SUMMARY. To quantify the importance of the carotid sinus baroreceptor reflex and the interaction with epinephrine infusion on total pulmonary vascular capacity and resistance, I have simultaneously measured total pulmonary vascular compliance, changes in pulmonary blood volumes, and changes in resistances in seven sodium pentobarbital-anesthetized dogs. A preparation was used that bypasses the right and left hearts allowing for the simultaneous measurement of the pulmonary as well as the systemic vascular bed parameters. At intrasinus pressures of 50, 125, and 200 mm Hg, without epinephrine infusion, the pulmonary vascular resistance was 0.134, 0.121, and 0.109 mm Hg/(ml per min per kg) and the systemic vascular resistance was 1.21, 0.87, and 0.63 mm Hg/(ml per min per kg). Epinephrine infusion of 1 µg/min per kg at each intrasinus pressure caused the resistances of both vascular beds to increase. Pulmonary vascular resistance increased to 0.157 mm Hg/(ml per min per kg) and showed no further changes with changes in ISP. However, systemic vascular resistance did decrease from 1.49 to 1.25 at intrasinus pressures of 50, 125, and 200 mm Hg. During control runs, pulmonary vascular capacity changed 1.06 ml/kg and systemic capacity increased to 2.07 ml/mm Hg per kg at an ISP of 50 mm Hg and increased to 2.39 ml/mm Hg per kg at an ISP of 200 mm Hg during control runs. After epinephrine infusion, the systemic compliance was 1.89 ml/mm Hg per kg and again showed no changes with ISP. These data indicate that the baroreceptor reflex can exert control of pulmonary and systemic vascular resistance and capacitance and epinephrine can greatly attenuate the reflex control of both vascular beds. (Circ Res 51: 95-101, 1982)
differences in reported results have led Yu (1969) to state, "whether pulmonary blood volume decreases or increases after epinephrine infusion remains to be determined." One possible interfering factor in the measurement of pulmonary blood volume is that the apparent action of epinephrine could be buffered by the carotid sinus reflex system. This interaction has been described for the entire circulation in our previous study (Shoukas et al., 1980).

The purpose of the present study was primarily to quantify the effects of the carotid sinus baroreceptor reflex system on pulmonary vascular resistance and, particularly, capacitance. In addition, another purpose was to study the interaction between epinephrine infusion and the reflex system on pulmonary vascular resistance and capacitance.

Methods

Surgical Preparation

From a group of 14 mongrel dogs, I obtained seven technically successful experiments. The seven dogs (19.48 ± 0.88 kg) were anesthetized with sodium pentobarbital (30 mg/kg, iv). The trachea was intubated with an endotracheal tube in which a catheter was placed to monitor tracheal pressure. The endotracheal tube was connected to a respirator (Harvard; Variable Phase Dog Ventilator, model 613) breathing room air supplemented with 95% O₂ and 5% CO₂. Heat cautery and ligation of cut tissue masses were used to minimize blood loss.

The left and right carotid sinuses were isolated (Shoukas and Sagawa, 1973) from the rest of the circulatory system. The internal and external carotid arteries and any small branches originating from the carotid bifurcation were completely ligated. These surgical procedures completely isolated the carotid sinuses from the rest of the circulation. 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 servocontrolled nonpulsatile pressure-generating system. The proximal end of the right common carotid artery was clamped when intrasinus pressure was to be controlled. Mean intrasinus pressure was monitored via catheters placed in the left and right lingual arteries and commonly joined to a pressure transducer (Statham P23AC). The cervical vagosympathetic trunks were exposed and cut to eliminate the buffering effect of the aortic arch baroreceptor reflex and the cardiopulmonary receptor reflexes. Intrasinus pressure was initially set at 125 mm Hg and maintained at that level during the following bypass surgery.

The chest was opened by mid-sternal thoracotomy. Figure 1 illustrates the surgical preparation and the perfusion circuit necessary to measure simultaneous changes in pulmonary and systemic vascular capacity and resistance. The entire perfusion system was initially primed with approximately 800 ml of heparinized whole blood from another dog. If additional fluid was needed because of capillary filtration or uncontrolled bleeding, no more than 350 ml of whole blood were added, which represents less than 20% of the total blood volume of the dog and perfusion system. The left and right femoral arteries were cannulated distally and proximally and connected to a perfusion pump, Pump 2 (Sarns, model SM6002). The pulmonary artery was cannulated next, using a special cannula with an inflatable balloon. A purse-string then was tied. Normal right ventricular ejection continued throughout this procedure. The pulmonary artery cannula was connected to the outflow of a perfusion pump, Pump 1, (Sarns, model SM6002). A large bore cannula with multiple side holes was placed into the right ventricle via the right atrial appendage. All blood returning to the right heart would drain into reservoir no. 1. The balloon around the pulmonary artery cannula was inflated and perfusion Pump 1 started. The dog was allowed to stabilize for approximately 5 minutes so that the dog's arterial pressure would be within 10 mm Hg prior to the initiation of the right heart bypass. The final procedure was to bypass the left ventricle. A large bore cannula with side holes was introduced into the left ventricular lumen and its tip positioned into the left atrium through the mitral valve. Blood returning from the pulmonary vascular bed was drained into reservoir no. 2. Perfusion Pump 2 was immediately started at a rate equal to the flow of Pump 1. The heart was then purposely fibrillated. Perfusion flow rate averaged 117.0 ± 12.5 ml/min per kg for the seven dogs.

Systemic mean arterial pressure was measured through a catheter placed in the thoracic aorta via the left common carotid artery and connected to a pressure transducer (Statham P23AC). Mean pulmonary artery pressure was measured with a multiple side-hole catheter connected to a pressure transducer (Statham P23Db). Mean central venous and mean left ventricular pressures were measured with catheters equipped inside the canulas inserted in the right atrium and left ventricle, respectively, and connected to pressure transducers (Statham P23BB). Left atrial pressure was measured via a catheter sutured into the left atrial appendage and connected to a pressure transducer (Statham P23Db). Zero pressure reference for all pressure measurements was set at the junction of the inferior vena cava and the right heart under direct inspection. Central venous pressure and left atrial pressure were controlled by changing
the levels of the outflow tubes draining the right and left sides of the heart.

Blood volumes in both reservoirs were monitored continuously by recording the hydrostatic pressures of the columns of blood with pressure transducers (Beckman, model 807, 215071). The system was calibrated by changing the reservoir blood volumes by a known amount and recording the corresponding pressure changes. The resolutions of the blood volume changes were 2.5 and 1.0 ml for reservoirs 1 and 2, respectively. Pumps 1 and 2 were equipped with tachometers which produced an electrical signal that was proportional to the speed of each pump. The speeds were recorded and calibrated against flows measured with a stopwatch and graduated cylinder. All pressure, flow, and volume signals were smoothed by a low-pass filter with a time constant of 1 second and recorded on ink recorders (Brush, models 2800 and 2400). All data presented were normalized to individual body weights to allow comparison among the dogs.

The height of the opening of the tube draining the systemic vascular bed into reservoir no. 1 was adjusted such that mean central venous pressure measured 5 mm Hg. It was previously found that at central venous pressures below 3.0 mm Hg, there was a pressure-dependent nonlinearity of compliance (Shoukas and Sagawa, 1971, 1973). I therefore chose a value above 3 mm Hg to minimize the nonlinearity in the compliance measurements. Mean left atrial pressure was set between 4 and 6 mm Hg by adjusting the height of the opening of the tube draining the pulmonary vascular bed. End expiratory pressure was kept at 3 cm H2O. Before each experimental run, the end expiratory pressure was temporarily raised to approximately 15 mm Hg to prevent the development of atelectasis.

Only after all pressures and volumes reached steady state were experiments performed. At an intrasinus pressure of 125 mm Hg, the systemic vascular resistance was calculated from the difference in mean arterial pressure and mean central venous pressure divided by systemic flow and the pulmonary vascular resistance was calculated from the difference in mean pulmonary artery pressure and mean left atrial pressure divided by pulmonary blood flow.

Intrasinus pressure was set at 200 mm Hg and systemic and pulmonary compliances were measured as follows. To determine the total systemic vascular compliance, the height of the systemic outflow tube was quickly raised, in less than 5 seconds, increasing central venous pressure by approximately 2 mm Hg. The blood volume in reservoir no. 1 decreased while the venous pressure increased and reached a steady state value after 2-3 minutes. This change in steady state volume divided by the change in steady state left atrial pressure is a measure of the total pulmonary vascular compliance. The outflow tube was lowered and the procedure repeated. This resulted in four values of total pulmonary vascular compliance between atrial pressures over the range from 4 to 9 mm Hg. These four values were averaged for comparison purposes. I had previously found a linear relationship of the pulmonary venous pressure-volume relationship over this range of pressure (Shoukas, 1975).

At an intrasinus pressure of 200 mm Hg, the systemic vascular and pulmonary vascular resistances were calculated again, in the manner previously described.

Intrasinus pressure then was decreased from 200 to 50 mm Hg while central venous pressure, left atrial pressure, systemic blood flow, and pulmonary blood flow were kept constant. This decrease in intrasinus pressure always caused concomitant increases in mean pulmonary artery pressure as well as in mean arterial pressure. Changes in total systemic vascular capacity and changes in pulmonary vascular capacity were determined by measuring shifts of blood between the systemic vascular bed and reservoir no. 2. Decreasing the intrasinus pressure from 200 to 50 mm Hg always resulted in an increase in blood volume in reservoirs no. 1 and 2, indicating a decrease in systemic and pulmonary vascular capacity.

At this new level of intrasinus pressure of 50 mm Hg, the total systemic and total pulmonary vascular compliances again were determined as previously described. Total systemic peripheral vascular resistance and total pulmonary vascular resistance also were calculated. Intrasinus pressure then was elevated to 200 mm Hg and shifts of blood volumes between the dog and reservoirs were measured, as well as systemic and pulmonary vascular resistances and capacities.

After completing the control runs, I set intrasinus pressure at 125 mm Hg. All pressures and reservoir volumes were allowed to reach steady state values. While flows, intrasinus pressure, and central venous and left atrial pressures were maintained constant, epinephrine was infused at a constant rate which averaged 1.13 μg/min per kg into reservoir no. 1. Blood volume changes in reservoirs no. 1 and 2, mean arterial pressure, and mean pulmonary arterial pressure then were measured. Epinephrine was infused at a constant rate and the entire experimental procedure of changing intrasinus pressure was repeated as in the control runs.

All data are reported as the means ± SEM (n = 7 dogs). Paired t-tests and two-way analysis of variance were performed for data at ISP of 50, 125, and 200 mm Hg. Significance levels were set at P values <0.05.

Results

Table 1 give the systemic and pulmonary arterial pressures at three intrasinus pressures during control and during epinephrine infusions.

Total systemic vascular resistance, shown in Figure 2, during control runs showed significant decrease when intrasinus pressure was changed between 50, 125, and 200 mm Hg. Epinephrine infusion caused the resistance to increase significantly at each intrasinus pressure. During the epinephrine infusion, the systemic vascular resistance still decreased signifi-
Table 1

<table>
<thead>
<tr>
<th>Intrasinus</th>
<th>Pulmonary arterial pressure</th>
<th>Systemic arterial pressure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pressure</td>
<td>(mm Hg)</td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td></td>
<td></td>
</tr>
<tr>
<td>50</td>
<td>12.6 ± 0.6</td>
<td>142.4 ± 8.4</td>
</tr>
<tr>
<td>125</td>
<td>11.1 ± 0.9</td>
<td>99.7 ± 6.7</td>
</tr>
<tr>
<td>200</td>
<td>9.6 ± 0.8</td>
<td>73.4 ± 8.1</td>
</tr>
<tr>
<td>Epinephrine infusions</td>
<td></td>
<td></td>
</tr>
<tr>
<td>50</td>
<td>14.2 ± 0.6</td>
<td>172.3 ± 7.1</td>
</tr>
<tr>
<td>125</td>
<td>15.1 ± 0.7</td>
<td>161.2 ± 4.2</td>
</tr>
<tr>
<td>200</td>
<td>14.7 ± 0.7</td>
<td>145.8 ± 6.1</td>
</tr>
</tbody>
</table>

Significantly when intrasinus pressure was elevated from 50 to 125 and to 200 mm Hg. The changes in resistance between intrasinus pressures of 50, 125, and 200 mm Hg during epinephrine infusion were smaller than the control value change (P < 0.01).

Shown in Figure 3 are the pulmonary vascular resistances before and during epinephrine infusion at intrasinus pressures of 50, 125, and 200 mm Hg. As was seen with systemic vascular resistance, the pulmonary vascular resistance decreases with increases in intrasinus pressures of 50, 125, and 200 mm Hg. Epinephrine caused the resistance value to increase significantly (P < 0.02) at intrasinus pressures of 125 and 200, whereas at an intrasinus pressure of 50 mm Hg the increase was not significant. Unlike the response seen in systemic vascular resistance, the baroreceptor reflex did not change pulmonary vascular resistance when intrasinus pressure was changed from 50 to 125, and to 200 mm Hg during the epinephrine infusion.
**Discussion**

This experimental study demonstrates that the carotid sinus baroreceptor reflex exerts control over resistive and capacitive properties of the pulmonary as well as systemic vascular beds.

The reflex increase in pulmonary vascular resistance during control runs, caused by changing intrasinus pressure from 200 to 50 mm Hg, equaled 28%. This change in resistance is consistent with, although slightly higher than, the changes in pulmonary artery pressure of approximately 2 cm H$_2$O, reported by Daly and Daly (1959). One difference in results could be caused by the fact that these investigators only changed carotid sinus pressure between 200 and 100 mm Hg, whereas I changed carotid sinus pressure over a wider range.

To the best of my knowledge, there is no published information about the carotid sinus baroreceptor reflex control of pulmonary vascular capacitance. Therefore, direct comparison of my data with others is impossible. During control runs, when intrasinus pressure was changed from 200 to 50 mm Hg at constant left atrial pressure, pulmonary reservoir blood volume increased 1.06 ml/kg showing a definite
decrease in pulmonary vascular capacitance by either a decrease in compliance, the slope of the pressure-volume relationship, or a change in unstressed vascular volume, the volume intercept at zero pressure. Ingram et al. (1970) have shown that the pulmonary artery pressure-diameter relationship changes its slope with sympathetic nerve stimulation, whereas norepinephrine caused a parallel shift in the relationship. More recently, Hakim et al. (1979), in an isolated lobe of dog lung, have shown changes in pulmonary vascular compliance caused by nerve stimulation, hypoxia, and hormones. Since there was a significant pulmonary vascular compliance increase, from 0.30 to 0.33 ml/mm Hg per kg, I cannot rule out either possibility.

The changes in systemic variables are consistent with our previous findings (Schmidt et al., 1971; Shoukas and Sagawa, 1973; Drees and Rothe, 1974; Numao, 1977; Shoukas et al., 1980; Shoukas et al., 1981). In addition, the pulmonary compliance values I obtained in this series of experiments (0.30 ml/mm Hg per kg at intrasinus pressure of 50 mm Hg and 0.33 ml/mm Hg per kg intrasinus pressure of 200 mm Hg) are consistent with the sum of the arterial and venous compliances that I reported previously using an entirely different technique (Shoukas, 1975). These results are also consistent with the values reported by Milnor et al. (1960) for humans and those of Lanari and Agresti (1970) for dogs.

One limitation, though not specific to my method, is that the measured total pulmonary vascular compliance value is the sum of many segmental compliances specified at different pressures. However, this feature is not necessarily a drawback from a physiological standpoint, because those different segments of the pulmonary vascular tree are normally exposed to those different pressures rather than a single uniform pressure. For this reason, the sum of compliances measured at the physiological pressure environments of these vascular segments may be a more useful measure of the total pulmonary compliance in the real situation. In addition, the measured total pulmonary compliance includes the compliances of the fibrillating left atrium and ventricle. However, the sum of atrial and ventricular compliances is 0.05 ml/mm Hg per kg (Suga et al., 1974; Shoukas, 1975). This amounts to only 10 to 15% of the measured total pulmonary compliance value.

Epinephrine infusion at an intrasinus pressure of 125 mm Hg always caused a consistent increase in pulmonary arterial pressure as well as a decrease in pulmonary vascular capacity at constant flow. The change in pulmonary reservoir volume caused by infusion of epinephrine at constant intrasinus pressure agrees with the finding of Daly et al. (1940) who reported approximately 30-ml changes in large dogs. The blood volume shifts in the pulmonary vascular bed seen with epinephrine infusion at constant intrasinus pressure can be, in part, caused by changes in unstressed vascular volume, as well as changes in vascular compliance. However, I cannot rule out the possibility that epinephrine relaxes airways and might reduce vascular volume, thus expelling blood from the pulmonary vascular bed. Permutt et al. (1961) showed that the direction of the changes in pulmonary blood volume during lung inflation depended on the transpulmonary pressure and found that there is no simple answer to the question: does the pulmonary vascular bed get bigger or smaller with lung inflation? With epinephrine infusion, the problem may be more involved. The net effect that I have seen in this series of experiments is that epinephrine, by whatever mechanism, caused pulmonary blood volume to decrease.

Feeley et al. (1963) have shown in the intact dog that pulmonary blood volume increases rather than decreases with infusion of epinephrine at rates equal to 1.0 μg/min per kg. They attribute the differences in results to opposing factors: (1) increased vasomotor tone or stiffness from the direct action of epinephrine on pulmonary vessels in the isolated preparation causing blood volume to decrease, and (2) increased transmural distending pressure resulting from the action of epinephrine on the heart and systemic vascular bed which tends to increase blood volume in the intact dog.

Feeley measured increases in pulmonary arterial and venous pressures of approximately 5 and 4 mm Hg, respectively, during infusions of epinephrine. Using data I had previously published on isolated pulmonary vascular bed compliances (Shoukas, 1975), and an overall systems approach, I can calculate the increase in pulmonary blood volume caused by distention. Using a pulmonary arterial compliance of 0.18 ml/mm Hg per kg and the 5 mm Hg increase in pulmonary arterial pressure, I calculate a 0.90 ml/kg increase in pulmonary arterial volume. Similarly, for the venous side of the pulmonary vascular bed, a compliance of 0.13 ml/mm Hg per kg and a 4 mm Hg increase in venous pressure results in a 0.52 ml/kg increase in pulmonary venous blood volume. The sum, 1.42 ml/kg, is the total increase in pulmonary blood volume that would be expected by distention of the pulmonary vasculature. This value is slightly greater than the decrease reported here, namely 1.25 ml/kg, seen when epinephrine was infused at constant sinus pressure. The difference in these values, 0.17 ml/kg, would show a net increase in pulmonary blood volume in the intact dog. This value is an underestimation, since, in the intact dog, epinephrine infusion would also cause arterial pressure and therefore intrasinus pressure to increase from approximately 100 to 160 mm Hg. This increase in intrasinus pressure would cause a neurally mediated vasodilation and increase in pulmonary blood volume of 0.53 ml/kg. The value of 0.53 ml/kg is one-half the blood volume shift seen when intrasinus pressure was changed from 50 to 200 mm Hg. The value of 0.53 ml/kg added to the value of 0.17 ml/kg gives a 0.70 ml/kg increase in pulmonary blood volume. This value is approximately one-third the value obtained by Feeley et al. (1963). In the intact animal, not only
do the carotid sinus baroreceptors affect the pulmonary vasculature, but the aortic arch baroreceptors may play an important role. Preliminary evidence from our laboratory suggests that the aortic baroreceptors are as important as the carotid sinus baroreceptors for control of pulmonary resistance and capacity and that the 0.70 ml/kg could be as large as 1.40 ml/kg.

Therefore, I cannot refute the assertion of Feeley et al. (1963) that the net effect would be an increase in pulmonary blood volume in the intact dog, despite the existence of a decrease in blood volume caused by epinephrine in the isolated pulmonary vascular bed. Furthermore, the increase in pulmonary blood volume may to a large extent be caused by the participation of both the carotid sinus and aortic arch baroreceptors.

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