Increased propensity for apnea in response to acute elevations in left atrial pressure during sleep in the dog

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Chenuel, Bruno J., Curtis A. Smith, James B. Skatrud, Kathleen S. Henderson, and Jerome A. Dempsey. Increased propensity for apnea in response to acute elevations in left atrial pressure during sleep in the dog. J Appl Physiol 101: 76–83, 2006. First published April 20, 2006; doi:10.1152/japplphysiol.01617.2005.—Periodic breathing is commonly observed in chronic heart failure (CHF) when pulmonary capillary wedge pressure is abnormally high and there is usually concomitant tachypneic hyperventilation. We hypothesized that acute pulmonary hypertension at pressures encountered in CHF and involving all of the lungs and pulmonary vessels would predispose to apnea/unstable breathing during sleep. We tested this in a chronically instrumented, unanesthetized dog model during non-rapid eye movement (NREM) sleep. Pulmonary hypertension was created by partial occlusion of the left atrium by means of an implanted balloon catheter in the atrial lumen. Raising mean left atrial pressure by 5.7 ± 1.1 Torr resulted immediately in tachypneic hyperventilation [breathing frequency increased significantly from 13.8 to 19.9 breaths/min; end-tidal PCO2 (PETCO2) fell significantly from 38.5 to 35.9 Torr]. This tachypneic hyperventilation was present during wakefulness, NREM sleep, and rapid eye movement sleep. In NREM sleep, this increase in left atrial pressure increased the gain of the ventilatory response to CO2 below eupnea (1.3 to 2.2 l·min⁻¹·Torr⁻¹) and thereby narrowed the CO2 reserve [PETCO2 (apneic threshold) – PETCO2 (eupnea)], despite the decreased plant gain resulting from the hyperventilation. We conclude that acute pulmonary hypertension during sleep results in a narrowed CO2 reserve and thus predisposes toward apnea/unstable breathing and may, therefore, contribute to the breathing instability observed in CHF.

PERIODIC BREATHING DURING SLEEP is a common feature of chronic heart failure (CHF). Many potential contributors to this complex phenomenon have been suggested, including reduced cardiac output and prolonged circulation time (10), enhanced peripheral (38) or central (14, 40) chemoreceptor sensitivity, and reduced cerebral blood flow (44). We have observed that CHF patients with central sleep apnea and/or periodic breathing did not show a significant normal hypoventilation at sleep onset; they also showed a reduced difference between eupneic arterial PCO2 (PaCO2) and the apneic threshold PCO2 during sleep (i.e., a narrowed CO2 reserve) because the slope of the ventilatory response to CO2 below eupnea was increased (45). Others have emphasized the potential importance of pulmonary vascular congestion and increased capillary wedge pressure, which, when present in CHF, is often accompanied by a chronic tachypneic hyperventilation and periodic breathing during sleep (3, 31, 37). With treatment of the heart failure, as capillary wedge pressure fell, both the baseline hyperventilation and the periodic breathing during sleep were resolved.

Based on these correlative data in heart failure patients, we tested the hypothesis that acute pulmonary hypertension at pressures encountered in CHF and involving the lungs, pulmonary artery and vein, and the heart would predispose to hyperventilation and to apnea/unstable breathing during sleep. We used a chronically instrumented healthy dog model in which we produced reversible increases in left atrial pressure (LAP) during sleep and determined the CO2 reserve [eupneic end-tidal PCO2 (PETCO2) – apneic threshold PETCO2], an index of propensity for apnea/unstable breathing. We found that relatively small increases in LAP during sleep resulted in tachypneic hyperventilation and narrowed the CO2 reserve, thus predisposing toward apnea and unstable breathing.

METHODS

Five unanesthetized female mixed-breed dogs weighing between 19 and 24 kg were studied during non-rapid eye movement (NREM) sleep. The dogs were trained to lie quietly and sleep in an air-conditioned (19–22°C) sound-attenuated chamber. The dogs’ behavior was monitored throughout all experiments by an investigator seated within the chamber and also by closed-circuit television. The surgical and experimental protocols of this study were approved by the Animal Care and Use Committee of the University of Wisconsin-Madison.

Chronic Instrumentation

Two surgical procedures were performed under general anesthesia, with strict sterile surgical techniques and appropriate postoperative analgesics and antibiotics. In the first procedure, a chronic tracheotomy was created, and a five-lead electroencephalogram (EEG)/electrooculogram montage and chronic femoral arterial catheter were installed. After at least a 3-wk recovery, a second procedure was performed to install a 20-mm ultrasonic flow probe (Transonic Systems, Ithaca, NY) around the ascending aorta (one dog only) and a balloon-tipped catheter in the left atrium (all dogs). The balloon-tipped catheter was a custom-made Silastic catheter (SMI, Saginaw, MI) with a 30-ml balloon volume. Inflation of this balloon partially occluded the left atrium, resulting in elevated LAP and presumably upstream pressures in the pulmonary vein and lung vasculature. Catheters and electrode wires were tunneled subcutaneously to the cephalad portion of the dog’s back where they were exteriorized. This
chronically instrumented model has been described in detail elsewhere (30).

Measurements

The dogs were intubated via the chronic tracheostomy with auffed endotracheal tube (10-mm outer diameter; Shiley, Irvine, CA). Airflow was measured via a heated pneumotachograph system (model 3700, Hans Rudolph, Kansas City, MO, and model MP-45–14–871, Validyne, Northridge, CA) connected to the endotracheal tube. The pneumotachograph was calibrated before each study with four known flows. Tracheal pressure was measured with a pressure transducer (model MP-45–14–871, Validyne) connected to a port in the endotracheal tube by means of 1.7-mm-inner-diameter high-durometer polyvinyl chloride tubing (Abbott Laboratories, North Chicago, IL). The pressure transducer was calibrated before each study by applying six known pressures. Systemic arterial blood pressure and LAP were recorded from pressure transducers (Statham) connected to the exteriorized catheters. The blood pressure transducers were calibrated daily against five known pressures. Airway PCO2 was monitored by means of an infrared CO2 analyzer (Sable Systems, Las Vegas, NV) through a second port in the endotracheal tube. The pressure support ventilator (Veolar, Hamilton Medical, Rhazuns, Switzerland) was connected to the pneumotachograph using a silent balloon-valve system such that the dog could breath spontaneously from room air or be switched abruptly to pressure support ventilation (PSV) by inflation of the balloon. All signals were digitized (128-Hz sampling frequency) and stored on the hard disk of a personal computer for subsequent analysis. Key signals were also recorded continuously on a polygraph (AstroMed K2G, West Warick, RI). All ventilatory and blood pressure data were analyzed on a breath-by-breath or beat-by-beat basis by means of custom analysis software developed in our laboratory.

Staging of Sleep State

Standard canine criteria were applied to identify the sleep stages (32). NREM sleep was defined as a synchronized low-frequency (<10 Hz) EEG associated with an absence of rapid eye movement (REM). EEG arousal was defined as a desynchronization and speeding (>10 Hz) of the EEG for >3 s. All trials that had arousals and/or sleep state change during the control or experimental periods were excluded from further analysis.

Experimental Protocols

One dog was used primarily to examine the effects of increased LAP on cardiac output and ventilatory and cardiovascular variables across sleep states. Insufficient apneic threshold data were obtained in this dog to warrant analysis, so data from this animal are not included in the mean data for the other four dogs.

Studies in each of the remaining four dogs were performed over the course of several days during periods of NREM sleep and wakefulness. The animals were unrestrained during the experiments, and the body position in which they chose to sleep was not restricted. The dogs breathed through their tracheostomies throughout the experiment. The apneic threshold for CO2 was determined by means of PSV (see below) during normoxia with no increase in LAP (control) or when LAP had been raised acutely by inflating the implanted left atrial balloon. Inflation periods were kept short (usually <2 min), and mean LAP was maintained <8 mmHg for PSV trials (additional trials without PSV were used to generate stimulus-response relationships; see below) (mean = 6.4 ± 0.8 mmHg) to minimize the likelihood of pulmonary edema.

Use of PSV to Define the Apneic Threshold

Dogs breathed room air spontaneously through the open port in the balloon valve (see Measurements). The ventilator was set in the pressure support mode, and the trigger sensitivity was set as low as possible (approximately −1.5 cmH2O), and the expiratory positive airway pressure was set at 0 cmH2O. When the balloon was inflated and the low-resistance shunt to the room sealed, the ventilator delivered preset levels of inspiratory pressure support whenever the trigger threshold was reached [i.e., the dog set its own frequency; increased pressure support resulted in increased tidal volume (Vt)]. Each pressure support level was maintained for 2 min, and then the balloon was deflated and the dog was allowed to breathe spontaneously again. At least 2 min elapsed before another PSV trial was performed. PSV was increased in steps of 1–2 cmH2O (range 2–20 cmH2O) until apneas and periodic breathing were observed. Expiratory time (TE) was measured from the end of the inspiratory flow to the onset of the next inspiration. Periodic breathing was identified visually by the presence of at least three cycles of hyperpnea and apnea with a consistent periodicity (see Fig. 1). Furthermore, the apnea lengths had to be at least 3 SDs greater than the baseline TE. The apneic threshold was taken to be the PetCO2 observed in the breath immediately after the left atrial balloon was fully inflated, tachypnea ensued immediately and remained stable. PSV [abrupt appearance of large peaks in tracheal pressure (Ptr)] caused an immediate fall in end-tidal Pco2 (PetCO2) and the appearance of periodic breathing after the fourth PSV breath. Vt, tidal volume; BP, systemic blood pressure; LAP, mean left atrial pressure.

Fig. 1. Polygraph recording of a representative trial using pressure support ventilation (PSV) to determine the apneic threshold during non-rapid eye movement (NREM) sleep. Note that, after the left atrial balloon was fully inflated, tachypnea ensued immediately and remained stable. PSV [abrupt appearance of large peaks in tracheal pressure (Ptr)] caused an immediate fall in end-tidal Pco2 (PetCO2) and the appearance of periodic breathing after the fourth PSV breath. Vt, tidal volume; BP, systemic blood pressure; LAP, mean left atrial pressure.
breathing frequency (fb; This hyperventilation was achieved by a marked increase in

Across all dogs, the mean inspired ventilation (V˙I) increased been reached, however, hyperventilation ensued immediately.

Interpreting the CO₂ Reserve

The CO₂ reserve, as defined in the previous paragraph, is an index of the propensity for apnea at the prevailing background ventilatory drive. It is the result of two factors, namely the gain of the ventilatory response to CO₂ below eupnea and the “plant gain” [ΔPaCO₂/Δalveolar ventilation (Va)] as determined under the prevailing eupneic conditions [i.e., by the point of intersection of PaCO₂ with Va along a given isometabolic line defined by the Va equation: PaCO₂ = (V˙CO₂/Va)·k, where VCO₂ is CO₂ production, and k is a constant; see Fig. 7].

In quantifying the apneic threshold and the CO₂ reserve using PSV, we presume that the cause of the apnea is due to a transient reduction in PaCO₂ induced via PSV. We previously confirmed this assumption by preventing reductions in CO₂ during PSV via added inspired CO₂ fraction (30). It was significantly prolonged but only by 10–25% compared with 200–350% prolongation when hypocapnia was permitted to occur. Studies in the carotid body-denervated dog (29), in which apneas virtually never occur in response to PSV, provided additional confirmation of the critical importance of hypocapnia in causing apnea during PSV.

RESULTS

Effect of Increased LAP on Ventilation

Figure 2 illustrates the effect on breathing of an increase in mean LAP during NREM sleep. Approximately 30 s were required to inflate the left atrial balloon sufficiently to increase LAP by ~6 Torr (+5.7 ± 1.1 Torr). Once the target LAP had been reached, however, hyperventilation ensued immediately. Across all dogs, the mean inspired ventilation (Vi) increased from 4.84 ± 0.99 to 5.65 ± 1.04 l/min (P = 0.008), resulting in a mean reduction in PetCO₂ of 2.6 ± 1.5 Torr (P = 0.037). This hyperventilation was achieved by a marked increase in breathing frequency (fb; +5.9 ± 1.7 breaths/min; P = 0.001), which more than compensated for the trend toward a reduced Vt from 0.35 ± 0.03 to 0.3 ± 0.04 liter (not significant) (Table 1).

The effects of increased LAP (+5.7 ± 1.4 Torr) were also studied during wakefulness in four of the five dogs (Table 2). These dogs showed quantitatively similar changes (vs. NREM) in mean Vi in response to increased LAP (4.67 ± 0.74 to 5.98 ± 0.52 l/min), which reduced the PaCO₂ in each dog (mean: 36.6 ± 1.4 to 34.9 ± 1.7 Torr, P < 0.05; no data available in 1 dog, therefore n = 4) by means of a significant increase in fb (14.4 ± 2.1 to 20.3 ± 1.7 breaths/min; P = 0.011), which more than compensated for the trend toward a reduced Vt (0.33 ± 0.01 to 0.30 ± 0.01 liter; not significant,

Table 1. Effect of increased LAP on steady-state breathing and PacO₂ during NREM sleep

<table>
<thead>
<tr>
<th>Dog</th>
<th>Increase in LAP, Torr</th>
<th>Mean PetCO₂, Torr</th>
<th>↑ LAP PetCO₂, Torr</th>
<th>Mean PaCO₂, Torr</th>
<th>↑ LAP PaCO₂, Torr</th>
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</tr>
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<td>34.5</td>
<td>35.1</td>
<td>33.9</td>
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<td>35.7</td>
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<td>34.2</td>
</tr>
<tr>
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<td>ND</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
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<td>37.1</td>
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</tr>
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<td>35.9*</td>
<td>36.6</td>
<td>34.9*</td>
</tr>
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<td>1.1</td>
<td>1.4</td>
<td>1.65</td>
</tr>
</tbody>
</table>

↑, Increase; LAP, left atrial pressure; PetCO₂, end-tidal PCO₂; PaCO₂, arterial PCO₂; Vi, inspired ventilation; Vt, tidal volume; fb, breathing frequency; ND, no data. *Significantly different from control, P < 0.05.

Fig. 2. Polygraph recording showing the effect of increased left atrial pressure (LAP) on breathing and cardiovascular variables during NREM sleep. Note that, after the left atrial balloon was fully inflated, bradypnea ensued immediately. There was a concomitant transient fall in BP, which rapidly returned to control levels accompanied by an increased heart rate (HR). Cardiac output fell and remained at the new lower level until LAP was returned to normal.
P > 0.14). Figure 3 is an example that illustrates that the tachypneic hyperventilation in response to increased LAP persisted across wakefulness and NREM sleep. In this animal, the tachypneic hyperventilation even persisted in REM sleep as well, although we did not examine REM systematically in this study.

Figure 4 plots regression lines of the increase in V˙I and fb as functions of increased LAP for all of the trials in all dogs. Figure 4 illustrates that, despite some variability, there is a clear linear relationship between increased LAP and ventilation (V˙I = 0.135ΔLAP + 0.65; F < 0.000) or fb (fb = 0.74ΔLAP + 1.77; F < 0.000). Individual trials showed clearly that increases in LAP as small as 1–3 Torr caused an immediate increase in fb and V˙I.

**Effect of Increased LAP on Blood Pressure, Heart Rate, and Cardiac Output**

**NREM sleep.** During NREM sleep, increased LAP resulted in an initial decrease in systemic mean arterial pressure, which gradually increased toward normal over approximately the next 60 s, at which time mean blood pressure was unchanged from control (P > 0.3). This compensation was achieved by means of an increased HR (mean = +47 beats/min; P = 0.005) in the face of a decreased pulse pressure (mean = −16.6 mmHg; P = 0.004) (Fig. 2 and Table 3). When data from all the dogs were combined, there was a significant linear relationship between HR and increasing LAP (ΔHR = 4.84ΔLAP + 21.4; F < 0.001; Fig. 5).

**Wakefulness.** The four dogs studied during wakefulness showed quantitatively similar changes (vs. NREM sleep) in cardiovascular variables in response to increased LAP. That is, increased LAP resulted in an initial decrease in systemic mean arterial pressure, which gradually increased toward normal over approximately the next 60 s, at which time mean blood pressure was unchanged from control (P > 0.3). This compensation was achieved by means of an increased HR (mean = +52 beats/min; P = 0.005) in the face of a decreased pulse pressure (mean = −14.1 mmHg; P = 0.013) (Table 4). HR tended to increase as LAP increased, although there was considerable variability during wakefulness and the regression did not achieve statistical significance (F > 0.1).

In the one dog instrumented for the measurement of cardiac output, increased LAP (+5.9 ± 0.8 mmHg; P = 0.001) caused a persistent decrease in cardiac output of 0.31 ± 0.35 l/min during wakefulness, NREM sleep, and REM sleep (P = 0.001) (Figs. 2 and 3).

**Effect of Increased LAP on the CO₂ Reserve**

Increased LAP during NREM sleep resulted in a narrowed CO₂ reserve [PETCO₂ (eupnea) − PETCO₂ (apneic threshold)] in all four dogs subjected to PSV (3.8 ± 0.98 Torr in control vs. 2.6 ± 0.66 Torr; P = 0.01; Fig. 6). This narrowed CO₂ reserve

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Table 2. Effect of increased LAP on steady-state breathing during wakefulness

<table>
<thead>
<tr>
<th>Dog</th>
<th>Mean Increase in LAP, Torr</th>
<th>Control V˙I, l/min</th>
<th>↑ LAP V˙I, l/min</th>
<th>Control VT, liter</th>
<th>↑ LAP VT, liter</th>
<th>Control fb, breaths/min</th>
<th>↑ LAP fb, breaths/min</th>
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<tr>
<td>B</td>
<td>3.6</td>
<td>5.46</td>
<td>6.65</td>
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<td>0.31</td>
<td>16.4</td>
<td>22.0</td>
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<tr>
<td>C</td>
<td>6.7</td>
<td>3.78</td>
<td>5.44</td>
<td>0.32</td>
<td>0.29</td>
<td>12.2</td>
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<td>0.33</td>
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<td>0.30</td>
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<td>20.3*</td>
</tr>
<tr>
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<td>0.52</td>
<td>0.01</td>
<td>0.03</td>
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<td>1.7</td>
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*Significantly different from control, P < 0.05.
resulted from a decrease in eupneic PETCO2 (−2.6 ± 1.5 Torr) that was greater than the decrease in the apneic threshold (−1.5 ± 1.4 Torr). The slope of the CO2 response below eupnea increased during elevated LAP in each of the four dogs (Table 5). The mean increase was from 1.31 ± 0.24 l·min⁻¹·Torr⁻¹ in normal control conditions to 2.20 ± 0.19 l·min⁻¹·Torr⁻¹ during increased LAP (P < 0.002; Fig. 7).

It is noteworthy that, in some trials in two of our dogs, the increased LAP alone produced spontaneous waxing and waning of eupneic Vt (although no apneas were observed) and systemic arterial blood pressure, despite no further change in LAP (Fig. 8). The reason for this waxing and waning was unclear; with the present techniques, we could not distinguish whether blood pressure leads the ventilatory oscillation or vice versa. However, the narrowed CO2 reserve persisted, whether Vt and blood pressure were stable or oscillatory.

**DISCUSSION**

Our major finding was that pulmonary hypertension, produced via acute increases in LAP during NREM sleep and wakefulness, caused a significant tachypneic hyperventilation and increased the slope of the ventilatory response to CO2 below eupnea. Thus the net effect of acute pulmonary hypertension was to decrease the CO2 reserve [PETCO2 (eupnea) − PETCO2 (apneic threshold)], thereby increasing the susceptibility for apnea and unstable breathing. Tachypneic hyperventilation could be elicited by increases of only 2–3 Torr in LAP, and this response occurred during both wakefulness and all stages of sleep.

**Causes of the Tachypneic Hyperventilation Induced by Pulmonary Hypertension**

We think that our study provides unique data demonstrating that a global acute pulmonary hypertension during NREM sleep provided an increased drive to breathe. The pulmonary hypertension that we produced probably also resulted in mild, reversible pulmonary congestion.

There is no consensus in the literature concerning the ventilatory effects of raised LAP or pulmonary hypertension/congestion. Tachypnea, bradypnea, and no ventilatory change have all been observed in anesthetized preparations (6, 8, 11, 19, 24, 26, 27, 34, 42). To our knowledge, the only study of the ventilatory effects of pulmonary hypertension in unanesthe-

**Table 3. Effect of increased LAP on steady-state heart rate and blood pressure during non-rapid eye movement sleep**

<table>
<thead>
<tr>
<th>Dog</th>
<th>Mean Increase in LAP, Torr</th>
<th>Control HR, beats/min</th>
<th>↑ LAP HR, beats/min</th>
<th>Control MAP, Torr</th>
<th>↑ LAP MAP, Torr</th>
<th>Control PP, Torr</th>
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<tr>
<td>B</td>
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<td>L</td>
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<tr>
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<td>11.1</td>
<td>10.4</td>
<td>13.1</td>
<td>12.3</td>
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</table>

HR, heart rate; MAP, mean arterial pressure; PP, pulse pressure. *Significantly different from control, P < 0.05.
tized animals is that of Giesbrecht and Younes (8). Our findings are the opposite of Giesbrecht and Younes in that we observed tachypneic hyperventilation, whereas they observed bradypnea. The reasons for this apparent disagreement are not clear but are likely due to differences in experimental design. Their study was designed to test the specific effect of pulmonary venous hypertension induced by increasing flow through a single lung lobe with varying degrees of restriction of venous outflow. Consequently, it is difficult to compare their results with our more global pulmonary hypertension produced via the inflation of a balloon in the left atrium.

Is there a role for baroreceptors in the ventilatory response to acute pulmonary hypertension? Increased LAP resulted initially in a decrease in mean systemic blood pressure followed by tachycardia, such that mean blood pressure was almost completely compensated at a time when tachypneic hyperventilation and increased LAP persisted and were stable (see Fig. 2 and Table 3). However, pulse pressure in our dogs was reduced, even though there was little or no change in mean pressure, and there is evidence from hemorrhage experiments to suggest that aortic baroreceptor discharge increases with reductions in pulse pressure, even in the face of maintained mean arterial pressure (9). While reductions in pulse pressure appear to be important to maintaining mean systemic pressure via the aortic baroreflex, available evidence does not support a significant role for either aortic or carotid sinus baroreceptors in the control of breathing in response to substantial reductions in arterial pressure. Thus Brunner et al. (2) showed no effect of changing (isolated) aortic pressure of −25 mmHg on ventilation in anesthetized dogs. In unanesthetized sleeping dogs, Saupe et al. (36) found no effect on eupneic ventilation of abruptly removing normal pulsatile pressure in the isolated carotid sinus or of reducing mean carotid sinus pressure up to 25 mmHg.

Based on a consensus of findings primarily from studies in anesthetized animals, it appears that several receptor types may be involved in the highly sensitive tachypneic hyperventilatory response to pulmonary congestion achieved via raised LAP. Our interpretation of reported findings is that the tachypneic hyperventilation likely arises from multiple sources. Activation of pulmonary vagal receptors, especially rapidly adapting receptors, in response to increased interstitial fluid pressure comparable to that induced by increased LAP in this study has been demonstrated by Kappagoda et al. (17, 18). Pulmonary C fibers (8, 11, 19, 34) and stretch receptors in the left atrium or pulmonary vein (25, 27) may also play a role. The marked tachycardic response to increased LAP in the face of a near constant mean arterial pressure was probably due to sympathetic and parasympathetic reflexes originating from receptors in the atria, ventricles, and pulmonary veins, which played a major role in causing sympathetic- and parasympathetic-mediated increases in HR that were observed in the face of a near normal systemic mean arterial blood pressure (7, 16, 21, 39, 41).

Relevance to Unstable Breathing in CHF

The magnitude of the CO₂ reserve during sleep is influenced by changes in plant gain (due primarily to the position of eupneic ventilation and PaCO₂ on the isometabolic line; see Fig. 7) and in controller gain (specifically the slope of the CO₂

### Table 4. Effect of increased LAP on steady-state heart rate and blood pressure during wakefulness

<table>
<thead>
<tr>
<th>Dog</th>
<th>Mean Increase in LAP, Torr</th>
<th>Control HR, beats/min</th>
<th>↑ LAP HR, beats/min</th>
<th>Control MAP, Torr</th>
<th>↑ LAP MAP, Torr</th>
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<td>116.1</td>
<td>109.4</td>
</tr>
<tr>
<td>Mean</td>
<td>5.7*</td>
<td>106</td>
<td>158*</td>
<td>91.0</td>
<td>95.9</td>
</tr>
<tr>
<td>SD</td>
<td>1.4</td>
<td>35</td>
<td>24</td>
<td>16.9</td>
<td>10.3</td>
</tr>
</tbody>
</table>

*Significantly different from control, P < 0.05.

### Table 5. Slopes of the ventilatory response to CO₂ below eupnea

<table>
<thead>
<tr>
<th>Dog</th>
<th>Normal control slope, 1/min-1/Torr</th>
<th>Increased LAP slope, 1/min-1/Torr</th>
<th>Normal control slope, 1/min-1/Torr</th>
<th>Increased LAP slope, 1/min-1/Torr</th>
</tr>
</thead>
<tbody>
<tr>
<td>L</td>
<td>1.18</td>
<td>1.95</td>
<td>0.77</td>
<td>1.19</td>
</tr>
<tr>
<td>B</td>
<td>1.38</td>
<td>2.30</td>
<td>0.71</td>
<td>1.17</td>
</tr>
<tr>
<td>C</td>
<td>1.63</td>
<td>2.39</td>
<td>1.41</td>
<td>1.97</td>
</tr>
<tr>
<td>T</td>
<td>1.07</td>
<td>2.17</td>
<td>0.94</td>
<td>1.54</td>
</tr>
<tr>
<td>Mean</td>
<td>1.31</td>
<td>2.20*</td>
<td>0.96</td>
<td>1.44*</td>
</tr>
<tr>
<td>SD</td>
<td>0.24</td>
<td>0.19</td>
<td>0.32</td>
<td>0.40</td>
</tr>
</tbody>
</table>

Normal vs. increased LAP was calculated for both V̇I and alveolar ventilation (VA) (assuming CO₂ production of 150 ml/min for VA calculation). *Significantly different from normal control, P < 0.05.
response below eupnea) (20, 30, 46). For example, in many cases of hypoventilation, such as with dopamine infusion or metabolic alkalosis, the CO2 reserve is narrowed only because of an increased plant gain, with no change in controller gain (4, 30). The opposite effect occurs for many cases of hyperventilation (hypoxia is an exception; see below), such as with acetazolamide administration (metabolic acidosis) or almitrine (a specific carotid body stimulus), i.e., reduced plant gain with no change in the CO2 response slope.

In the conditions causing hypoventilation mentioned above, breathing pattern is easily destabilized. In contrast, in the two conditions with high ventilatory drive, breathing is quite stable, which explains why pharmacological ventilatory stimulants such as acetazolamide and theophylline are effective in promoting stable breathing in patients with CHF and periodic breathing (12, 15). On the other hand, in acute hypoxia (30, 43) or in CHF patients (45), despite a reduced plant gain secondary to hyperventilation, the CO2 reserve is markedly reduced because of increased controller gain secondary to an increased slope of the CO2 response below eupnea.

Like the CHF patients of Xie et al. (45), our present findings show that mimicking acutely the pulmonary hypertension of heart failure in otherwise healthy sleeping dogs also causes tachypneic hyperventilation and sensitizes the slope of the CO2 response below eupnea. These findings suggest that pulmonary hypertension/congestion and stimulation of receptors in the lung vasculature (see DISCUSSION above) are important contributors to an increase in controller gain and, therefore, breathing instability during sleep in CHF. Our findings are consistent with the clinical data of Naughton et al. (31), who reported that high pulmonary capillary wedge pressures in CHF patients coincided with periodic breathing. However, we differ in interpretation, because these authors postulated that chronic hyperventilation was the key effect of the pulmonary congestion that caused apnea and periodic breathing. As explained above, hyperventilation, by itself, stabilizes ventilation, because it reduces plant gain and widens the CO2 reserve. Alternatively, we propose that the major destabilizing feature of pulmonary congestion is the narrowing of the CO2 reserve, because the apneic threshold for PaCO2 is reduced to a lesser extent than is the reduction in eupneic PaCO2, due to increased controller gain below eupnea.

An important caveat here is that the pulmonary hypertension induced by left atrial balloon inflation in the present study was an acute stimulus and may not have completely mimicked the stimuli and/or receptor characteristics of the long-term pulmonary hypertension observed in CHF. Furthermore, our acute perturbations did not mimic the effects of chronic pulmonary edema, alterations in cerebral vascular responsiveness, or cardiac dilation attending CHF.

In summary, we postulate that pulmonary hypertension/congestion is a significant contributor to chronic hyperventilation, apnea, and periodic breathing in CHF because it increases controller gain below eupnea. However, this is certainly not the only mechanism with the potential for contributing to breathing instability during sleep in CHF. For example, an enhanced sensitivity of the carotid chemoreceptor occurs in CHF (5, 28, 33, 38). This sensitization could lead to greater transient ventilatory overshoots during sleep and, given the pivotal role of the carotid chemoreceptor in sensing transient reductions in Pco2, also to a
more sensitive apneic threshold (29). In addition, cerebral vascular responses to hyper- and hypocapnia are significantly reduced in CHF patients with periodic breathing (44). In turn, this could also lead to a compromised protection of brain extracellular fluid PCO2 and medullary chemoreceptor [H+] in the presence of hyper- and hypocapnia and therefore to a greater propensity for increased ventilatory responsiveness above and below eupnea.

REFERENCES