Hemodynamic effects of periodic obstructive apneas in sedated pigs with congestive heart failure

LING CHEN,1 QUIHU SHI,2 AND STEVEN M. SCHARF 1
1Pulmonary and Critical Care Division, Long Island Jewish Medical Center, Long Island Campus for Albert Einstein College of Medicine, Hew Hyde Park 11042; and 2Department of Biostatistics, North Shore University Hospital, Manhasset, New York 11030

Chen, Ling, Quihu Shi, and Steven M. Scharf. Hemodynamic effects of periodic obstructive apneas in sedated pigs with congestive heart failure. J. Appl. Physiol. 88: 1051–1060, 2000.—Because of similar physiological changes such as increased left ventricular (LV) afterload and sympathetic tone, an exaggerated depression in cardiac output (CO) could be expected in patients with coexisting obstructive sleep apnea and congestive heart failure (CHF). To determine cardiovascular effects and mechanisms of periodic obstructive apnea in the presence of CHF, 11 sedated and chronically instrumented pigs with CHF (rapid pacing) were tested with upper airway occlusion under room air breathing (RA), O2 breathing (O2), and room air breathing after hexamethonium (Hex). All conditions led to large negative swings in intrathoracic pressure (−30 to −39 Torr) and hypercapnia (Pco2 = 60 Torr), and RA and Hex also caused hypoxia (to −42 Torr). Relative to baseline, RA increased mean arterial pressure (from 97.5 ± 5.0 to 107.3 ± 5.7 Torr, P < 0.01), systemic vascular resistance, LV end-diastolic pressure, and LV end-systolic length while it decreased CO (from 2.17 ± 0.27 to 1.52 ± 0.31 l/min, P < 0.01), stroke volume (SV; from 23.5 ± 2.4 to 16.0 ± 4.0 ml, P < 0.01), and LV end-diastolic length (LVEDL). O2 and Hex decreased mean arterial pressure [from 102.3 ± 4.1 to 16.0 ± 4.0 Torr (P < 0.01) with O2 and from 86.0 ± 8.5 to 78.1 ± 8.7 Torr (P < 0.05) with Hex] and blunted the reduction in CO [from 2.09 ± 0.15 to 1.78 ± 0.18 l/ml for O2 and from 2.91 ± 0.43 to 2.50 ± 0.35 l/ml for Hex (both P < 0.05)] and SV. However, the reduction in LVEDL and LV end-diastolic pressure was the same as with RA. There was no change in systemic vascular resistance and LVEDL during O2 and Hex relative to baseline. In the CHF pigs during apnea, there was an exaggerated reduction in CO and SV relative to our previously published data from normal sedated pigs under similar conditions. The primary difference between CHF (present study) and the normal animals is that, in addition to increased LV afterload, there was a decrease in LV preload in CHF contributing to SV depression not seen in normal animals. The decrease in LV preload during apneas in CHF may be related to effects of ventricular interdependence. sleep apnea (OSA) (6). These include large inspiratory swings in intrathoracic pressure, hypoxia, and possibly hypercapnia and sleep state changes, including arousals after apnea termination and resumption of ventilation (6). Early studies on Mueller maneuvers suggested an important effect of inspiratory intrathoracic pressure swings leading to cardiac output (CO) depression during OSA, primarily by increases in left ventricular (LV) afterload (for review see Ref. 24). However, recent studies in normal animals demonstrated that reflex factors related to hypoxia and events after apnea termination, such as arousal and hyperventilation, are more important than intrathoracic pressure swings in determining the effect of apneas on LV function (8, 9, 25, 32).

It has been demonstrated that OSA commonly coexists with congestive heart failure (CHF) (19). Both diseases are associated with adverse cardiac loading conditions and an elevation in sympathetic tone. Thus exaggerated cardiovascular responses to OSA could be expected in patients with coexisting CHF. Because the failing heart is more sensitive to the adverse effects of increases in LV afterload (27), increased LV afterload by negative swings in intrathoracic pressure during OSA may lead to a larger impact on CO in the presence than in the absence of CHF. Thus the impact of obstructive apneas might be greater in the presence than in the absence of CHF.

To our knowledge, effects of periodic obstructive apnea on cardiovascular function have not been systematically examined in animal models of failing hearts. Thus the present study was undertaken to determine the acute cardiovascular effects of periodic obstructive apnea in sedated pigs with pacing-induced CHF. We hypothesized that 1) relative to our published data from normal hearts (8, 9), obstructive apneas lead to greater pressor and CO responses and 2) in failing hearts, because the mechanical effects of negative swings in intrathoracic pressure are important, eliminating hypoxia and sympathetic blockade will not abolish the effects of obstructive apnea on CO.

METHODS

Eleven female Yorkshire farm pigs (Sus scrofa, 18–22 kg body wt) were used for this study, which was carried out in three phases: the instrumentation phase, the pacing phase, and the data-collection phase. The local Institutional Animal

THE INTERACTION OF SEVERAL physiological factors determines the acute cardiovascular response to obstructive apnea; cardiac output; hexamethonium; hypoxia
Care and Use Committee, in accordance with National Institutes of Health guidelines, approved all methods and protocols involved in the study.

Instrumentation Phase

The animals were instrumented with an electromagnetic flow probe, a pacer lead, and a pair of sonomicrometer crystals under aseptic conditions under general anesthesia. The method has been reported in detail in our previous studies (8–11, 28). Briefly, the animals were anesthetized with 20 mg/kg of ketamine and 2 mg/kg of xylazine. They were intubated and mechanically ventilated through an endotracheal tube. Anesthesia was maintained with 0.75–1.0% halothane. Under sterile surgery, a left thoracotomy was done and the pericardium was opened. A square-wave electromagnetic flow probe (Biotronix Laboratories, St. Petersburg, FL) was placed around the ascending aorta (14–18 mm, depending on the size of the aorta). One pair of sonomicrometer crystals (Crystal Biotech, Triton Technology, San Diego, CA) was placed into the midmyocardium of the LV in the orientation of the superficial fibers. A unipolar electrode attached to an externally programmable pacemaker (Medtronic, Secaucus, NJ) was screwed into the base of the LV and sutured in place. The program of the pacemaker had been modified to allow for rapid rates in the temporary mode, which was externally programmable. Initial pacemaker rate was set at 30 beats/min, which is far lower than the physiological rate of the animal. The incision on the pericardium was loosely closed. The wires, the leads, and the pacers were led out to a subcutaneous pocket. The chest was closed in layers. Penicillin, dihydrostreptomycin, and morphine sulfate were administered intramuscularly for antibiotic prophylaxis and pain control.

Pacing Phase

The animals were trained to allow daily electrocardiogram recording in the conscious and unfastened state. Three days after initial surgery, with use of an external radio-frequency programmer, the pacing rate increased to 200 beats/min for 2 days and then to 240 beats/min for 7–9 days. The expected heart rate (HR) of animals was confirmed daily by electrocardiogram until data acquisition.

Data-Collection Phase

This phase took place 12–14 days after instrumentation surgery. Immediately before anesthesia, the pacing rate was set to the minimal rate (30 beats/min).

Anesthesia, continuous sedation, and euthanasia. Animals were anesthetized using a mixture of 20 mg/kg of ketamine and 2 mg/kg of xylazine. This produced 45–60 min of surgical-plane anesthesia. Animals were intubated and, if necessary, mechanically ventilated during the surgical preparation to keep arterial blood-gas tensions in the normal range. Approxi- mately 20 min after initial anesthesia, an infusion of a mixture of 0.9% alphaxalone and 0.3% alphadolone (Saffan, Pittman-Moore, Uxbridge, Middlesex, UK) was begun at a rate of 3–4 mg·kg\(^{-1}\)·h\(^{-1}\) and continued throughout the data-collection phase. In pigs this rate is sufficient to produce heavy sedation but not surgical-plane anesthesia. At the end of the experiments, animals were euthanized intravenously by a bolus injection of 0.3 ml/kg of Euthanasia-S solution (Veterinary Laboratories, Lenexa, KY), which contains 5 g/ml of pentobarbital sodium in 40% isopropyl alcohol and 2% propylene glycol.

Surgical preparation. During surgical-plane anesthesia, after local skin infiltration with 2% lidocaine, the wires and leads in the subcutaneous pocket were exposed. The following procedures were done via skin cut-down. For measurement of LV pressure and the maximal rate of rise in LV pressure ($+\text{dP}/\text{dt}$), a 5-F micrometer-tipped catheter (Millar Instrument, Houston, TX) was passed via the exposed left carotid artery and advanced into the LV. The $+\text{dP}/\text{dt}$ was obtained by electrical integration of the LV pressure signal. A 7-F catheter was inserted into the right femoral artery and advanced into the ascending aorta for measurement of blood pressure and collection of blood-gas samples. A 7-F balloon-tipped catheter with a thermistor was inserted into the pulmonary artery via the right femoral vein. This catheter served for administration of fluids and medications and calibration of the aortic flow probe by the thermodilution technique.

Protocols. After surgical preparation the animals were placed on the right side and allowed to breathe spontaneously. A period of stabilization was allowed for ≥60 min after the initial anesthetized injection. Arterial gas tensions were required to be in the normal range at the beginning of data collection. Periodic obstructive apneas were produced by occluding the endotracheal tube at end expiration. Apnea periodicity was set as airway occlusion (apneic phase) for 30 s followed by the release of the airway occlusion (interapnea interval) for 30 s. Thus an apneal–interapnea cycle lasted for 60 s. The effects of apneas were tested under the following conditions: 1) room air breathing (RA), 2) 100% O\(_2\) administered to the entry port of the endotracheal tube to eliminate hypoxia during apneas (O2), and 3) room air breathing after a bolus injection of 10 mg/kg hexamethonium dichloride (Hex; RBI, Natick, MA). The order of performing the RA and O2 studies was randomized. Because Hex is essentially irreversible, these studies were done last.

Measurements were done at baseline, the period after a 20-min stabilization under the experimental conditions but without any apnea intervention, as well as at recovery (Rec), the same state as baseline but after a 20-min stabilization after the end of the apneal–interapnea intervention. Effects of periodic apneas were represented by data from the fifth apnea–interapnea cycle, since cardiorespiratory changes had become stable by this time.

Data were digitized synchronously at 100-Hz sampling rate and streamed through to a hard disk of a computer with use of commercially available software (ACQ4600, Gould, Cleveland, OH). The following parameters were recorded: blood pressure, LV pressure, $+\text{dP}/\text{dt}$, aortic flow, stroke volume (SV; integrated from aortic flow probe signals), LV regional myocardial length, and airway pressure (Paw; from a lateral tap placed in the endotracheal tube). Arterial gas tensions were measured. During the fifth apnea–interapnea cycle, one blood-gas sample was taken from a specified 10-s period, i.e., over the 25th–30th s of the apneic phase and the first 5-s after resumption of ventilation.

Data analysis. Data were analyzed off-line using commercially available software (View II, Gould, Cleveland, OH). Four specified data points were taken from the fifth apnea–interapnea cycle, each point representing a 5-s period: early apnea (EAP, the first 5 s of the apneic phase), late apnea (LAP, the 25th–30th s of the apneic phase), early interapnea (EIA, the first 5 s after resumption of ventilation), and late interapnea (LIA, the 25th–30th s after resumption of ventilation). The following variables were measured as a mean over the 5-s period: mean arterial pressure (MAP), HR (from blood pressure tracing), and CO (from aortic flow tracing). Systemic vascular resistance (SVR) was calculated as (MAP/CO) × 79.9 (dyn·s·cm\(^{-5}\)). Other parameters were calculated as a mean of triple beat-by-beat measurements at end expiration: SV, LV end-diastolic pressure (LVEDP), $+\text{dP}/\text{dt}$, LV regional myocar
dial end-diastolic length (LVEDL), and LV regional myocardial end-systolic length (LVESL). End diastole was defined as the beginning point of the rapid upstroke of the dP/dt tracing and end systole as the end point of downstroke after ejection of the dP/dt tracing. Paw was measured via a side hole in the endotracheal tube. With obstructive apnea, the maximal difference between inspiratory and expiratory Paw (ΔPaw) was assumed to be equal to intrathoracic pressure changes (no air).

Statistical analysis Data were compiled and presented as means ± SE. Repeated-measures ANOVA was carried out using the mixed-model approach (PROC MIXED, SAS Institute, Cary, NC). The model used two “within-subjects” (i.e., repeated) factors: treatment condition (RA, O2, Hex) and time (EAP, LAP, EIA, LIA, Rec). The baseline value of a given parameter observed at the beginning of each new treatment condition was introduced as a continuous covariate in the model. In this way, the data over the five time points could be adjusted for any differences in baseline values. When the interaction between fixed effects was significant, differences between individual pairs of the adjusted treatment/time means were also analyzed. Previous experience with this model (8–11, 13, 29) has demonstrated that, relative to baseline, a given variable may change in different directions with different treatments and that there is a great deal of biological variability between responses in different animals. Thus we also explored differences relative to baseline for any given treatment by hypothesizing no changes in a given variable with time (within treatment). This was done using repeated-measures one-way ANOVA. Dunnett's test was used to determine the significance of differences between means at different points in the apnea-interapnea cycle (EAP, LAP, EIA, LIA, Rec) and baseline. The null hypothesis was rejected at the 5% level.

RESULTS

Blood-Gas Tensions and Paw

Table 1 demonstrates arterial blood-gas tensions and Paw. There were no significant differences between baseline and Rec. For pH and PCO2 there were no differences at baseline between conditions. As expected, PO2 was greater under O2 conditions. Under all conditions, apneas caused equal increases in arterial PCO2 and decreases in pH relative to baseline. Periodic apneas without O2 supplementation (RA and Hex) led to hypoxemia. In contrast, O2 was associated with hyperoxia, even during apneas. Periodic obstructive apneas under all three conditions caused large negative swings in ΔPaw during the apnea phase. With O2, ΔPaw during the apnea phase was significantly less than with RA or Hex (P < 0.05).

Under no conditions were there any significant differences between baseline and Rec (1-way ANOVA), indicating time stability of the preparation. In Figs. 1–9, we have illustrated the results of the repeated-measures one-way ANOVA with significance assessed relative to baseline. The results of the mixed-models ANOVA are illustrated in Table 2. In Table 2, we have illustrated the significant differences between individual cells during Rec and during the apnea-interapnea cycle at comparable time periods between treatments only when the least-squares adjusted means were significant. (The complete analysis is available from the corresponding author.)

LVEDP

With all the treatment conditions, baseline LVEDP (26–29 Torr) was elevated above the normal range (Fig. 1). Overall, LVEDP was significantly lower during apneas with Hex than with RA or O2 (Table 2). Overall, LVEDP was significantly greater during the apnea cycle than in Rec (Table 2). This was also found relative to baseline for LAP for all conditions using one-way ANOVA and at EAP for RA.

CO and SV

Baseline CO for RA was 2.2 L/min, which is lower than previously reported values for normal pigs under these conditions (Figs. 2 and 3) (8, 9). When adjusted for baseline (Table 2), significance was demonstrated between LAP and LIA and between LAP and Rec. With treatments analyzed separately (1-way ANOVA), significance from baseline was demonstrated for LAP for all treatment groups and for EIA for RA.

For SV, when adjusted for baseline (Table 2), significant treatment differences were demonstrated between Hex and RA and between O2 and RA. Significant differences over the apnea-interapnea cycle were demonstrated between LAP and LIA and between LAP and Rec (similar to CO). With individual treatment groups analyzed separately, with RA, significance from baseline was shown for EAP, LAP, and EIA. With Hex and O2, significance from baseline was only demonstrated for LAP.

Table 1. Effects of periodic apneas on blood-gas tensions and Paw

<table>
<thead>
<tr>
<th></th>
<th>RA</th>
<th>O2</th>
<th>Hex</th>
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<td></td>
<td>Base</td>
<td>Apnea</td>
<td>Rec</td>
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<tr>
<td>pH, unit</td>
<td>7.39 ± 0.02</td>
<td>7.33 ± 0.02*</td>
<td>7.39 ± 0.01</td>
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<tr>
<td>PCO2, Torr</td>
<td>47.8 ± 2.0</td>
<td>56.8 ± 2.6*</td>
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<tr>
<td>P2, Torr</td>
<td>84.1 ± 4.7</td>
<td>42.3 ± 9.1*</td>
<td>88.3 ± 2.9</td>
</tr>
<tr>
<td>ΔPaw, Torr</td>
<td>-38.7 ± 3.4</td>
<td>-29.8 ± 3.8</td>
<td>35.0 ± 3.2</td>
</tr>
</tbody>
</table>

Values are means ± SE; n = 11. ΔPaw, maximal differences in inspiratory and expiratory airway pressure (Paw) during 5th apnea-interapnea cycle; RA, room air breathing; O2, oxygen supplementation; Hex, room air breathing after hexamethonium; Base, baseline; Rec, recovery. For blood-gas tensions, Apnea represents a 10-s period over 25th–30th s of apnea phase and first 5 s after resumption of ventilation of 5th apnea-interapnea cycle; for ΔPaw, Apnea represents apnea phase of 5th apnea-interapnea cycle. *P < 0.01 compared with baseline; †P < 0.05 compared with Apnea under RA conditions.
The fact that baseline LVEDP is greater and CO is less than previously reported values in normal animals (8, 9) is consistent with the development of heart failure in these animals (12, 13).

HR and Blood Pressure

As shown in Table 2, with HR, there were significant time, treatment, and interaction effects (Figs. 4 and 5). Significance for time was between LIA and EIA, whereas treatment differences were significant between O2 and RA. For O2, all time periods in the apnea-interapnea cycle were significantly different from Rec. For RA, EIA and LAP were significantly different from Rec. Rec with O2 was significantly different from Rec with Hex. When treatment groups were analyzed separately for differences from baseline (1-way ANOVA), for RA there were significant increases in EAP and LIA. With O2, there were no changes relative to baseline. For Hex, only LIA was significant relative to baseline.

For MAP, when adjusted for baseline (Table 2), significance was noted only for treatment effects between Hex and RA and between O2 and RA. When analyzed separately for differences from baseline, MAP increased with RA over the apnea-interapnea cycle and decreased for O2 and Hex during apneas.

SVR

When adjusted for baseline (Table 2), there were significant effects of time (between LAP and Rec) and treatment (between Hex and RA and between O2 and RA) and a significant interaction between treatment and time (Fig. 6). For O2, all points in the apnea-interapnea cycle were significant relative to Rec. There were also significant differences between LAP, EIA, and Rec for RA. There were no significant differences with Hex. For differences from baseline (1-way ANOVA), significance was demonstrated at LAP for RA and O2.

LV Regional Myocardial Lengths

With adjustment for baseline (Table 2), only time and treatment effects were significant (Figs. 7 and 8). The source of significance for time was LAP, LAP/Rec, and EIA.

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**Table 2. Results of mixed-models analysis**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Fixed Effects</th>
<th>P (Adjusted)</th>
<th>Source*</th>
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<tbody>
<tr>
<td>SVR</td>
<td>Base 0.0001</td>
<td>Time 0.0011</td>
<td>Txt 0.0016</td>
</tr>
<tr>
<td></td>
<td>Txt+Time 0.0465</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MAP</td>
<td>Base 0.0001</td>
<td>Time 0.0022</td>
<td>Txt 0.0001</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CO</td>
<td>Base 0.0001</td>
<td>Time 0.0001</td>
<td>Txt 0.0001</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>SV</td>
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<td>Time 0.0001</td>
<td>Txt 0.0001</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
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<td>Time 0.0020</td>
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<td></td>
<td>Txt+Time 0.0001</td>
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<td>EDP</td>
<td>Base 0.0001</td>
<td>Time 0.0001</td>
<td>Txt 0.0002</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EDL</td>
<td>Base 0.0001</td>
<td>Time 0.0001</td>
<td>Txt 0.0001</td>
</tr>
</tbody>
</table>

Repeated-measures ANOVA was adjusted for baseline (see Statistical Analysis). Base, baseline; Time, time effects over apnea cycle; Txt, treatment effects; Time*Txt, time-treatment interaction (shown only if significant); LAP, late apnea; Rec, recovery; RA, room air breathing; Hex, RA after hexamethonium; O2, oxygen supplementation; LIA, late interapnea; EIA, early interapnea; SVR, systemic vascular resistance; MAP, mean arterial pressure; CO, cardiac output; SV, stroke volume; HR, heart rate; EDP, end-diastolic pressure; EDL, end-diastolic length; NS, not significant. Source of significance is between adjusted least-squares means. Only pairs of effects noted are those for which differences are found. P values are adjusted (Bonferroni’s correction) and only given to 4 significant digits. *Values in parentheses are P values.

The fact that baseline LVEDP is greater and CO is less than previously reported values in normal animals (8, 9) is consistent with the development of heart failure in these animals (12, 13).

HR and Blood Pressure

As shown in Table 2, with HR, there were significant time, treatment, and interaction effects (Figs. 4 and 5). Significance for time was between LIA and EIA, whereas treatment differences were significant between O2 and RA. For O2, all time periods in the apnea-interapnea cycle were significantly different from Rec. For RA, EIA and LAP were significantly different from Rec. Rec with O2 was significantly different from Rec with Hex. When treatment groups were analyzed separately for differences from baseline (1-way ANOVA), for RA there were significant increases in EAP and LIA. With O2, there were no changes relative to baseline. For Hex, only LIA was significant relative to baseline.

For MAP, when adjusted for baseline (Table 2), significance was noted only for treatment effects between Hex and RA and between O2 and RA. When analyzed separately for differences from baseline, MAP increased with RA over the apnea-interapnea cycle and decreased for O2 and Hex during apneas.

SVR

When adjusted for baseline (Table 2), there were significant effects of time (between LAP and Rec) and treatment (between Hex and RA and between O2 and RA) and a significant interaction between treatment and time (Fig. 6). For O2, all points in the apnea-interapnea cycle were significant relative to Rec. There were also significant differences between LAP, EIA, and Rec for RA. There were no significant differences with Hex. For differences from baseline (1-way ANOVA), significance was demonstrated at LAP for RA and O2.

LV Regional Myocardial Lengths

With adjustment for baseline (Table 2), only time and treatment effects were significant (Figs. 7 and 8). The source of significance for time was EAP, LAP, and EIA
and Rec. For treatment effects, the source of significance was Hex vs. O2 and Hex vs. RA. For within-treatment differences from baseline, RA was associated with a significant decrease in LVEDL, except at LAP. With O2 and Hex, LVEDL decreased significantly only at LAP relative to baseline.

For LVESL, with adjustment for baseline, only treatment differences between Hex and RA were significant. Compared with baseline (1-way ANOVA), only RA was associated with significant increases in LVESL during apnea. With O2 and Hex, there were no significant changes relative to baseline.

Fig. 2. Effects of periodic apneas on cardiac output. *P < 0.05; **P < 0.01 compared with baseline.

Fig. 3. Effects of periodic apneas on stroke volume. *P < 0.05; **P < 0.01 compared with baseline.

Fig. 4. Effects of periodic apneas on heart rate (n = 11). bpm. *P < 0.05; **P < 0.01 compared with baseline.

Fig. 5. Effects of periodic apneas on mean arterial pressure. *P < 0.05; **P < 0.01 compared with baseline.
Data for $\frac{dP}{dt}$ were normalized to baseline, which was set at 100% (Fig. 9). Hence, adjustment for baseline values was not done. For these data, two-way ANOVA for repeated measures was performed, with Dunnett's test used to determine the source of significance. With RA, $\frac{dP}{dt}$ was greater than with Hex or O2 ($P < 0.01$). Relative to baseline, there were significant increases in $\frac{dP}{dt}$ over all the points of the apnea-interapnea cycle ($P < 0.01$) with RA and at LIA.
with Hex (P < 0.05). There was no significant change relative to baseline with O2.

**DISCUSSION**

Major findings in this study may be summarized as follows. 1) RA led to a pressor response and a reduction in CO and SV. 2) O2 and Hex were associated with a depressor response and a reduction in CO and SV. 3) Analysis of LV loading suggests that, with RA, preload (LVEDL) decreased and afterload (LVESL) increased, whereas with O2 and Hex only preload decreased. Regarding our original hypotheses, we found that 1) although the CO response to apneas was indeed greater in failing than in previously studied normal hearts, the pressor response was actually less (Table 3) and 2) although the effects of apneas on CO were less after O2 and Hex, they were certainly not abolished, even though the swings in intrathoracic pressure were the same under all three conditions. In the ensuing discussion we consider the experimental preparation and these findings, especially in comparison to our published data (8, 9) from the normal sedated pigs with similar surgical preparation and similar changes in blood-gas tensions and intrathoracic pressure during periodic obstructive apnea.

**Experimental Preparation**

There were no significant differences in cardiorespiratory parameters between Rec and baseline for any condition. Thus this preparation demonstrated no time-related deterioration. Moreover, because this model utilized sedated and chronically instrumented animals, cardiorespiratory depression caused by anesthesia and acute major surgery was minimized. At a dose of 3 mg·kg\(^{-1}\)·h\(^{-1}\) of alphaxolone-alphadolone, this level of sedation is sufficient to eliminate pain and suffering but efficiently preserves spontaneous breathing and normal arterial blood-gas tensions. Inspiratory decreases in intrathoracic pressure during obstructive apnea were greater than those seen in the anesthetized dog model (29, 33, 34) and were comparable to the findings from some clinical studies (22). Finally, alphaxolone-alphadolone is known to preserve autonomic components of the alerting reaction associated with chemoreceptor stimulation (16) and produces minimal suppression of vagal and sympathetic activities associated with baroreceptor and chemoreceptor function (4).

The present preparation allows evaluation of the relative importance of some of the physiological factors in acute cardiovascular responses to apnea. Monitoring of the electroencephalogram during apneas demonstrated no changes in cortical state that suggest arousal during apnea in this model (10). Therefore, the confounding effects of arousals during apnea were isolated from overall cardiovascular responses. Moreover, hypoxemia, the major activating factor of chemoreflex afferents during apnea and the efferent branch of autonomic system, can be eliminated by supplementation of 100% O\(_2\) (O2) and by pretreatment with an autonomic ganglionic blocker (Hex), respectively.

Rapid ventricular pacing has been demonstrated to produce extremely reproducible pump dysfunction, including peripheral and myocardial changes similar to those found in CHF patients (7, 12, 23, 26, 28, 31, 37). The present data clearly demonstrate cardiac pump dysfunction at baseline in our paced animals compared with our published data from sedated normal pigs with similar body weight and similar chronic surgical preparation (8, 9). These include lower baseline CO (2.2 l/min) and SV (24 ml) than in normal hearts (–3.0–3.2 l/min and 31–32 ml, respectively) (8, 9), as well as higher baseline LVEDP (26 Torr) and SVR (4,000 dyn·s·cm\(^{-5}\)) than in normal animals (10 Torr (10) and 2,600–2,800 dyn·s·cm\(^{-5}\) (8, 9), respectively). Increased baseline SVR suggests increased baseline sympathetic tone, and in a previous study baseline plasma norepinephrine levels were elevated in pigs with pacing-induced CHF (28).

**Cardiovascular Effects of Obstructive Apneas**

With RA, we observed increased HR (Fig. 4) at early apnea and LIA relative to baseline. With O2 HR did not change with apneas, and with Hex HR increased only at LIA. For RA and Hex, HR was less at end apnea than during the interapneic interval (Fig. 5). These findings are consistent with our previous studies showing that HR is lower at end apnea than during interapnea. In previous studies (11, 30) we thoroughly discussed the reasons for the HR changes, and we only briefly summarize here. Hypoxia-induced vagal stimulation from carotid chemoreceptors is one likely reason for the HR slowing during apnea relative to interapnea. Furthermore, with the onset of ventilation, HR increases, probably in association with pulmonary stretch receptor stimulation (25, 34). With O2, there were no significant changes in HR over the apnea-interapnea cycle. This suggests the importance of hypoxic stimulation as an essential component of the HR swings, a finding corroborating that in anesthetized dogs (34). Finally, with Hex, HR was also lower during apnea than at LIA.

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Table 3. Maximal and normalized changes during apnea in failing and in normal hearts

<table>
<thead>
<tr>
<th></th>
<th>Failing Hearts</th>
<th>Normal Hearts</th>
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<tbody>
<tr>
<td></td>
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</tr>
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<td>LVEDL</td>
<td>-3†</td>
<td>-3†</td>
</tr>
<tr>
<td>LVESL</td>
<td>+3†</td>
<td>-1</td>
</tr>
</tbody>
</table>

*To assist in comparisons, data are presented as maximum change in 5th apnea cycle, expressed as percentage of preapnea baseline. Data from normal hearts are from our previous studies (8, 9) in which pigs were instrumented and sedated identically to the present study. LVEDP, LVEDL, and LVESL, left ventricular end-diastolic pressure and length and left ventricular end-systolic length, respectively; N/A, not applicable. *P < 0.05; †P < 0.01 compared with baseline. Values are from experiments published in Ref. 9. Only shortening fraction, their derivative, was presented, but original data were not presented in Ref. 9.
This finding suggests that HR swings do not depend per se on respiratory-related changes in autonomic ganglionic transmission. This pattern persists even after vagotomy (30). The origin of the HR swings after Hex is thus not clear. However, direct effects of blood-gas swings on the cardiac pacemaker could be one explanation.

Cyclic LV function changes during periodic obstructive apnea have been well demonstrated in OSA patients and animal models with normal hearts. The changes include decreased CO and SV associated with an increase in MAP and SVR from late apnea to early postapnea (8, 25, 32, 34, 38). Consistent with the findings in normal hearts (8, 9), the present study demonstrated that periodic obstructive apnea led to a similar response pattern of LV function in the failing hearts, i.e., apnea-related decreases in CO and SV in combination with increases in blood pressure and SVR. Depression of CO and SV was observed during the late part of the apnea phase and immediately after resumption of ventilation. The parallel decreases in CO and SV suggest that changes in SV are the prime determinants of changes in CO. However, compared with our data from normal hearts with identical surgical preparation (8, 9), in failing hearts we observed an exaggerated apnea-related depression in CO and SV, although changes in blood-gas tensions and in Paw (or intrathoracic pressure) were comparable. As outlined in Table 3, the maximum decrease in CO during the apnea cycle was 30% from baseline in this study and only 14–22% (8, 9) in normal hearts. SV fell 32% in failing hearts but only 22% in normal hearts (9).

Theoretically, hemodynamic mechanisms for exaggerated SV reduction found in failing hearts include greater increases in LV afterload, greater decreases in LV preload, increased sensitivity to changes in LV afterload and preload, and depression of myocardial contractility. In the normal hearts, LV afterload as measured by arterial pressure has been shown to increase synchronously with SV decreases (8). The inverse relationship therefore suggests that increases in LV afterload are responsible for decreases in SV during apneas. In the myopathic hearts otherwise unmanipulated (RA), there was an increase in LV afterload resulting in increased LVESL (Fig. 8), increased MAP (Fig. 5), and increased SVR (Fig. 6) during apnea. However, unlike previous studies in normal hearts (8, 9), there was also a decrease in LVEDL (Fig. 7) during apnea, suggesting a concomitant decrease in LV preload (Table 3). Hence, in the present study, decreased LV preload and increased LV afterload contributed to decreased SV (Fig. 3) during apneas. During O2 and Hex conditions, MAP decreased during apnea. As expected, because afterload as measured by MAP did not increase, there was no increase in LVESL. However, LVEDL decreased during apneas in these conditions as well. This suggests that the decrease in SV during apneas under these circumstances (O2 and Hex) was driven by decreased LV preload, a change that was not observed in the normal hearts (8, 9) (Table 3). Furthermore, during RA and Hex conditions, since there was no change in SVR during apneas, the drop in CO was responsible for decreased MAP during apneas. As noted above, the change in CO was due primarily to a decrease in SV and, hence, LV preload during apneas.

We have assumed that the major contribution to LV afterload increases resulting in increased LVESL is increased MAP. It might have been thought that large inspiratory swings in intrathoracic pressure would also increase LV afterload (8, 34). Actually, increased LVESL was not seen with O2 and with Hex when MAP did not increase, but intrathoracic pressure swings continued to be large, suggesting that large negative swings in intrathoracic pressure with airway obstruction have little effect on LV afterload. This finding supports our previous conclusions in normal animals (8). We cannot rule out, however, some role for intrathoracic pressure. The finding that the decrease in MAP seen with O2 and Hex was not accompanied by a decrease in LVESL could be interpreted as meaning that some factor increasing LV afterload, possibly decreased intrathoracic pressure, partly countered the decreased afterload resulting from decreased MAP, such that LVESL did not decrease.

Myocardial contractility as suggested by changes in +dP/dt (Fig. 9) during apnea actually increased during RA. Thus contractility changes cannot be responsible for apnea-induced SV reduction. In contrast, changes in contractility would have offset the adverse effects of the changes in loading.

Previous studies (13, 14, 29) have suggested that negative inspiratory intrathoracic pressure can cause decreases in LV preload via ventricular interdependence. This occurs because, with decreased intrathoracic pressure, there is an increase in venous return and right ventricular dilation with a leftward shift of the septum. A leftward shift of the interventricular septum could also result from increased impedance to right ventricular emptying due to increased pulmonary arterial pressure or from impaired LV diastolic relaxation rate (29, 35, 36). Our data are consistent with interdependence effects on the LV during apneas. This is because in the present study, as well as previous studies (8–11), we have consistently observed an increase in LVEDP (Fig. 6) during apneas. Decreased preload and increased filling pressure are consistent with decreased LV end-diastolic compliance, a feature of diastolic interdependence effects on the LV due to increased right ventricular volume (17, 18). Thus we believe that, in failing hearts, decreased LV preload, probably due to interdependence effects, is an important mechanism leading to decreased CO and SV. This mechanism acts independently of increased afterload due to vasoconstriction and increased MAP.

Unlike the present study, previous data from the normal hearts demonstrated increased LV preload during obstructive apneas (8). To explain the different LV preload responses between the failing hearts and the normal hearts, we speculate that pericardial constraint may be greater in the failing hearts than in the normal hearts. Acute volume loading normally causes an increase in left and right ventricular end-diastolic vol-
umes until the pericardium becomes stretched to an elastic limit. Interdependence effects are greater in the presence of pericardial constraint (17), and any increase in right ventricular volume would have a greater effect to decrease LV volume. Such changes have been observed by acute volume loading in pulmonary embolism (3) and chronic obstructive pulmonary disease (18). In the present model, marked biventricular dilation has been observed by others (12) as well in this laboratory (13, 28). Thus the dilated cardiomyopathy produced by rapid ventricular pacing would have the effect of making the LV more sensitive to the interdependence (preload) effects of increased venous return and RV afterload likely to occur during obstructive apneas.

Limitations

The rapid ventricular pacing model produces changes in LV functional and neurohormonal characteristics similar to that of the clinical spectrum of CHF (6, 12, 13, 23, 26, 28, 31, 37). However, the changes in LV myocardial structure that occur with pacing-induced CHF may not be similar to clinical forms of CHF due to chronic ischemia or hypertensive disease. Thus extrapolation of the findings from this project to clinical forms of CHF should be done with caution. Moreover, it has been shown that the pericardium stretches in response to chronic cardiac dilation (5, 21). It is unclear whether similar pericardial adaptation occurs in our rapidly paced pigs during relatively short periods (9–10 days). Thus we cannot rule out the possibility that, in clinical CHF, preload changes during apneas may be unlike those reported here. Finally, the present model is not a sleeping model, and there are no arousals during periodic apnea (10). Arousal-associated changes in MAP and HR would be superimposed on the changes reported here.

We used myocardial segment length as an index of LV size. Because the LV is a complex three-dimensional structure, it must be acknowledged that volume may not be easily inferred from free wall segment length. For example, leftward septal shift resulting from increased venous return during inspiration would not be detected by our techniques.

We note that there are no outward signs of change in awareness in the animals. However, we stress that it remains possible that, at a subcortical level, there may be changes in awareness that influence the sympathoadrenal or other responses to apneas. Hence, we urge caution in extrapolating these results to clinical situations such as sleep apnea.

Clinical Correlation

The present data demonstrate an exaggerated SV and CO reduction during obstructive apneas in pigs with CHF. We have speculated that the exaggeration of SV responses is due to decreased LV preload in addition to increased afterload. An exaggerated reduction in SV (33%) has been reported in awake patients with cardiomyopathy during 15-s Mueller maneuvers without induction of hypoxia (14). Although increased LV afterload was important, decreased LV preload was demonstrated to be responsible for SV reduction at the end of the Mueller maneuvers (14). Similarly, a recent clinical study demonstrated that reduced LV diastolic filling by ventricular interdependence could be common in CHF patients (2). Thus interdependence-mediated decreases in LV preload in CHF appear to be important causes of decreased CO.

Exaggerated CO and SV reduction during periodic apnea in the failing hearts may contribute to the observed higher mortality rates in CHF patients with sleep apnea (1, 15). This could be due to increased MAP associated with apnea-induced hypoxia. Because CHF patients often suffer from inadequate tissue perfusion, any further reduction in systemic or regional blood flow during apnea could have greater functional importance and clinical impact.

Conclusion

In sedated, chronically instrumented pigs with pacing-induced cardiomyopathy, we have demonstrated an exaggerated decrease in SV and CO during obstructive apneas compared with our previous studies in normal hearts. The reason for the greater response seems to be decreases in LV preload during apneas, which were not found in normal hearts. Thus the combined effects of decreased LV preload and increased LV afterload act to decrease SV and CO in CHF. We speculate that interdependence effects are greater in the CHF model, since LV dilation would lead to increased pericardial constraint relative to normal hearts. Because venous return would be increased during obstructed inspirations, in CHF a given increase in venous return would be expected to cause a greater decrease in LV preload via interdependence mechanisms.

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Address for reprint requests and other correspondence: S. M. Scharf, Pulmonary and Critical Care Div., Long Island Jewish Medical Center, New Hyde Park, NY 11042.

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