Increased propensity for apnea via dopamine-induced carotid body inhibition in sleeping dogs

Bruno J. Chenuel, Curtis A. Smith, Kathleen S. Henderson, and Jerome A. Dempsey

In the present study, we used dopamine to assess the influence of specific carotid chemoreceptor inhibition on the CO2 reserve and its major determinants during sleep. Dopamine is a drug commonly used to provide inotropic support to critically ill patients; it is also known to decrease the slope of the ventilatory response slope to CO2 above eupnea (1, 2, 4, 9, 19). Dopamine is the primary inhibitory neurotransmitter in the carotid body, and its exogenous administration could be viewed as the inhibitory analog of the increased slope of the ventilatory response to CO2 above eupnea observed with hypoxia (6). Thus if dopamine were to decrease the ventilatory response slope below eupnea to a similar extent as it did above eupnea, we would predict a widening of the CO2 reserve and a reduced probability of apnea. On the other hand, if the increased plant gain attending any dopamine-induced hypoventilation was unopposed by a reduced ventilatory response slope to CO2 below eupnea, we would predict a narrowed CO2 reserve and increased propensity toward apnea.

METHODS

Six unanesthetized female mixed-breed dogs weighing between 19 and 25 kg were studied during 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 tracheostomy was created and a 5-lead EEG/electrooculogram montage was installed. After at least a 3-wk recovery, a second procedure was performed in three of the six dogs to install indwelling catheters in the left femoral artery and left femoral vein. 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 (17).

Carotid body denervation. In two dogs, an additional short surgical procedure was performed to bilaterally denervate the carotid bodies (CBX). Briefly, the carotid sinus region was exposed bilaterally and all tissues surrounding the carotid sinus were removed over a distance of 1–2 cm. CBX was confirmed before each experiment by a lack of a significant ventilatory response to intravenous bolus injection of 20–40 μg/kg of sodium cyanide.

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Measurements. The dogs were intubated via the chronic tracheostomy with a cuffed 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 (Ptr) 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. Airway PCO2 was monitored in Chicago, IL). The pressure transducer was calibrated before each study with four known flows. Tracheal pressure (Ptr) 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.

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 breathe 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 (22). NREM sleep was defined as a synchronized low-frequency (<10 Hz) EEG associated with an absence of rapid eye movement. 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. Studies in each dog were performed over the course of several days during periods of NREM sleep. 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 normoxic control conditions and during carotid body inhibition with steady-state dopamine infusion.

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 was 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. Inspiratory 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 three standard deviations greater than the baseline Te. The apneic threshold was taken to be the PETCO2 observed in the breath immediately preceding the start of periodic breathing (Fig. 1). The apneic threshold in each trial was normalized by expressing it as a difference in end-tidal PCO2 (PETCO2) from control, i.e., apneic threshold PETCO2 - eupneic PETCO2 (CO2 reserve). After examination of all trials (mean: 17 trials, range: 11–28) in a given dog, the CO2 reserve for a given condition was taken to be the narrowest CO2 reserve observed, i.e., the apneic threshold PETCO2 closest to the eupneic PETCO2.

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” (APETCO2/VA, where VA is alveolar ventilation) 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 = [VCO2/VA]*k, where VCO2 is CO2 production and k is a constant.

Intravenous infusion of dopamine. Dopamine solution was prepared on the day of each experiment. Dopamine HCl (Sigma, St. Louis, MO) was diluted in sterile saline (0.9% NaCl) to obtain the 1 mg/ml solution used for intravenous infusion. A pump was used for intravenous infusion (model 975, Harvard Apparatus, Holliston, MA), and its rate was modified to achieve a dose that provided a degree of peripheral chemoreceptor inhibition sufficient to cause a moderate amount of steady-state hypoventilation and CO2 retention.

![Fig. 1. Method of determining apneic threshold with pressure support ventilation (PSV). PSV applied at arrow on tracheal pressure trace (Ptr). In intact dogs, when the appropriate pressure was reached, a pattern of 2–4 PSV breaths interspersed at regular intervals with apneas (a,b,c...e) ensued. Apneic threshold end-tidal Pco2 (AT PETCO2) was taken to be the PETCO2 of the breath immediately preceding the first clear apnea (see METHODS for criteria). CO2 reserve is the difference between the AT PETCO2 and the eupneic PETCO2. VT, tidal volume.](http://jap.physiology.org/)

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RESULTS

Ventilatory and cardiovascular effects of dopamine infusion alone. The effects of dopamine (3.7 ± 1.27 μg·kg⁻¹·min⁻¹) infusion on eupneic ventilation are illustrated in Fig. 2 and summarized in Table 1. After a mean delay of 38.8 ± 8.6 s after the initiation of intravenous infusion, ventilation decreased an average of 14.9 ± 5.7% for the six dogs (P = 0.033). This hypoventilation persisted for the duration of the infusion, causing a mean CO₂ retention of 3.9 ± 1.9 Torr (P = 0.004), which was largely the result of a significant reduction in breathing frequency (13.9 to 11.9 breaths/min; P = 0.04). All trials also showed an initial transient instability characterized by waxing and waning of VT (see Fig. 2). VT stabilized 1.5–2 min after the start of dopamine infusion and remained stable for the duration of the infusion period (range: 1–3 h). On cessation of dopamine infusion, ventilation returned to normal within 2 min. Arterial blood pressure and heart rate did not change with dopamine infusion.

Control infusions of physiological saline solution at the same flow rates used for dopamine infusion had no effect on ventilatory or cardiovascular variables.

Effects of dopamine infusion on the slope of the ventilatory response to CO₂ below eupnea. The average increase in eupneic PETCO₂ (3.9 ± 1.9 Torr) was less than the increase in the apneic threshold PETCO₂ (5.1 ± 1.9 Torr; see Table 2). As a result, the CO₂ reserve narrowed in all six dogs (mean of 3.9 ± 0.62 to 2.7 ± 0.78 Torr, P = 0.001; range −1.5 to −3.6 Torr; see Fig. 3 and Table 2).

Table 1. Ventilatory and cardiovascular effects of dopamine infusion

<table>
<thead>
<tr>
<th>Condition</th>
<th>Ti, s</th>
<th>Te, s</th>
<th>fᵦ, breaths/min</th>
<th>VT, liter</th>
<th>Vt/Ti, l/min</th>
<th>PETCO₂, Torr</th>
<th>Gp, Torr-¹/min-¹</th>
<th>BPa, mmHg</th>
<th>HR, beats/min</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control (n = 6)</td>
<td>1.5 (0.26)</td>
<td>3.36 (1.26)</td>
<td>14 (3.2)</td>
<td>0.28 (0.04)</td>
<td>3.83 (0.59)</td>
<td>0.19 (0.05)</td>
<td>40.2 (1.5)</td>
<td>12.78 (0.92)</td>
<td>129/61 (14/5)</td>
</tr>
<tr>
<td>Low-dose dopamine (n = 6)</td>
<td>1.53 (0.24)</td>
<td>3.76 (0.79)</td>
<td>11.9* (2.2)</td>
<td>0.28 (0.06)</td>
<td>3.26* (0.29)</td>
<td>0.19 (0.04)</td>
<td>44.1* (1.8)</td>
<td>15.4 (1.21)</td>
<td>126/59 (20/4)</td>
</tr>
</tbody>
</table>

Values are means (SD); n = 4 for arterial blood pressure (BPa) and heart rate (HR). Steady-state dopamine data were obtained from intervals of non-rapid eye movement (NREM) sleep of between 5 and 20 min in length that were observed between 10 min and 1 h after the start of dopamine infusion (3.27 ± 1.27 μg·kg⁻¹·min⁻¹). Ti and Te, inspiratory and expiratory time, respectively; fᵦ, breathing frequency; VT, tidal volume; Vt, inspired minute ventilation; PETCO₂, end-tidal PCO₂. Plant gain (Gp) calculated for an increment of 1 mmHg from the steady-state values using: alveolar ventilation (VA) = (k·VCO₂)/PCO₂ assuming a CO₂ production (VCO₂) of 150 ml/min and where k is a constant. *P < 0.05.
The determinants of the CO₂ reserve are illustrated in Fig. 4. The magnitude of the CO₂ reserve is determined by the slope of the ventilatory response to CO₂ below eupnea and the eupneic plant gain, i.e., the change in P_{ACO₂} for a given change in Vₐ (see METHODS). With dopamine infusion, the slope of the ventilatory response to CO₂ below eupnea was unchanged. The plant gain increased from 12.78 ± 0.92 (Torr/l) in control to 15.35 ± 1.21 during dopamine infusion. Thus the decrease in the CO₂ reserve resulted solely from the 20.5 ± 11.3% increase in plant gain that in turn resulted from the hypoventilation caused by dopamine infusion.

The decrease in the CO₂ reserve meant that the transient increase in Vₐ above eupnea required to reach the apneic threshold was decreased from 0.35 ± 0.06 in control to 0.19 ± 0.06 l/min during dopamine infusion (see Figs. 4 and 5, A and B, and Table 2). Figure 5, A and B, illustrates the effects of this increased plant gain on susceptibility to apnea with a representative example showing that, with dopamine infusion, apnea was achieved during pressure support ventilation at 6 cmH₂O and a decrease in P_{ETCO₂} of 3.3 Torr. On the other hand, in control conditions a slightly higher level of pressure support with a reduction in P_{ETCO₂} of 3.5 Torr had no effect on breath timing.

Effects of CBX on the ventilatory response to dopamine infusion. CBX caused a consistent hypoventilation during eupnea in NREM sleep (7 trials in 2 dogs) P_{ETCO₂}, (6.5 ± 1.1 Torr). CBX virtually abolished the hypoventilation induced by dopamine infusion that occurred when these dogs were intact. Figure 6 shows an example of dopamine infusion in a CBX dog in which no changes in P_{ETCO₂}, amplitude, or timing of ventilation, or blood pressure and heart rate are evident. Figure 7 illustrates all seven trials in the two CBX dogs and shows that there is no clear pattern of change in eupneic P_{ETCO₂} in response to dopamine infusion. This contrasts with the consistent response when the carotid bodies were intact and all trials in six dogs showed marked hypoventilation (mean P_{ETCO₂} increased 4 Torr; Table 1). Vₐ, breathing frequency, blood pressure, and heart rate also did not change consistently with dopamine infusion in the CBX dogs.

DISCUSSION

Our major finding was that specific, steady-state reduction in sensitivity of the carotid body chemoreceptors by means of dopamine infusion reduced the CO₂ reserve from −3.9 mmHg in control to −2.7 mmHg, i.e., a 31% narrowing. Thus dopamine increased the propensity for apnea in response to further small transient increases in Vₐ and reductions in P_{ACO₂}. We determined that dopamine infusion had no significant effect on the slope of the ventilatory response to CO₂ below eupnea. Accordingly, the narrowing of the CO₂ reserve was solely the result of the increased plant gain that accompanied the dopamine-induced hypoventilation as a consequence of the hyperbolic shape of the P_{ACO₂}/Vₐ.

Limitations/assumptions. We assumed that dopamine was a specific inhibitor of the carotid body chemoreceptors. We believe this is a reasonable assumption at moderate doses of dopamine. Although there appear to be some species- and dose-related differences, most literature supports the idea that dopamine is relatively specific for the carotid body chemoreceptors at moderate doses (1, 3, 9). Data from the present study are consistent with this idea; Figs. 6 and 7 show that in CBX dogs there is virtually no response to dopamine infusion at 4.6 ± 0.2 μg·kg⁻¹·min⁻¹. Thus the ventilatory inhibition that we observed with low-dose dopamine infusions can be attributed entirely to dopamine’s response to dopamine infusion.

Table 2. Effects of dopamine infusion on the CO₂ reserve (AT P_{ETCO₂} − eupneic P_{ETCO₂}) as determined by progressive pressure-support ventilation

<table>
<thead>
<tr>
<th>Condition</th>
<th>Pressure Applied, cmH₂O</th>
<th>Vₐ, liter</th>
<th>Apnea Duration, s</th>
<th>Eupneic P_{ETCO₂}, Torr</th>
<th>AT P_{ETCO₂}, Torr</th>
<th>CO₂ Reserve, Torr</th>
<th>CO₂ Response Slope, l/min·Torr⁻¹</th>
<th>ΔVₐ to Reach AT</th>
<th>l/min</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control (n = 6)</td>
<td>10.9 (1.2)</td>
<td>0.61 (0.05)</td>
<td>9.5 (2.5)</td>
<td>40.2 (1.5)</td>
<td>36.3 (1.46)</td>
<td>−3.9 (0.6)</td>
<td>0.92 (0.1)</td>
<td>0.35 (0.06)</td>
<td></td>
</tr>
<tr>
<td>Low-dose dopamine</td>
<td>7.4*(2.2)</td>
<td>0.38*(0.09)</td>
<td>8.5 (2.5)</td>
<td>44.1*(1.8)</td>
<td>41.4*(1.87)</td>
<td>−2.7*(0.78)</td>
<td>1.27 (0.56)</td>
<td>0.19*(0.06)</td>
<td></td>
</tr>
</tbody>
</table>

Values are means (SD). Pressure applied, pressure required to cause apnea/periodicity. CO₂ response is controller “gain” from eupnea to apneic threshold (AT). ΔVₐ assumes VCO₂ = 150 ml/min. *P < 0.05.
inhibitory effect on the carotid body chemoreceptors. Much higher dose dopamine infusions appear to have a delayed inhibitory effect on ventilation, which does not require the presence of carotid chemoreceptors (2).

In quantifying the apneic threshold using PSV, two types of feedback influences on the control of breathing have been identified, in both sleeping dogs and humans. First, a mechanical effect of PSV at raised VT occurs, as evidenced by an average 20% reduction in diaphragm EMG and a 30% prolongation of TE on the first breath of PSV and during the steady-state of PSV when inspired CO2 fraction was raised to hold PETCO2 constant at normocapnic levels (17). Second, the major influence of PSV at raised VT is hypocapnia, which, at the apneic threshold PETCO2, results in TE prolongation of 2.5–3.5 times control TE. That hypocapnia was required to cause apnea immediately after a transient increase in VT via PSV was confirmed by showing that CBX prevented the occurrence of apnea with the rapid time course and moderate CO2 reserve observed in the intact animal (16).

Also, it is important to recognize that although a greater or lesser propensity for apnea is clearly an important determinant of periodic breathing, our findings speak only to the initiation of apnea as commonly occurs after a transient ventilatory overshoot in sleep and is critically dependant on the magnitude of the CO2 reserve below eupnea. The mechanisms that perpetuate periodic apneas and/or unstable breathing are also determined by the propensity for transient hyperventilation and other factors, which we have not measured in this study (see below).

Lability of the CO2 reserve and the propensity for apnea. Several stimuli that cause hyperventilation have been shown to change the susceptibility for apnea by increasing or decreasing the CO2 reserve below eupnea during sleep. Some of these influences, together with the present findings with dopamine infusion are compared in Fig. 8. Hyperventilation, as induced by metabolic acidosis, or carotid body-specific almitrine infusion were both accompanied by an increased CO2 reserve, as the PETCO2 at the apneic threshold was reduced out of proportion to the reduction in the eupneic PETCO2. The slope of the CO2 response between eupnea and apnea was not changed significantly; thus the increased CO2 reserve was due entirely to the reduction in plant gain. In contrast, in hypoxia the CO2 reserve during NREM sleep was narrowed in healthy dogs (17) and humans (27), as eupneic PaCO2 was reduced more than the apneic threshold PETCO2. Similar findings were observed in human patients with chronic heart failure and Cheyne-Stokes respiration during sleep (28). In both of these instances, the CO2 reserve was reduced despite an accompanying hyperventilation and reduced plant gain, because the slope of the CO2 response below eupnea was increased.

In the present study we used dopamine to create hyperventilation via carotid chemoreceptor-specific inhibition of ventilatory drive. Dopamine infusion showed a reduction in CO2 reserve, solely because of the accompanying hyperventilation and increased plant gain, with no significant change in the slope of the ventilatory response to reduced Pco2 between eupnea and apnea. The narrowing of the CO2 reserve caused by dopamine was identical to that previously shown during short-term metabolic alkalosis in the sleeping dog (17). Also, during metabolic alkalosis, the decrease in CO2 reserve was attribut-

Fig. 5. PSV trials in the same dog during control and during dopamine infusion. In control (A), a PSV level of 7 cmH2O did not result in periodic breathing, whereas a PSV level of 6 cmH2O (and therefore less hypocapnia; see text) did elicit periodicity in the steady state of low-dose dopamine infusion (B).
able solely to the increased plant gain resulting from the accompanying hypoventilation.

In summary, changes in chemoreceptor drive all have significant effects on the CO2 reserve that are predictable based on the direction of the change in eupneic \( P_{aCO_2} \) when only the plant gain is altered and in the absence of any significant change in the slope of the CO2 response below eupnea. The exceptions observed to date are hypoxia and chronic heart failure, conditions that enhance the slope of the CO2 response below eupnea, thereby markedly reducing the CO2 reserve even in the face of the reductions in plant gain that accompany the background hyperventilation.

**Carotid chemoreceptor inhibition vs. denervation.** The reduced CO2 reserve during dopamine infusion in the present study contrasts with the marked resistance to apnea observed after CBX in the sleeping dog (16). Nakayama et al. (16) observed that after CBX, twice as much hypocapnia was

![Fig. 6. A dopamine infusion trial after carotid body denervation (CBX). Note lack of effect on ventilation, blood pressure (BP), or heart rate. Contrast this with the effects of low-dose dopamine in the intact dog (Fig. 2).](image)

![Fig. 7. Mean \( P_{ETCO_2} \) changes for all dopamine infusion trials in the 2 CBX dogs contrasted with the mean change for these 2 dogs when they were intact (dashed). Note the lack of a consistent effect after CBX.](image)

![Fig. 8. Schema illustrating the effect of different background ventilatory drives on the ventilatory response slope to CO2 below eupnea (dashed lines) and the apneic threshold assuming isometabolic conditions (CO2 production = 150 ml/min). Control and dopamine infusion data are from the present study (Fig. 4). Almitrine and hypoxia data are replotted from Nakayama et al. (17). Note that almitrine has a widened CO2 reserve as one would predict given its unchanged CO2 response slope below eupnea. That is, analogous to the effects of dopamine in the inhibitory direction, almitrine’s widened CO2 reserve is due to the decreased plant gain that accompanied the hyperventilation. Contrast this with the hypoxia data, which have a narrower CO2 reserve despite a similar hyperventilation; the increase in the CO2 response slope below eupnea more than compensated for the increased plant gain met, Metabolic.](image)
required (using pressure support ventilation) to produce apneas equal in length to those observed when the dogs were intact. In addition, acute steady-state hyperoxia, which is well known to reduce carotid sinus nerve activity, had no effect (compared with normoxia) on eupneic $P_{\text{ET}}^{\text{CO}_{2}}$, the apneic threshold, or $CO_{2}$ reserve in sleeping dogs. Furthermore, periodic breathing during pressure support ventilation was never observed in the CBX animal in contrast to the periodicity readily produced during dopamine infusion in the intact animal.

This difference between carotid chemoreceptor inhibition and denervation is not explained by differences in plant gain, because background hypoxemia is substantially more severe after carotid body denervation (+9 Torr $P_{\text{ACO}_{2}}$, > intact control) vs. dopamine infusion (+4 Torr $P_{\text{ACO}_{2}}$). The difference lies, then, in a much greater $CO_{2}$ response gain below eupnea when the carotid chemoreceptors are intact, and this difference underscores the critical importance of the carotid chemoreceptor in causing apnea in response to a transient hyperventilation (16). Therefore, carotid chemoreceptors retain an important role in causing hypocapnia-induced apnea even when their baseline output is markedly depressed.

Chemoreceptor-induced breathing periodicity and changes in the $CO_{2}$ reserve. It has been proposed that the propensity for breathing instability and periodicity during sleep is enhanced by the relative dominance of carotid (over central) chemoreceptor contributions to the total ventilatory drive (11). This idea was supported by the increased instability in breathing pattern observed when carotid chemoreceptor sensitivity was enhanced pharmacologically via infusion of the dopamine antagonist domperidone in anesthetized cats (8) or of adenosine in sleeping humans (7). Significant correlations have also been reported in humans between the propensity for periodic breathing during sleep in hypoxia (13) or in chronic heart failure (25, 26) and an enhanced ventilatory response to carotid chemoreceptor stimulation. Furthermore, the sleeping dog demonstrated periodic breathing during pressure support ventilation only when the carotid bodies were intact (16).

On the other hand, our current evidence with dopamine infusion has shown that specific carotid chemoreceptor inhibition does not protect against a propensity for apnea in response to transient hyperventilation. To the contrary, the increased plant gain and unchanged ventilatory response slope below eupnea reduced the $CO_{2}$ reserve; spontaneous breathing was also momentarily unstable during dopamine infusion (see Fig. 2). In contrast, specific stimulation of carotid chemoreceptors via almitrine widened the $CO_{2}$ reserve (via reduced plant gain and unchanged ventilatory response slope below eupnea), thereby reducing the propensity for apnea in response to transient hyperventilation (17).

These apparently conflicting sets of evidence concerning the effect of specific carotid body chemoreceptor inhibition are compatible if one considers that periodic breathing requires the repetitive cycling of both a ventilatory overshoot and an undershoot. Thus together the data suggest that the propensity for periodic breathing will be increased in those situations where the ventilatory response slopes above and below eupnea are increased, thus increasing the likelihood of ventilatory overshoots as well as reducing the efficacy of undershoots despite the increased plant gain. The finding that an unstable spontaneous breathing pattern was short lived during dopamine infusion (or during metabolic alkalosis (17)) demonstrates that a reduced $CO_{2}$ reserve will enhance the propensity for apnea but is not sufficient, by itself, to perpetuate ventilatory instability or periodic breathing.

$CO_{2}$ responsiveness above and below eupnea. Traditionally, the ventilatory response slope to hypercapnia (i.e., above eupnea) has been used to define chemoreceptor sensitivity to $CO_{2}$. It is usually assumed that the slope of this response may be extrapolated below eupnea, where the apneic threshold for $CO_{2}$ is defined as the $P_{\text{CO}_{2}}$ intercept at zero ventilation (6). This extrapolation may be justified under certain conditions, such as moderate-to-severe hypoxia, which has been shown to increase the slope of the ventilatory response both above (18) and below (15) eupnea. Similarly, congestive heart failure patients experience periodic breathing in sleep and tend to have enhanced $CO_{2}$ response slopes both above (10) and below (28) eupnea. However, there are also circumstances where these slopes are not comparable. In sleeping dogs, Nakayama et al. (17) showed that almitrine administration results in no change in the slope of the ventilatory response to $CO_{2}$ below eupnea, yet this drug is known to cause an increase in slope above eupnea (12, 14, 20, 21, 24). Furthermore, in the present study, we demonstrate that dopamine administration, despite its reported slope-decreasing properties above eupnea (1, 2, 4, 9, 19) results in an essentially normal slope below eupnea. Mateika and Ellythy (15) assessed the ventilatory response to $CO_{2}$ during wakefulness in normal and obstructive sleep apnea patients. Both groups had comparable response slopes above what they term the ventilatory recruitment threshold but this threshold itself was elevated in the obstructive sleep apnea group as a result of an increased ventilatory response slope below eupnea. Thus an altered response slope above eupnea does not always mandate a similar slope change below eupnea and, therefore, extrapolation for the determination of the apneic threshold and $CO_{2}$ reserve is not universally justified (6).

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