Carotid Sinus Baroreceptor Reflex Control of Respiration

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SUMMARY. We have studied the effect of the carotid sinus baroreceptor reflex on respiration in 10 vagotomized, spontaneously breathing, pentobarbital anesthetized dogs. The carotid body chemoreceptor reflex response was eliminated by surgically excluding the carotid bodies from the carotid sinus baroreceptor area. Steady state frequency, tidal volume, and minute ventilation were measured after 25 mm Hg step changes in intrasinus pressure between 50 and 200 mm Hg. Over this range, the step decreases in intrasinus pressure caused concomitant increases in mean arterial pressure from 86 to 182 mm Hg. All of the respiratory response curves were sigmoidal in shape. Decreasing intrasinus pressure from 200 to 50 mm Hg caused respiratory frequency to increase from 4.8 to 9.7/min, and tidal volume to decrease from 704 to 515 ml. The calculated total ventilation, however, increased from 3180 to 4530 ml/min. The time of inspiration decreased from 3.7 to 2.4 seconds, and the time of expiration decreased from 9.8 to 4.1 seconds. These ventilatory responses are shown to be baroreceptor reflex mediated, and not secondary to changes in arterial pressure. These findings indicate that not only does the carotid sinus baroreceptor reflex control arterial pressure, but it also simultaneously influences ventilation, through changes in both respiratory frequency and tidal volume. (Circ Res 51: 624–636, 1982)
carotid sinus baroreceptors. The internal and external carotid arteries and any small branches originating from the carotid bifurcation were completely ligated. A catheter was placed in each lingual artery. The two lingual catheters were joined and connected to a pressure transducer (Statham P23AC) for recording intrasinus pressure. Sodium cyanide (2 ml of 0.003 N) was injected into the carotid bifurcation through the lingual catheter. The occipital artery then was ligated at its origin from the external carotid, and the cyanide injection was repeated in order to test the completeness of removal of the carotid body from the pressoreceptor area. Control injections of 2 ml of saline were performed before and after occipital ligations. By ligation of the occipital artery at this point, the blood supply to the carotid body is interrupted, and the carotid body is excluded from the “blind sac” (Schmidt, 1932). Thus, the carotid body is not exposed to changes in intrasinus pressure. Any branches of the occipital artery distal to the carotid body were also ligated to prevent backflow into the carotid body.

On two occasions, the carotid sinus baroreceptors were inadvertently denervated as a result of these procedures. The immediate reflex hypertensive response was seen and there were no further arterial pressure changes in response to carotid occlusion. These two animals were not used for this study. One other animal whose occipital artery arose from the internal carotid artery distal to the carotid bifurcation was also excluded.

When the carotid sinus baroreceptor isolation was complete, the left common carotid artery was tied, and a four-way connector was attached to the distal segment of each common carotid artery, the proximal end of the right common carotid artery, and a servo-controlled, nonpulsatile pressure-generating system (see Fig. 1B). This system allowed normal blood pressure until the proximal end of the right common carotid artery was clamped when intrasinus pressure was to be controlled (Shoukas and Sagawa, 1973).
In the second series of experiments, five dogs (19.6 ± 1.3 kg) were prepared as described above. In addition, both femoral arteries were cannulated and connected to an external reservoir, the height of which was adjusted to maintain arterial pressure constant.

For both series of experiments, pulsatile and mean arterial pressure, intrasinus pressure, ventilatory flow, and integrated tidal volume were recorded using ink recorders (Brush models 2800 and 2400).

### Experimental Protocol

In the first series of experiments, intrasinus pressure was initially held constant at 125 mm Hg. At 5- to 10-minute intervals, respiratory frequency, tidal volume, and total ventilation were monitored. Over the course of the next 30-60 minutes, and at intrasinus pressure equal to 125 mm Hg, the pentobarbital infusion rate was adjusted until the monitored respiratory variables had reached steady values. The rate of infusion which ranged from 25 to 150 mg/hr was then maintained constant over the subsequent 1-hour experimental period during which intrasinus pressure was step-changed. If, at the end of the 1-hour experimental period, the respiratory variables returned to within ±15% of the original control values, we considered that a constant level of anesthesia had been sustained during the experimental run.

Arterial blood samples were taken every 15 minutes during the control period. Arterial blood PCO₂, PO₂, and pH were measured with a blood gas analyzer (Instrumentation Laboratory). Supplemental oxygen was given to maintain the PaO₂ at or above 100 mg Hg. Arterial pH was maintained at 7.4 by infusion (50 ml/hr) of 1% sodium bicarbonate when necessary, but never during an experimental run.

In series 1 dogs, intrasinus pressure was step changed between 50 and 200 mm Hg. Between each step change in intrasinus pressure, the dog was allowed to reach a steady state. Steady state values of mean arterial pressure, frequency, tidal volume, and ventilation were monitored.

In some dogs, following the first experimental run, intrasinus pressure was again held constant for another control period while the rate of anesthetic infusion was again adjusted. At this new anesthetic infusion rate, a second run was performed, starting at an intrasinus pressure of either 50 or 200 mm Hg. Intrasinus pressure was increased and decreased over the same range as before. For each of the 10 dogs, either the experimental run or the average of two runs is reported.

Arterial blood samples were taken at intrasinus pressures of 50, 125, and 200 mm Hg for blood gas analysis.

In the second series of experiments, intrasinus pressure was held constant at 125 mm Hg for a similar control period until respiratory variables reached steady values. Intrasinus pressure was step changed to only three different levels: 50, 125, and 200 mm Hg. Intrasinus pressure was changed under two conditions: first, when arterial pressure was allowed to vary, as in the previous experiments, and second, when arterial pressure was held constant at 100 mm Hg.

For the first series of experiments, data analyses were performed in two steps. In the first step, we examined the shape of the relationship of each variable with intrasinus pressure. Data recorded when intrasinus pressure was increasing and decreasing were analyzed separately. The repeated measures analysis of variance was applied using the intrasinus pressure factors with seven levels (50 through 200 mm Hg). All variables demonstrated overall significant differences (at least P < 0.05) within animals, i.e., between intrasinus pressure levels. Linear, quadratic, and cubic orthogonal contrasts were used to test for linear, quadratic, and sigmoidal relationships. A sigmoidal relationship with intrasinus pressure was found for all variables. The associated P values for these sigmoidal relationships are presented here.

In a previous paper (Shoukas and Brunner, 1980), we had described hysteresis in the arterial pressure response to changes in carotid sinus pressure. We expected that we might see similar behavior in the respiratory responses to the same stimuli. To test for a hysteresis difference between responses to increasing and decreasing intrasinus pressure, only the 100, 125, and 150 mm Hg intrasinus pressure levels were examined. A repeated measures analysis of variance was used with one direction of change factor (with two levels) and one intrasinus pressure factor (with three levels). The repeated measures analysis assumes that the intrasinus pressure and direction of change factors are fixed and that the dog (subject) factor is random. The model used is saturated, i.e., includes all two- and three-way interactions.

Inspiratory and expiratory times were determined in only five of the dogs. Values obtained at intrasinus pressures of 50 and 200 mm Hg were compared using a t-test on paired data.

In the second series of experiments, arterial pressure, respiratory frequency, tidal volume, and ventilation at intrasinus pressures of 50, 125, 200 with arterial pressure uncontrolled and controlled were compared by two-way analysis of variance.

The maximum changes in each variable over the full 50 to 200 mm Hg range for the uncontrolled and controlled arterial pressure conditions were compared by paired t-test. For all analyses, a P value less than 0.05 was considered to be significant.

### Results

Figure 2 shows the typical responses to saline and sodium cyanide injection performed at the time of selective isolation of carotid sinus baroreceptors from the chemoreceptors. Before the occipital artery was tied, intracarotid injection of saline, but particularly sodium cyanide, caused carotid chemoreceptor reflex increases in ventilatory flow, respiratory frequency, and mean arterial pressure. After ligation of the occipital artery, the responses to saline and cyanide injection were abolished. We therefore considered that the carotid body chemoreceptors had been excluded from the area exposed to the changes in intrasinus pressure.

Figure 3 shows a recording during 75 mm Hg step changes in intrasinus pressure between 50 and 200 mm Hg. These large steps were used for the purpose of illustration of clear-cut changes in respiration. Decreasing intrasinus pressure from 200 to 125 mm Hg caused the characteristic reflex increase in mean arterial pressure from 60 to 107 mm Hg. The time constant of the response was 8–12 seconds. Respiratory frequency increased from 5.5 to 7.3 breaths/min. Tidal volume decreased from 670 to 530 ml. Ventilation increased from 3690 to 3870 ml/min. Respiratory changes occurred with a similar onset of responses. Decreasing intrasinus pressure from 125 to 50 mm Hg caused a further increase in mean arterial pressure (107 to 160 mm Hg), an increase in respiratory frequency from 7.3 to 10.4/min, and in an increase in ventilation from 3870 to 4890 ml/min. Furthermore, there was a decrease in tidal volume (530–470 ml).
Increasing the intrasinus pressure resulted in opposite changes in all the measured variables.

Arterial Blood Gases
Listed in Table 1 are the mean values for arterial \( P_{aO_2} \), \( P_{aCO_2} \) and pH measured at intrasinus pressures of 50, 125, and 200 mm Hg. Blood gas measurements were obtained at the three intrasinus pressures for most of the dogs. Although the vagotomy resulted in a slight respiratory alkalosis (Lim, 1958), the dogs maintained good acid-base balance through the course of the experiment. Along with the resulting

Figure 2. The ventilatory responses to saline and sodium cyanide before and after occipital artery ligation. See text for explanation.

Figure 3. Recording of arterial pressure and ventilatory changes in response to changes in intrasinus pressure. See text for details.
changes in ventilation caused by changes in intrasinus pressure, there were predictable changes in arterial blood gas values.

Series I: Arterial Pressure Response to Changes in Intrasinus Pressure

As intrasinus pressure was decreased from 200 to 50 mm Hg, mean arterial pressure increased significantly from a mean value of 85.9 ± 7.4 to 181.9 ± 18.5 mm Hg (n = 10) in a sigmoidal manner (P < 0.001). When intrasinus pressure was increased from 50 to 200 mm Hg, the reflex decrease in mean arterial pressure from 183.0 ± 18.0 to 88.3 ± 7.8 mm Hg was also sigmoidal in shape (P < 0.001), but followed a curve that always fell below the curve for decreasing intrasinus pressure (P < 0.01). The hysteresis in the arterial pressure-intrasinus pressure relation curve was seen consistently in all the animals.

Figure 4 shows mean arterial pressure loops for all 10 animals (panel A and B). Panel C shows mean values for the 10 dogs. Listed in Table 2 are the mean values of mean arterial pressure at each intrasinus pressure.

Response of Respiratory Frequency to Changes in Intrasinus Pressure

Stepwise decreases in intrasinus pressure from 200 to 50 mm Hg caused increases in respiratory frequency from 4.8 ± 0.53 to 9.7 ± 1.31 breaths/min. Changes in intrasinus pressure resulted in consistent changes in respiratory frequency. The dependency of frequency upon intrasinus pressure was found to be significant (P < 0.001). The shape of the frequency-intrasinus pressure relation curve was sigmoidal (P < 0.01). Using the values of frequency at 100, 125, and 150 mm Hg intrasinus pressure, we could not demonstrate a statistical difference between frequency responses to increasing versus decreasing intrasinus pressure. Therefore, in panels A and B of Figure 5, frequency responses for individual dogs for increasing and decreasing pressure were pooled together. However, at intrasinus pressure of 100 mm Hg alone, frequency responses when intrasinus pressure was decreasing were found to be significantly larger than responses to increasing intrasinus pressure (P < 0.02). Figure 5 shows respiratory frequency responses from dogs 1 through 5 (panel A), 6 through 10 (panel B), and mean values for 10 dogs (panel C).

Table 1: Arterial Blood Gas Values Measured at Three Intrasinus Pressures

<table>
<thead>
<tr>
<th>Intrasinus Pressure (mm Hg)</th>
<th>ISP = 50 (n = 9)</th>
<th>ISP = 125 (n = 9)</th>
<th>ISP = 200 (n = 7)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pao₂ (mm Hg)</td>
<td>128 ± 10</td>
<td>122 ± 28</td>
<td>102 ± 11</td>
</tr>
<tr>
<td>Paco₂ (mm Hg)</td>
<td>26.5 ± 2.0</td>
<td>30.8 ± 2.8</td>
<td>27.0 ± 3.1</td>
</tr>
<tr>
<td>pH</td>
<td>7.46 ± 0.08</td>
<td>7.42 ± 0.06</td>
<td>7.37 ± 0.09</td>
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</table>

Dogs #1 and 4 exhibited nearly identical mean arterial pressure responses to changes in intrasinus pressure. However, their respiratory frequency responses were quite different. First, the baseline values of frequency at intrasinus pressure of 125 mm Hg were very different (4.9 for dog #1 and 14.0 for dog #4). Also, their sensitivities to changes in intrasinus pressure were different. Over the full range of intrasinus pressures tested, dog #4 changed frequency from 19.7/min at intrasinus pressure of 50 to 6.9/min at intrasinus pressure of 200 mm Hg. Dog #1 changed frequency from 5.8 to 4.2/min for the same change in intrasinus pressure. We believe that this variability in the baseline values and in the sensitivity of reflex changes in ventilation is probably due to differing levels of anesthesia maintained over the experimental run. Although each dog was maintained at a constant anesthetic level, dog #1 appeared to be more deeply anesthetized than dog #4. The reflex changes in respiratory variables appeared to be much more sensitive to the level of anesthesia than did the mean arterial pressure responses.

Tidal Volume Response to Changes in Intrasinus Pressure

Figure 6 shows tidal volume responses to a change in intrasinus pressure. As intrasinus pressure was stepwise decreased from 200 to 50 mm Hg, the tidal volume decreased from 704 ± 47 to 515 ± 49 ml. Tidal volume responses were found to be dependent upon changes in intrasinus pressure (P < 0.001), and sigmoidal in shape (P < 0.01). We could not demonstrate statistically significant hysteresis in the tidal volume response to increasing vs. decreasing intrasinus pressures. Increasing and decreasing intrasinus pressure responses at a given intrasinus pressure were averaged and are shown in Figure 6, A and B.

As in the case of respiratory frequency, there are differences in the responses of different animals. At an intrasinus pressure of 125 mm Hg, dog #4 was breathing at a higher frequency and lower tidal volume than dog #1. The tidal volume response of dog #4 to changes in intrasinus pressure (i.e., the sensitivity of the reflex response) was greater than dog #1. Again, although these differences in baseline values and sensitivities are present, changes in intrasinus pressure caused consistent changes in tidal volume.

Minute Ventilation Response to Changes in Intrasinus Pressure

Responses of minute ventilation (frequency times tidal volume) are plotted in Figure 7. Stepwise reductions in intrasinus pressure from 200 to 50 mm Hg resulted in increases in minute ventilation from 3180 ± 210 to 4530 ± 250 ml/min. For the ventilatory response, it can also be seen that there exists a wide variability in the baseline ventilations at the intrasinus pressure of 125 mm Hg and that there are differences in the sensitivity of the reflex response among individual animals. Minute ventilation was dependent...
Figure 4. Mean arterial pressure responses to changes in intrasinus pressure in dogs 1-5 (panel A), 6-10 (panel B), and mean values for 10 dogs (panel C). Arrows indicate direction of intrasinus pressure change.

upon intrasinus pressure ($P < 0.001$), and the relation curve was sigmoidal in shape ($P < 0.05$). There is an apparent minute ventilation response difference between increasing and decreasing intrasinus pressure, but comparing values at intrasinus pressure of 100, 125, and 150 mm Hg, these differences were slightly larger than the 5% significance level ($P < 0.08$). However, direct comparison of ventilation responses at 100 mm Hg intrasinus pressure shows a significantly greater ($P < 0.005$) ventilation when intrasinus pressure was decreasing than when intrasinus pressure was increasing.

Inspiratory and Expiratory Durations

The inverse of respiratory frequency, the respiratory period, varies from 13.7 ± 2.6 sec at an intrasinus pressure of 200, to 6.7 ± 0.7 sec at an intrasinus pressure of 50 mm Hg. In five dogs, the partition of respiratory period into inspiratory and expiratory phases was studied.

The duration of inspiration varied as a function of intrasinus pressure, exhibiting a curve which was
similar in shape to that of the respiratory period (see Fig. 8). At an intrasinus pressure of 200 mm Hg, inspiratory duration was $3.7 \pm 0.33$ sec, and at an intrasinus pressure of 50 mm Hg, inspiratory duration was $2.4 \pm 0.17$ seconds. A t-test on paired data showed a significant difference ($P < 0.01$) between these two values of intrasinus pressures in the five dogs.

Expiratory duration was also affected by changes in intrasinus pressure. The duration of expiration at an intrasinus pressure of 200 mm Hg was $9.8 \pm 1.6$ sec, and at an intrasinus pressure of 50 mm Hg, expiratory duration was $4.1 \pm 0.3$ sec. For expiratory durations, a t-test using paired data showed a significant difference ($P < 0.05$) between the two values of intrasinus pressure.

**Series II: Influence of Arterial Pressure**

Figure 9 shows a chart recording of a typical experiment. In panel A, intrasinus pressure was increased when arterial pressure was allowed to decrease. Respiratory frequency and ventilation decreased, and tidal volume increased. Panel B shows the response in the same dog when arterial pressure was controlled at 100 mm Hg. The response is very similar to that when arterial pressure varied.

Results of series II experiments ($n = 5$ dogs) are listed in Table 3. Regardless of whether arterial pressure was controlled, changes in intrasinus pressure always resulted in statistically significant changes in respiratory frequency, tidal volume, and ventilation.

Changes in each variable, over the full range of values (50 to 200 mm Hg intrasinus pressure) were compared for controlled and uncontrolled arterial pressure conditions using a paired t-test. Changes in tidal volume and ventilation were not significantly different when arterial pressure was controlled. However, changes in respiratory frequency were significantly greater ($P < 0.05$) when arterial pressure was controlled than when it was allowed to vary.

**Discussion**

The results presented demonstrated that the carotid sinus baroreceptor reflex controls ventilation through changes in both frequency and tidal volume. In addition, both inspiratory and expiratory durations were shown to be affected by the carotid sinus baroreceptor reflex.

This study employed a vagotomized preparation. The advantages of this approach are that we could eliminate vagal afferents which mediate aortic baroreceptor, chemoreceptor, and lung inflation reflexes. However, we could not eliminate inputs from non-vagally mediated afferents, and it is possible that reflex effects mediated by these afferents could be activated as a result of changes in pulmonary pressures and volumes, and could contribute to steady state ventilatory changes. However, the ventilatory responses to changes in intrasinus pressure occur within the first breath and therefore could not be due solely to changes in the pulmonary circulation.

The stimuli used in this study were confined specifically to the carotid sinus baroreceptors. Although the blood supply to the carotid bodies was eliminated, it is possible that they continued to function. At the end of two experiments, we injected sodium cyanide directly into the carotid body through a distal branch of the occipital artery. There was no ventilatory or circulatory response to the injection at this point, some 4 hours after the isolation procedure. If any peripheral chemoreceptor activity had remained during the course of the experiment, it would tend to oppose the action of the carotid sinus baroreceptor responses measured. For example, as intrasinus pressure was decreased from 200 to 50 mm Hg, systemic

<table>
<thead>
<tr>
<th>Intrasinus pressure (mm Hg)</th>
<th>Respiratory frequency (min⁻¹)</th>
<th>Tidal volume (ml)</th>
<th>Minute ventilation (ml/min)</th>
<th>Duration of inspiration (sec)</th>
<th>Duration of expiration (sec)</th>
</tr>
</thead>
<tbody>
<tr>
<td>n = 10</td>
<td>n = 10</td>
<td>n = 10</td>
<td>n = 10</td>
<td>n = 5</td>
<td>n = 5</td>
</tr>
<tr>
<td>200</td>
<td>85.9 ± 18.5</td>
<td>704 ± 180</td>
<td>3180 ± 332</td>
<td>3.7 ± 1.7</td>
<td>9.8 ± 1.6</td>
</tr>
<tr>
<td>175</td>
<td>92.6 ± 9.0</td>
<td>691 ± 332</td>
<td>3130 ± 3.6</td>
<td>3.6 ± 10.1</td>
<td>10.1 ± 1.6</td>
</tr>
<tr>
<td>150</td>
<td>101.3 ± 9.4</td>
<td>668 ± 320</td>
<td>3320 ± 3.4</td>
<td>3.4 ± 9.8</td>
<td>9.8 ± 1.7</td>
</tr>
<tr>
<td>125</td>
<td>134.8 ± 9.6</td>
<td>615 ± 3910</td>
<td>3180 ± 3 ± 7</td>
<td>3.1 ± 7.5</td>
<td>7.5 ± 1.6</td>
</tr>
<tr>
<td>100</td>
<td>176.5 ± 7.5</td>
<td>337 ± 4590</td>
<td>3180 ± 2.6</td>
<td>4.9 ± 9.9</td>
<td>4.9 ± 1.6</td>
</tr>
<tr>
<td>75</td>
<td>191.4 ± 7.5</td>
<td>514 ± 4600</td>
<td>3180 ± 2.2</td>
<td>4.1 ± 2.3</td>
<td>4.1 ± 1.6</td>
</tr>
<tr>
<td>50</td>
<td>181.9 ± 7.5</td>
<td>515 ± 4530</td>
<td>3180 ± 2.0</td>
<td>4.1 ± 2.3</td>
<td>4.1 ± 0.5</td>
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</tbody>
</table>
arterial pressure and ventilation rose. This increase in arterial pressure might have caused an increase in backflow to the carotid bodies, through residual anastomoses. Since a steady state increase in perfusion pressure to the carotid body has been shown not to affect or to decrease ventilation (Biscoe et al., 1970), the baroreflex increase in arterial pressure could only buffer and not augment the ventilatory response to baroreceptor stimulation.

The same argument holds for the participation of the central chemoreceptors during carotid sinus baroreceptor pressure changes. Increasing intrasinus pressure from 50 to 200 mm Hg would decrease arterial pressure. The accompanying decreases in cerebral perfusion pressure and pH, and increases in Paco2 would only cause ventilation to increase. However, we always saw decreases in ventilation under this condition. These measured decreases in ventilation may have, in fact, been buffered by any response to cerebral ischemia. In order to avoid cerebral hypoxia, we maintained the Pao2 above 100 mm Hg throughout the experiment. Cerebral ischemia was unlikely since, in most of the dogs, arterial pressure did not fall below 80 mm Hg, even at high intrasinus pressures. An adequate cerebral blood supply through the vertebral arteries must have existed throughout this experiment, since baroreceptor reflex control of arterial pressure was always present.

Nevertheless, decreases in cerebral perfusion pressure could possibly have influenced the respiratory changes which we have attributed to carotid sinus baroreceptors. Nonvagally mediated afferents could also respond to drastic changes in arterial pressure. If
changes in ventilation were due simply to decreases in cerebral perfusion pressure, then one would not expect to see respiratory changes when arterial pressure was controlled. However, we always saw changes in ventilation with baroreceptor stimulation when arterial pressure was controlled. For the five dogs studied, the changes in respiratory frequency when mean arterial pressure was controlled (as in Fig. 9B) were significantly greater ($P < 0.05$) than when mean arterial pressure was allowed to vary.

To see whether changes in mean arterial pressure per se could influence ventilation, intrasinus pressure was held constant, and arterial pressure was step changed in some series II animals. Small changes in ventilation were seen when arterial pressure was increased above 80 mm Hg. However, when mean arterial pressure was decreased below this point, consistent increases in ventilation were seen, most probably due to a cerebral ischemic response. This was opposite to the response seen when intrasinus pressure was increased to 200 mm Hg; arterial pressure fell and ventilation decreased. The ventilatory responses to increasing intrasinus pressures which we are reporting could only have been blunted by any cerebral ischemic response. Therefore, our results may actually underestimate the contribution of the reflex system in this range of arterial pressure below 80 mm Hg. The amount of increase in ventilation seen when arterial pressure was lowered was dependent upon the level at which intrasinus pressure was held.
constant. For the same decrease in mean arterial pressure (from 150 to 60 mm Hg), ventilation increased by 100% when intrasinus pressure was 50 mm Hg, but increased only 30% when intrasinus pressure was 200 mm Hg. These intriguing results may imply an interaction between baroreceptor inputs and the cerebral ischemic response and warrant further, more rigorous study.

Of the 10 animals whose arterial pressure responses are shown in Figure 4, only three (dogs 2, 3, and 8) ever fell below the level of 80 mm Hg. Thus, in the remaining seven animals, the observed responses to changes in mean arterial pressure could not have contributed to the changes in ventilation seen. These changes can therefore be considered to be due to changes in baroreceptor input alone, and not secondary to changes in mean arterial pressure. This gives further proof that the arterial baroreceptor reflex does control ventilation.

The respiratory responses to carotid sinus baroreceptor pressure changes were similar to the mean arterial pressure responses. After each step change in intrasinus pressure, the onset of the respiratory responses was identical to that of the pressor response. The responses occurred within the first breath, with a time constant of 8–12 seconds. The steady state changes in all respiratory variables were also similar to the pressor response. All respiratory response curves followed the characteristic sigmoidal shape of the pressor response.
Hysteresis was always clearly seen in the mean arterial pressure response to changes in intrasinus pressure. These findings confirm results of a previous study (Shoukas and Brunner, 1980) in which intrasinus pressure was changed in steps of 25 mm Hg. The mean arterial pressure response to decreasing intrasinus pressure always followed a curve which was greater than that of increasing intrasinus pressure. Recently, Coleridge et al. (1981) have shown that this hysteresis, for the aortic baroreceptors, occurs at the receptor level—that is, that baroreceptors in the aortic nerve fired more when the aortic pressure was increasing than when it was decreasing. This behavior could explain the hysteresis seen in our mean arterial pressure and ventilatory response curves. If hysteresis does occur at the level of the receptor, one would expect to see such behavior in both the pressor and the respiratory responses to changes in intrasinus pressure. If hysteresis was found in the respiratory response as well as the pressor response, then this would clearly indicate that the changes in ventilation seen are indeed due to the carotid sinus baroreceptor reflex. We could not demonstrate statistically that hysteresis in the frequency, tidal volume, and ventilation curves was present at three levels of intrasinus pressure as we found in the pressor response. However, we could show that at an intrasinus pressure of 100 mm Hg, frequency and ventilation were greater when intrasinus pressure was decreasing than when intrasinus pressure was increasing. Hysteresis was never seen in the tidal volume responses. In any single animal, our ability to see hysteresis clearly in the ventilatory responses depended upon the constancy of anesthesia maintained during the experimental run, as discussed below. The most probable explanation for the difference between observed behavior of hysteresis in the pressor and ventilatory responses con-

Figure 8. Respiratory period, expiratory and inspiratory duration responses to changes in intrasinus pressures. Mean values for dogs 6-10 are shown. Arrows indicate direction of intrasinus pressure changes.

Figure 9. Effect of arterial pressure on ventilatory changes due to increasing intrasinus pressure from 125 to 200 mm Hg. Panel A: Response when arterial pressure is allowed to decrease reflexly. Panel B: Response when reflex decrease in arterial pressure is prevented; arterial pressure controlled at 100 mm Hg.
cens the difference in sensitivity of the two responses to different levels of anesthesia.

The major differences between respiratory and circulatory responses to changes in intrasinus pressure seemed to be related to the level of anesthesia in a particular animal. Pressor responses seemed to be relatively insensitive to an individual dog's anesthetic level. Threshold and saturation levels of pressure for the pressor reflex as well as the reflex sensitivity (gain) remained fairly constant over differing levels of anesthesia. However, for the respiratory response curves, there seemed to be a consistent dependence of thresholds, saturations, and sensitivities upon the level of anesthesia. In two of the dogs, repeated runs at different levels of anesthesia produced different respiratory response curves without affecting the pressor response curve. Although we have no objective measure of the depth of anesthesia attained, it should be fairly apparent that the anesthetic level was well correlated with the different sensitivities of the respiratory responses. Regardless of anesthetic level, changes in intrasinus pressure always caused directionally similar, if not equivalent, changes in ventilatory variables. The five dogs used in series II experiments were most probably on a lighter anesthetic plane, and exhibited higher respiratory frequencies and ventilations than those of the series I experiments. We conclude that pentobarbital anesthesia affects the respiratory response limb of the carotid sinus baroreceptor reflex much more than it affects the pressor response limb. This may account for the statistical differences in hysteresis behavior of the pressor and respiratory responses.

The increase in frequency and ventilation seen when intrasinus pressure is decreased is in agreement with earlier studies. Schmidt (1932) and Bishop (1974) both reported increases in frequency with decreases in vasopressor response limb. Levy (1966) reported a decrease in respiratory frequency when isolated aortic arch baroreceptor pressure was increased. These experiments were performed in vagally intact animals.

However, it has also been reported that, in response to aortic balloon inflation (Grunstein, 1975) and hemorrhage (Misericocchi, 1980), respiratory frequency did not change in vagotomized cats. In our vagotomized preparation, we always found increases in steady state respiratory frequency when intrasinus pressure was decreased from 200 to 50 mm Hg. The differences in results may be due to the difference in species used, or in specificity of the baroreceptor stimulus. Both the removal of vagal afferents and the elimination of carotid chemoreceptors in our preparation may be an important factor in accounting for differences in results.

We have shown that carotid sinus baroreceptors can influence both the inspiratory and expiratory duration. Bishop (1974) showed that decreasing intrasinus pressure increased both diaphragm and abdominal muscle activity. Gabriel and Seller (1969) showed an increased expiratory neuron activity when carotid sinus pressure was increased, thereby demonstrating that baroreceptors have medullary connections with expiratory neurons. Our data support the postulate that carotid sinus baroreceptors project to both inspiratory and expiratory neurons.

The tidal volume responses reported here are in direct disagreement with data reported by Heistad et al. (1975), Grunstein et al. (1975), and Misericocchi and Quinn (1980). Grunstein reported a decrease in tidal volume (for the same Paco2) with aortic balloon inflation in neurally intact cats. Misericocchi reported an increase in tidal volume following hemorrhage in neurally intact cats. In both of these studies, sodium pentobarbital was the anesthetic used. Again, the differences in results could very well be due to the intact vagus nerve and differences in stimuli used.

Heistad et al. showed that tidal volume and frequency decreased with increasing perfusing pressure on the isolated left carotid sinus. They showed a linear inverse relationship between carotid perfusion pressure and minute ventilation. Their anesthetic was chloralose-urethane. With vagi and peripheral chemoreceptors intact, an increase in carotid perfusion pressure from 100 to 200 mm Hg caused ventilation to decrease from 10.5 to 10.0 l/min. In our vagoto-

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**Table 3**

<table>
<thead>
<tr>
<th>Uncontrolled arterial pressure (n = 5)</th>
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<tbody>
<tr>
<td>Intrasinus pressure (mm Hg)</td>
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<tr>
<td>--------------------------------</td>
</tr>
<tr>
<td>50</td>
</tr>
<tr>
<td>125</td>
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<td>200</td>
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*P < 0.005

<table>
<thead>
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<th>Controlled arterial pressure (n = 5)</th>
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<td>-------------------------------------</td>
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<tr>
<td>Intrasinus pressure (mm Hg)</td>
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<tr>
<td>--------------------------------</td>
</tr>
<tr>
<td>50</td>
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<td>125</td>
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<td>200</td>
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N.S. *P < 0.005

*P < 0.025

*P < 0.025
mized, peripherally chemodenervated dogs, the total ventilation at any intrasinus pressure was lower, but changed to a larger degree for the same intrasinus pressure change, from 4.4 to 3.2 l/min. We also saw a sigmoidal relationship between ventilation and intrasinus pressure. They reported results from only two levels of intrasinus pressure; the exact shape of the ventilation-intrasinus pressure relationship was not a main focus of their study. However, they did show an important interaction between carotid baroreceptor and chemoreceptor stimulation. When both receptors are simultaneously activated, the combined response is greater than the sum of separate individual stimulations. This emphasized the importance in this experiment of separating individual effects in order to characterize the sole contribution of carotid sinus baroreceptors in the control of ventilation. It may be that during a complex stimulus like hemorrhage, where many reflexes act in concert, carotid baroreceptor reflex control of ventilation is, in fact, augmented, and plays a significant role in the maintenance of homeostasis.

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INDEX TERMS: Respiratory frequency • Tidal volume • Ventilation • Respiratory control