate analyses were used to compare baseline with the apnea-interapnea and for comparisons of values within the apnea-interapnea cycle. If significance was found, a Newman-Keuls procedure was used to analyze the difference between each pair of values. Two-way analysis of variance was used for testing the differences between OA and CA from baseline to the apnea-interapnea cycle. The null hypothesis was rejected at the 5% level.
RESULTS

Blood Gases, Airway Pressure, and Preparation Stability

Table 1 demonstrates the changes in blood gases and airway pressure. OA induced exaggerated inspiratory swings in airway pressure during apneas. There were no significant differences in blood-gas values between recovery and baseline, or between OA and CA, for either periodicity. As expected, the longer the apnea duration the greater the change in blood-gas values and swings in airway pressure (for OA). In addition, there were no significant differences between baseline and recovery under any conditions for MAP, CO, HR, SV, LVEDP, LVEDL, LVESEL, or SVR. Thus this preparation demonstrated no time-related deterioration.

Hemodynamic Effects

Figures 2 and 3 demonstrate examples of airway pressure and hemodynamics at baseline and over the fifth apnea-interapnea cycle in a representative pig with OA (Fig. 2) and CA 30/30 (Fig. 3). With OA, there were fluctuations of airway pressure during the apneic phase. Both apnea types were associated with increases in MAP and LV pressure and lengths as well as decreases in HR, Q˙ao, and SV. CA (Fig. 3) caused greater changes in MAP, Q˙ao, and LV pressure and lengths compared with OA (Fig. 2), although blood gases at end apnea and apnea periodicity were the same.

We present the comparison of the hemodynamic values as follows: 1) changes relative to baseline, 2) changes within the apnea-interapnea cycle, 3) differences between OA and CA, and 4) differences between short- and long-duration apneas.

Changes during the cycle vs. baseline. Relative to baseline, MAP (Fig. 4) increased significantly except at end interapnea for periodicity 15/45 OA. CO (Fig. 5) was significantly lower than baseline only at late apnea and early interapnea for periodicity 15/45 for both OA and CA. However, for periodicity 30/30, CO was decreased significantly at almost all points in the apnea-interapnea cycle for both OA and CA. With OA, for both periodicities, HR (Fig. 6) was significantly less than baseline at all points except at late interapnea with 30/30 and at end interapnea with 15/45. However, with CA, HR decreased only at midapnea for 30/30 and late apnea for both periodicities. With CA, SV (Fig. 7) was significantly lower than baseline at every point during the cycle except at end interapnea with 15/45. For OA, SV was less than baseline only with 30/30 at late apnea. For both periodicities, LVEDP (Fig. 8) increased significantly at late apnea with OA and at every point for CA except at end interapnea with 15/45. With periodicity 30/30 for both OA and CA,

<table>
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<th>Variables</th>
<th>Obstructive Apneas</th>
<th>Simulated Central Apneas</th>
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<tr>
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<td>-2.5 ± 0.8</td>
<td>-20.5 ± 4.3*</td>
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<td>pH units</td>
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<td>Paco2, Torr</td>
<td>45.8 ± 0.6</td>
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Values are means ± SE with range in parentheses. ΔPaw, maximum difference between inspiratory and expiratory airway pressure during apnea; Pao2, arterial P o2; Paco2, arterial PCo2; 15/45, 15-s apnea and 45-s interapneic interval; 30/30, 30-s apnea and 30-s interapneic interval. *P < 0.01 compared with baseline. †P < 0.01 compared with 15/45.
LVEDL (Fig. 9) increased significantly at all points except at late interapnea for CA. With 15/45, LVEDL increased at late apnea and early interapnea for both apnea types and at early apnea with OA. LVESL (Fig. 10) increased significantly only at late apnea and early interapnea with CA of both periodicities but did not increase at all with OA. SVR (Fig. 11) increased significantly under all conditions and at all points except for late and end interapnea of OA 15/45.

Changes within the apnea-interapnea cycle. MAP (Fig. 4) did not change during the apnea-interapnea cycle compared with early apnea. CO (Fig. 5) decreased significantly relative to early apnea only with periodicity 30/30 for CA and only at early interapnea. HR (Fig. 6) decreased significantly relative to early apnea only at late apnea and with periodicity 30/30 for CA. SV (Fig. 7) decreased significantly relative early apnea only at early interapnea with CA for both periodicities.

Fig. 2. Polygraph recordings of obstructive apneas in a representative sedated pig. Displayed are blood pressure (BP), airway pressure (Paw), aortic flow (Qao), left ventricular pressure (LVP), stroke volume (SV), and left ventricular myocardial segment length (LVL); baseline, measurement before any apnea manipulation. Note that obstructive apneas caused large swings in Paw. Moreover, compared with baseline, there were higher systolic and diastolic BPs, LVP, and LVL but lower Qao and SV during apnea-interapnea cycle.

Fig. 3. Polygraph recordings of simulated central apneas in same pig used in Fig. 1. Note that simulated central apneas produced same response pattern as did obstructive apneas but more severe cardiovascular changes. Heart rate (not shown) was slower in this animal for central than for obstructive apnea. However, this was not characteristic of the entire study.
LVEDP (Fig. 8) increased relative to early apnea with CA 15/45 and relative to late apnea with CA and OA 30/30. LVEDL (Fig. 9) increased relative to early apnea with CA for both periodicities at late apnea and with CA 15/45 at early interapnea. There were no significant changes in LVESL (Fig. 10) compared with early apnea.

SVR (Fig. 11) increased relative to early apnea with CA for both periodicities at early interapnea. When changes from late apnea to early interapnea were compared with CA 30/30, there were significant increases in HR (P < 0.01) and SVR (P < 0.01) and decreases in LVEDL (P < 0.01). For OA, only LVEDP decreased from late apnea to early interapnea (P < 0.01).

OA vs. CA. With both periodicities, CA was associated with a significantly higher MAP (Fig. 4) and SVR (Fig. 11) than was OA. In addition, CA 30/30 caused greater decreases in CO (Fig. 5) and SV (Fig. 7) than did OA 30/30. For both periodicities of OA, there were significantly greater decreases in HR (Fig. 6) than for those of CA, but the minimum HR (at late apnea) was the same for both apnea types.

Effects of apnea periodicities. Compared with CA 15/45, CA 30/30 was associated with greater decreases in CO (late apnea, P < 0.05) and in SV (late apnea and early interapnea, both P < 0.05) and greater increases in SVR (late apnea, P < 0.05) and in LVEDP (early interapnea, P < 0.05). With OA, there were no significant differences in hemodynamics between the two periodicities.

**DISCUSSION**

In this study, we compared the hemodynamic responses to OA and CA when matched for apnea periodicities and blood-gas changes. There were three principal findings. 1) Both OA and CA were associated with decreased HR and CO and increased MAP compared with baseline. However, changes were more exaggerated with CA. 2) Although changes in preload were comparable under both conditions, changes in afterload were greater with CA. 3) Although increased apnea duration was associated with more severe alteration in blood gases, and, for OA, with greater swings in airway pressure, changes in MAP and HR were comparable to those of short-duration apneas. However, for CA, CO and SV decreased more, and LVEDP and SVR increased more, with long compared with short apnea duration.

**Experimental Preparation**

In the present study, we modified a previously described anesthetized dog model of OA and CA (19, 26–28). Because the preparation utilized preinstrumented sedated pigs, cardiorespiratory depression caused by anesthesia and acute major surgery were
minimized. Thus swings in ITP with OA were greater than those seen in the anesthetized dog model (Table 1; Refs. 19, 26, 28). Sleep apnea patients, as well as severe snorers, may generate changes in esophageal pressure of −37 to −60 Torr during the apneas (10). A number of authors have demonstrated significant changes in LV hemodynamics with sustained decreases in ITP of 20–40 Torr (11). In present study, with OA, changes in ITP as judged by the difference between inspiratory and expiratory airway pressures at iso-lung volume were comparable to these values.

Alphaxalone and alphadolone acetate (Saffan) is known to preserve autonomic components of the alerting reaction associated with chemoreceptor stimulation (8) and to produce minimal suppression of vagal and sympathetic activities associated with baroreceptor and chemoreceptor function (1). We observed that, with a continuous intravenous drip at 3 mg·kg⁻¹·h⁻¹, there was moderate sedation, but the animals preserved corneal reflexes, spontaneous ventilation, and responses to very loud noises and severely painful stimuli. We observed no signs of distress such as tachycardia during the paralysis phase, and we were careful to maintain a continuous drip. In several animals, we doubled the dose of sedative and observed the same response in blood pressure and HR reported here, suggesting that the observed changes were not due to a nonspecific response to pain or discomfort or inadequate sedation.

It would have been ideal to randomize the order in which animals received OA and CA. However, the wait for full recovery from paralysis prolonged the experiment considerably. We did reverse the order of applying CA and OA in two animals, and the results were not different from those of the other five.

There are several differences between clinical sleep apnea and our model. First, sedation is not equivalent to sleep. A previous study found spontaneous changes in cortical arousal during sedation with Saffan (21), such as spontaneous switch from predominantly delta to predominantly beta and theta waves. However, changes in the electroencephalogram state over the apnea-interapnea cycles suggestive of arousal reaction are not seen in this model (unpublished data). Second, our CA model differs from patients with CA during sleep. In patients, there is suppression of both afferent input from respiratory and chest wall mechanoreceptors as well as efferent output from respiratory centers. However, with paralysis-induced CA, afferent input from mechanoreceptors is eliminated, but efferent central output continues (20) and even increases progressively during apnea. Thus CA-mediated cardiorespiratory coupling continues. Although in anesthetized animals this leads to swings in MAP (27, 28) during the apnea, these swings were not observed in our sedated

Fig. 6. Effects of periodic apneas on heart rate. Each data point represents 5 s of data that end with times shown at data point. Other points were taken from fifth apnea-interapnea cycle. Arrow, end of apnea and beginning of interapnea phase. bpm, Beats/min. * P < 0.05 compared with baseline. ** P < 0.01 compared with baseline. *** P < 0.01 compared with early apnea.

Fig. 7. Effects of periodic apneas on stroke volume measured from aortic flow probe. Each data point represents 5 s of data that end with times shown. Other points were taken from fifth apnea-interapnea cycle. Arrow, end of apnea and beginning of interapnea phase. * P < 0.05 compared with baseline. ** P < 0.01 compared with baseline. *** P < 0.01 compared with early apnea.
animals. Finally, patients with sleep apnea usually take several large tidal volume breaths immediately after apnea termination. In contrast, our CA model was terminated by resumption of tidal volumes from the ventilator, which were unchanged from baseline. It is possible that differences in postapneic breathing pattern influenced the difference between OA and CA immediately after apnea termination, even though blood-gas values were identical at end apnea with OA and CA.

Hemodynamic Effects: Apnea Type

Although numerous investigations have explored the blood pressure and HR response to OA, because of the difficulties in measuring CO and LV dimensions on a beat-by-beat basis during the respiratory cycle in patients with sleep apnea, there have been few studies that have examined beat-by-beat changes in cardiac function. Thermodilution methods only provide CO data averaged over several cardiac cycles. Thus it is not surprising that earlier studies (7, 15) reported variable trends in CO. There are several recent clinical studies that used noninvasive beat-by-beat techniques, including thoracic electrical impedance (25, 31) or nuclear cardiographic devices (5, 6). Tolle et al. (29) reported that both LV SV and HR decreased during the apnea compared with values when the patients were awake, leading to a substantial (27%) reduction in CO. They speculated that decreased SV was attributable to a reduction in preload. Stroehs and Guilleminault (25) reported a decrease in SV during obstructive apneas but no further change in SV during the interapnea interval. Using a nuclear cardiographic technique to monitor LV volume, Garpestad et al. (5, 6) reported a significant decrease in SV from early apnea to late apnea and a further decrease immediately after apnea termination (early interapnea). Because of the inverse relationship between afterload (MAP) and SV, Garpestad et al. suggested that increased afterload was responsible for decreased SV. However, artifacts caused by lung inflation and body movements, as well as difficulties in calibration, limit collection of data and interpretation of these results.

In present study, both OA and CA were associated with increased LV afterload as measured by MAP and with decreased CO during apnea. Increased MAP was likely related to arterial constriction, as reflected by the increase in SVR. With OA, changes in CO reflected primarily changes in HR, although with OA 30/30 decreased SV at late apnea and early interapnea also contributed to changes in CO. However, with CA, decreased CO reflected decreases in both SV and HR. It is likely that the decrease in SV with CA was due to the greater increase in LV afterload with this type of apnea. This is shown by the fact that although changes in preload as measured by LVEDL and LVEDP were the same for CA as for OA, indexes of afterload such as
LVESL and MAP increased more with CA. We cannot rule out changes in cardiac contractility with CA, which could contribute to these effects; however, we think this possibility is unlikely.

In this study, the maximum decrease in HR (at late apnea) during apneas compared with baseline was approximately the same for OA and CA (12–16% from baseline). In previous studies from this laboratory in which anesthetized dogs were used, HR decreased 24–27% with OA (19, 26, 27) and 44–47% with CA (27, 28). It has been postulated that reflex autonomic activation is involved in cardiovascular responses to the apneas. Therefore, the differences in HR between the present study and the previous studies may reflect less depression of sympathoadrenal tone in sedated vs. anesthetized animals. Differences in responses could also reflect species differences.

We did not record inspiratory-expiratory differences in LV function. During loaded inspiration, LV afterload may increase and preload may decrease (16, 19). It could be argued that by recording only at end expiration these effects were missed. However, trends in CO measured over several cardiac cycles, and at least one respiratory cycle, agreed with those recorded directly from the flow probe at end expiration. Thus any effects attributable to changes in loading conditions during inspiration were likely to be small. The cardinal point here is that although there may be some changes during inspiration associated with ITP, these were clearly dominated by changes in MAP and SVR, which were greater when ITP did not change (CA).

There are several reasons that may explain the differences in hemodynamic responses to apneas between OA and CA. We originally postulated that LV afterload effects of decreasing ITP would render OA a more severe depressant of CO. However, the present study showed that CA elicited more profound changes in MAP and LV function than did OA. One possible reason is that CA elicits a greater sympathetic neural response than does OA. Thus these findings suggest that changes in afterload due to neural reflex mechanisms, not to decreased ITP, are the dominant factor controlling CO. These conclusions are consistent with previous work. In conscious humans, development of a large negative ITP during a 20-s Mueller maneuver augmented MAP and postganglionic muscular sympathetic nerve activity less than did a simple breath hold of comparable duration made at end expiration (12). In the autonomically blocked dog, there was no increase in MAP either during or after a period of airway obstruction in non-rapid-eye-movement sleep, and, in fact, MAP fell in the postobstructive period whether or not arousal occurred (13). In anesthetized baboons with OA and paralysis-induced CA, MAP elevation in OA and CA did not differ for any duration apnea, and HR remained the same with both apnea types (30). In that study, White et al. (30) measured CO by thermodilution and reported no difference in CO between OA and CA.

Fig. 10. Effects of periodic apneas on LV end-systolic segment length. Each data point represents 5 s of data that end with times shown. Other points were taken from fifth apnea-interapnea cycle. Arrow, end of apnea and beginning of interapnea phase. *P < 0.05 compared with baseline.

Fig. 11. Effects of periodic apneas on systemic vascular resistance. Each data point represents 5 s of data that end with times shown. Other points were taken from fifth apnea-interapnea cycle. Arrow, end of apnea and beginning of interapnea phase. **P < 0.01 compared with baseline. ###P < 0.01 compared with early apnea.
In anesthetized dogs, Tarasiuk and Scharf (27) found HR and CO decreased more with CA compared with OA when matched for blood gases and apnea periodicity, although neither changed MAP. Unlike the present study, however, changes in CO were due to decreased HR because SV did not change. The present study thus extends the above observations and demonstrates that increases in MAP were more exaggerated and were associated with greater decrease in SV with CA than OA. One possible explanation for the attenuated MAP and SVR response in OA compared with CA is that negative ITP suppressed the sympathetic response engendered by hypoxia. Somers et al. (23) demonstrated this in normal humans by comparing blood pressure and sympathetic responses to a Mueller maneuver maintained for 20 s to effects of an equal period of end-expiratory apnea. They suggested that dilation of the LV associated with the Mueller maneuver stimulated LV afferents, which decreased sympathetic activity. It is equally possible, however, that increased aortic baroreceptor transmural pressure during obstructed inspirations could have the same effect (3). Another possibility is that with OA hypoxic reflexes may be modified from right atrial distension or pulmonary congestion related to increased venous return during inspiration.

Blood pressure changes during and after apnea have been attributed to the interaction between the reflexes related to hypoxia and those of arousal (2). Because arousal during the apneas is not observed in the present model (unpublished data), changes in MAP are most likely due to the effects of hypoxemia and/or hypercapnia. However, they are modified by the apnea type. Early studies on steady-state hypoxia also reported that ventilatory pattern influences the cardiovascular response (9). The afferent reflexes responsible for these differences are not known. One possibility is that the differences between OA and CA are due to afferent inputs from respiratory and other skeletal muscles with OA. For example, the increases in muscle sympathetic nerve activity from the stimulation of chemoreceptors in awake humans can be augmented by voluntary apneas (23, 24). These results suggest that the loss of inputs from lung or chest wall afferents or intrathoracic receptors may modify chemoreceptor activation of the autonomic nervous system. With CA and OA, HR increased considerably during early interapnea (with resumption of breathing) compared with late apnea, although only increases with CA showed statistical significance (Fig. 6). This rapid rise in HR, within one to two breaths, was also noted in previous studies in anesthetized dogs (27, 28). It is unlikely that changes in HR of this rapidity can be explained by changes in blood gases. It is more likely that they are due to pulmonary stretch receptor stimulation associated with lung inflation (9, 27). Thus the interaction of blood-gas changes, pulmonary parenchymal, intrathoracic vascular, and possibly chest wall mechanoreceptors determines the overall response. Finally, increased MAP would also be expected to invoke baroreceptor responses. However, unmodified baroreceptor responses are not likely to be responsible for changes in HR. This is because with CA, MAP at early apnea was greater than with OA. Yet initial HR was greater with CA. During the apnea phase, MAP did not increase significantly (compared with early apnea), yet with CA, HR fell during the apnea phase. Thus, although baroreceptor reflexes may contribute to changes in HR, it would appear that there must be a modification of the set point and/or sensitivity.

Hemodynamic Effects: Apnea Duration

Increasing apnea duration and decreasing interapnea time caused more severe hypoxia and hypercapnia. However, there are surprisingly few hemodynamic differences between the apnea durations for OA. With CA 30/30, CO, SV, and SVR at late apnea, and LVEDL at early interapnea, were more affected than with CA 15/45. Other variables changed similarly between the two apnea durations. One reason that long apnea duration might not result in more severe cardiovascular responses with OA is that hypoxia induces coactivation of two antagonistic mechanisms, i.e., sympathetic and parasympathetic responses (4). Furthermore, the local vascular effects of hypoxia are inhibitory and tend to reduce blood pressure by vasodilatation. The interplay of these antagonistic mechanisms may prevent consistent changes in blood pressure despite greater blood-gas changes. Second, the confounding effects of chest wall and lung mechanoreceptors and/or intrathoracic vascular receptors may dampen the effects of worsening hypoxemia with OA.

These studies may have clinical relevance, especially in patients with compromised LV function. Many of these patents exhibit Cheyne-Stokes breathing at night. If the CA phase of Cheyne-Stokes breathing results in elevated MAP and SVR, as does the simulated CA in our studies, this could, by increasing LV afterload, further compromise LV function and adversely affect clinical outcome.

In summary, when matched for periodicity and blood-gas changes, CA produced greater depression of CO and was associated with greater changes of afterload-related LV dysfunction compared with OA. This was likely related to a greater increase in MAP and LV afterload with CA. Therefore, decreased ITP plays only a small role in determining LV function with OA. The reason for the greater effects of CA are unknown, but loss of mechanoreceptor or pulmonary vascular receptor afferent input may be responsible.

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