The Importance of the Spleen in Blood Volume Shifts of the Systemic Vascular Bed Caused by the Carotid Sinus Baroreceptor Reflex in the Dog

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SUMMARY To quantify the relative importance of the spleen in the carotid sinus baroreceptor reflex control of total blood volume, we studied the reflex control of systemic vascular capacity before and after removal of the spleen in 18 sodium pentobarbital-anesthetized dogs. Venous return was diverted into a reservoir while cardiac output and venous pressure were maintained constant. Intrasinus pressure was either raised or lowered between 50 and 200 mm Hg, and this mobilized blood into or out of the reservoir. Two sets of experiments were performed: one in which the spleen was acutely removed and the other in which a snare occluder was placed around the spleen. In the first series with the spleen intact, the volume shift amounted to 8.42 ml/kg and after splenectomy the volume shift was attenuated to 5.17 ml/kg. The average difference in these responses amounted to 2.59 ml/kg. In the second series of experiments in which we repeatedly measured volume shifts with spleen intact and spleen removed, the volume shift amounted to 19.57 ml/kg with spleen intact and 8.20 ml/kg with spleen removed. The average difference amounted to 2.37 ml/kg. There was a significant increase in total systemic vascular compliance for all dogs tested in both sets of experiments from 2.15 ± 0.08 to 2.41 ± 0.12 ml/mm Hg per kg when intrasinus pressure was increased from 50 to 200 mm Hg before splenectomy. After splenectomy, the compliance still increased significantly from 2.17 ± 0.12 to 2.47 ml/mm Hg per kg when intrasinus pressure was increased from 50 to 200 mm Hg. However, total systemic vascular compliance before and after splenectomy at the same intrasinus pressure showed no significant differences. We conclude that, although the spleen contributes significantly to the blood volume mobilization, it is not the major contributor to total systemic blood volume shifts caused by carotid sinus baroreceptor reflex in dogs. Circ Res 49: 759-765, 1981

PREVIOUS studies (Shoukas and Sagawa, 1973; Shoukas and Brunner, 1980) have demonstrated that the carotid sinus baroreceptor reflex is capable of changing total systemic vascular capacity. The reflex blood volume shift was as large as 13 ml/kg when intrasinus pressure was changed between 50 and 200 mm Hg while keeping cardiac output and central venous pressure constant. However, it is not clear which specific organs or vascular beds contribute to the total blood volume shift. Donald and Aarhus (1974) have reported that during supramaximal splenic nerve stimulation the spleen can expel a mean of 148 ml for a 10-kg dog, or 14.8 ml/kg. Karim and Hainsworth (1976) measured capacitance changes in the isolated abdominal vascular bed of the dog during bilateral stimulation of the splanchnic sympathetic nerves. Their data show a 39% reduction, or 2.21 ml/kg, in response after splenectomy. More recently, Carneiro and Donald (1977) have reported that the spleen is capable of expelling only 2.5 ml/kg during carotid occlusion.

Although there are quantitative data on isolated splenic blood volume shifts, as well as total systemic blood volume shifts caused by the reflex, to our knowledge there are no reported studies which measured both in the same animal. The purpose of this investigation was to quantify to what extent the spleen contributes to the total systemic blood volume shift caused by the carotid sinus baroreceptor reflex.

Methods

Since two different series of experiments were performed in two groups of dogs, we will describe only those surgical and experimental procedures common to both experiments. Those procedures specific to each series will be described under Specific Procedures and Protocols.

Eighteen mongrel dogs (21.3 ± 1.7 kg) were anesthetized with sodium pentobarbital (30 mg/kg, iv). Heat cautization and complete ligation of the cut tissue masses were used for every incision 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. A four-way glass 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 connected 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.

A right thoracotomy was performed at the 5th intercostal space under positive pressure ventilation with 95% O2 and 5% CO2. Figure 1 illustrates the surgical preparation and the perfusion circuit necessary to measure changes in systemic vascular capacity. The right atrial appendage was cannulated first and connected to the outflow side of a perfusion pump (Sarns model 5M6002) primed with whole blood from another dog. In our first series of experiments only whole blood was used throughout. The superior vena cava then was cannulated, and pump flow was readjusted to maintain reservoir volume, we supplemented with Ringer's solution. No more than 400 ml were added; this represents less than 20% of the total blood volume of the dog and perfusion system. In the second series, only whole blood was used throughout the experiments. The superior vena cava then was cannulated and blood drained into a reservoir. Perfusion was immediately started with an initial flow of 30 ml/min per kg. The inferior vena cava then was cannulated, and pump flow was readjusted so that arterial pressure approximated the level that existed before atrial cannulation and was maintained constant throughout the experiment. Careful attention was placed on maintaining the dogs' body temperature constant at 37.5°C throughout the experiments. Perfusion flow rate averaged 112 ± 6 (sd) ml/min per kg for the dogs tested. Ligature of the azygos vein completed the surgery.

Central mean arterial and venous pressures were measured through catheters placed in the thoracic aorta and the inferior vena cava via the right femoral artery and vein, respectively, and connected to pressure transducers (Statham P23AC and P23BB). Zero pressure was referenced at the junction of the inferior vena cava and the right heart under direct inspection. Blood volume in the reservoir was continuously monitored by recording the hydrostatic pressure of the column of blood with a pressure transducer (Beckman model 807, 215071). The system was calibrated by changing the reservoir blood volume by a known amount and recording the corresponding pressure change. The resolution of the blood volume change was 2.0 ml. All pressure, flow, and volume signals were smoothed by a filter with a time constant of 1 second and recorded on an ink recorder (Brush model Mark 200).

**Specific Procedures and Protocols**

**Series I: Nonreversible Spleen Elimination**

In nine dogs (23.4 ± 1.2 kg) the intrasinus pressure was initially fixed at 50 mm Hg. The height of the opening of the tube draining venous return into the reservoir 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). We therefore chose a value of 5 mm Hg to minimize the nonlinearity in the compliance measurements. Only after arterial and venous pressures and reservoir volume had reached steady states was the measurement of total systemic vascular compliance begun.

In order to determine the total vascular compliance, the height of the outflow tube was quickly raised, in less than 5 seconds, increasing central venous pressure by approximately 2 mm Hg. The blood volume in the reservoir 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 venous pressure is the total systemic vascular compliance. The height of the outflow tube was then lowered to its previous control level of 5 mm Hg which then caused a concomitant increase in steady state reservoir volume. Total systemic compliance was again calculated from the steady state changes in volume and venous pressure. The measurement of total compliance was repeated to check the reproducibility of the data. This resulted in four measurements of total compliance between a central venous pressure of 5-7 mm Hg and an intrasinus pressure of 50 mm Hg.

Changes in total vascular capacity caused by the carotid sinus baroreceptor reflex were determined.
by measuring shifts of blood between the systemic vascular bed and the reservoir. With venous pressure controlled at 5 mm Hg and systemic flow maintained constant, the pressure in the isolated sinuses was stepwise changed from 50 to 200 mm Hg. Four minutes later, or when a steady state had been reached, the reservoir blood volume decrease was determined as a measure of the increase in total vascular capacity. The changes in reservoir blood volume were corrected for blood loss and filtration. As seen in Figure 2, the dashed line is drawn parallel to the steady state slope of the volume signal. The volume changes were measured between the dashed line extended to zero time and the actual volume trace.

At this new level of intrasinus pressure of 200 mm Hg, the total systemic vascular compliance was again determined. Intrasinus pressure was decreased to 50 mm Hg and the shifts of blood volume between the animal and reservoir were measured. A minimum of four measurements of blood volume shifts was obtained for each animal.

Following these control procedures and while intrasinus pressure was set at 50 mm Hg, the dogs were splenectomized through a midline abdominal incision. All arterial and venous branches communicating with the spleen were completely ligated. The spleen was then removed and the incision sutured closed. This entire procedure took no more than 7 minutes to perform. Again arterial and venous pressures and reservoir volume were allowed to reach steady state values. The entire experimental procedure was then repeated as in the control runs described above, but without the spleen.

Series II: Reversible Spleen Elimination

In order to test the possibility that any reductions in vascular capacity changes after splenectomy might in part be related to surgical trauma and deterioration with time, we performed another set of experiments.

Experiments were performed on an additional nine dogs (19.6 ± 1.6 kg) using the same techniques as previously described to measure the total systemic vascular compliance and vascular capacity changes. Changes in systemic vascular capacity caused by the carotid baroreceptor reflex were initially determined prior to any abdominal surgery. At least four determinations of blood volume shifts and two determinations of total systemic vascular compliances were performed.

After this initial period of measurements, the spleen was exposed through a midline abdominal incision and umbilical tape was placed loosely around all arteries and veins communicating with the spleen. The two ends of the ties were passed through stiff plastic tubing to form a snare occluder. With the snare occluder in place, but not occluding the blood vessels, the spleen was repositioned into the abdomen and the incision loosely sutured closed.

After all pressures and volume had reached steady state, intrasinus pressure was again changed between 50 and 200 mm Hg and blood volume shifts into and out of the reservoir recorded. Measurements of total systemic vascular compliance were again made at the two intrasinus pressures. After these procedures, the snare occluder(s) was tightened, removing the spleen from the circulation. Measurements of blood volume shifts and total systemic vascular compliance were then repeated.

After this run, the snare was loosened and the experiments were repeated to check the reproducibility of results. The measurements of blood volume shifts were again repeated in each dog with a minimum of three determinations with no spleen in the circulation and five with the spleen in the circulation. The entire procedure took between 90 and 180 minutes to perform from the first determination of vascular capacity changes.

All data presented were normalized to individual body weights to allow comparison among the dogs. Data are reported as the mean value ± SEM. Linear regression and covariance analysis were performed on the data from series II experiments. A P value less than 0.05 was considered to be significant.

Results

Series I

Figure 2 shows an actual experimental run from one dog to determine the changes in vascular capacity before and after splenectomy. Prior to splenectomy when intrasinus pressure was decreased from 200 to 50 mm Hg, the arterial pressure rose from 75 to 120 mm Hg, a change of 45 mm Hg. In the present experiments since cardiac output is maintained constant, the change in arterial pressure reflects only the change in total peripheral resistance caused by the carotid sinus baroreceptor reflex. A larger increase in systemic blood pressure would have been seen if cardiac output had been allowed to vary. Steady state reservoir blood volume also increased by 175 ml within 5 to 6 minutes. After splenectomy, intrasinus pressure was changed from 200 to 50 mm Hg and arterial pressure rose from 80 to 120 mm Hg, a change of 40 mm Hg, which was nearly equal to the change observed prior to splenectomy. Steady state reservoir blood volume increased by 125 ml. This increase is 50 ml less than that before splenectomy.

Figure 3 shows the data for nine dogs in series I experiments. Shown in the upper panel is the change in reservoir blood volume and in the lower panel the change in arterial pressure in response to a change in intrasinus pressure between 50 and 200 mm Hg before and after splenectomy. Both qualitatively and quantitatively similar results were observed in seven of the nine dogs in these experiments. In the other two dogs, one showed no attenuation of the volume response after splenectomy and the other showed a larger response after sple-
Spleenectomy. In both dogs, however, prior to splenectomy, the arterial pressure responses were nearly 50% of the mean values of the other seven dogs. Prior to splenectomy the mean volume shift amounted to 8.42 ± 1.43 ml/kg, whereas after splenectomy the mean volume shift dropped to 5.17 ± 0.97 ml/kg. This difference was significant \( P < 0.01 \) by paired t-test of the mean values. The change in arterial pressure for all nine dogs averaged 49.87 ± 5.93 mm Hg prior to splenectomy and was 51.08 ± 5.62 mm Hg after splenectomy. There was no statistically significant difference in arterial pressure before and after splenectomy by paired t-test.

In only six of the nine dogs (dogs 1, 2, 6, 7, 8, and 9) tested could we get complete data on compliance to perform statistical analysis. Prior to splenectomy, at an intrasinus pressure of 50 mm Hg, the compliance was 2.11 ± 0.10 ml/min Hg per kg which significantly increased \( P < 0.05 \) \((n = 6)\) to 2.37 ± 0.21 ml/mm Hg per kg at an intrasinus pressure of 200 mm Hg by paired t-test of mean values. After splenectomy, at an intrasinus pressure of 50 mm Hg, the compliance was 2.17 ml/mm Hg per kg and again was found to significantly increase \( P < 0.05 \) \((n = 6)\) to 2.48 ml/mm Hg per kg at an intrasinus pressure of 200 mm Hg. The vascular compliances before and after splenectomy for each of the intrasinus pressures were not significantly different \( P > 0.3 \) \((n = 6)\).

Series II

Figure 4 shows the actual data on reservoir blood volume changes as a function of time from two different dogs. These data are typical of the data collected from all nine dogs. The right panel of Figure 4 shows the reservoir volume change invariant with time whereas in the left panel a definite increase in reservoir volume change with time. It should be noted, however, that the reservoir volume responses were clearly attenuated while the spleen was removed in both cases. Linear regression and covariance analyses were performed on the data from each dog with the spleen intact and with the spleen removed.

Table 1 summarizes the data on the linear regression for all nine dogs. In five of the dogs, the slope of the reservoir volume change as a function of time with the spleen intact or removed was not significantly different from zero. The other four dogs showed a consistent increase in volume change with time for the spleen intact or removed. Analysis of covariance of the volume change for each of the nine dogs indicated that the two curves, spleen intact and spleen removed, were significantly different. The slopes of the volume versus time curves for each dog for spleen intact and spleen removed were not significantly different, as Table 1 shows. Therefore, the difference in these curves arises from a decrease in the mean value when the spleen is removed. This mean value of the difference...
amounted to $2.37 \pm 0.25 \text{ ml/kg}$ for all nine dogs.

The changes in arterial pressures ranged from 35 to 115 mm Hg for a change in intrasinus pressure from 50 to 200 mm Hg. In no dog was there any statistically significant difference in arterial pressure changes with time. The change in arterial pressure for all nine dogs averaged 67.3 mm Hg. These results were not different whether the spleen was intact or removed from the circulation.

In all nine dogs, with the spleen intact, at an intrasinus pressure of 50 mm Hg, the compliance was $2.20 \pm 0.07 \text{ ml/mm Hg per kg}$, and this significantly increased ($P < 0.01$) to $2.44 \pm 0.10 \text{ ml/mm Hg per kg}$ at an intrasinus pressure of 200 mm Hg. After removal of the spleen, at an intrasinus pressure of 50 mm Hg, the compliance was $2.16 \pm 0.07 \text{ ml/mm Hg per kg}$ and again increased to $2.46 \pm 0.08 \text{ ml/mm Hg per kg}$ at an intrasinus pressure of 200 mm Hg. The compliances with the spleen intact and removed for each intrasinus pressure were not significantly different.

Discussion

The results of our study demonstrate that the entire systemic vascular bed is capable of changing its capacity to hold blood in response to the carotid sinus baroreceptor reflex.

In series I, the value of 8.42 ml/kg for an intrasinus pressure change between 50 and 200 mm Hg prior to splenectomy and the mean zero time intercept volume change with spleen intact, 10.51 ml/kg, were found to be statistically significantly different by t-test of the mean values. A notable difference in the two series of experiments is that the time needed to perform the carotid sinus isolation was reduced in the second series and the reflex system on the average caused larger changes in arterial pressure, 51.08 mm Hg compared to 67.3 mm Hg.
for the same intrasinus pressure change. Additionally, although the perfusion system was primed with whole blood, in series I experiments we supplemented with Ringer's solution, whereas in series II only whole blood was used. Therefore, lower responses in series I could have been in part caused by the more rapid deterioration of the preparation with time. Although a difference in responses does exist between series I and II, the data are consistent with our previous findings (Shoukas and Sagawa, 1973; Shoukas and Brurtner, 1980).

It was expected that surgical trauma and experimental conditions would cause an attenuation of the volume responses. This was specifically tested in series II experiments. Surprisingly, the volume change with time either showed no change or even increased in some dogs. This increase of volume change with time either showed no change or even increased in some dogs. This increase of volume change with time either showed no change or even increased in some dogs. Nevertheless, there was always a consistent attenuation in the volume response when the spleen was removed in both series of experiments. This is evident from both series I and II experiments. In series I experiments for all nine dogs, the volume change prior to splenectomy was taken as the control of 100%. After splenectomy the average change in reservoir volume for these dogs amounted to 68 ± 9% of the control. The difference, 32%, of the control amounted to 2.69 ml/kg in series I experiments. The mean difference in volume change between spleen intact and spleen removed from series II experiments was found to be 2.37 ml/kg. There was no statistically significant difference between series I and II experiments by t-test of the mean values.

For all 18 dogs tested there was an attenuation of 2.46 ml/kg in response after spleen removal which cannot be considered to be caused solely by the spleen. Carneiro and Donald (1977) have shown that blood mobilization caused by carotid occlusion from the intestine was greater in splenectomized dogs than when the spleen was left intact. Furthermore, acute laparotomy and manipulation of the intestinal vascular bed could further alter the responses after splenectomy. Therefore, we are cautious in ascribing the attenuation of 2.46 ml/kg in response after spleen removal to the spleen per se. Karin and Hainsworth (1976) used bilateral stimulation of the sympathetic splanchnic nerves to determine active vascular capacity changes in a constant flow isolated abdominal vascular bed preparation. They found a 39% reduction in vascular capacity changes when the spleen was intact compared to when the spleen was removed. The value of 2.46 ml/kg is consistent with the findings of Carneiro and Donald (1977) who found a value of 2.5 ml/kg caused by carotid occlusion. We used the data in Table 2 of the Karin and Hainsworth (1976) publication, and calculated the difference in vascular capacity change for the spleen intact and after its removal. This difference amounted to 2.21 ± 0.60 (SE) ml/kg, which is again very close to the value Carneiro and Donald (1977) and we obtained.

The overall range of volume changes of the spleen may be much greater than the volume change associated with the carotid sinus baroreceptor reflex. For example, the value we report is well below the values of blood volume changes for the spleen of 14.8 ml/kg reported by Donald and Aarhus (1974) for supramaximal splenic nerve stimulation. In addition, Rubin et al. (1979) investigated
the effects of nitroprusside on blood volume changes in the entire systemic vascular bed of dog and showed that the volume response was attenuated by as much as 80% in chronically splenectomized dogs compared to intact dogs. These authors therefore concluded that the spleen was the major site of volume changes, approximately 10 ml/kg, induced by sodium nitroprusside.

The total systemic vascular compliance in series I and II experiments is in agreement with previously reported values from our own laboratory (Shoukas and Sagawa, 1971, 1973), as well as that reported by others (Drees and Rothe, 1974; Numao and Iruichijima, 1977; Rubin et al., 1979). The significant increase in compliance of approximately 12% when intrasinus pressure was increased from 50 to 200 mm Hg, either before or after spleen removal, is consistent with more recent experiments by Shoukas and Brunner (1980), who found a 22% increase in compliance when intrasinus pressure was increased from 50 to 200 mm Hg. This result is clearly different from that of the study by Shoukas and Sagawa (1973) in which it was reported that the reflex did not significantly affect the mean compliance values between successive 25-mm Hg regions of intrasinus pressure between 75 and 175 mm Hg. In that study, the mean steady state compliance was reported as 2.01 ± 0.16 ml/mm Hg per kg at an intrasinus pressure of 75 mm Hg and 2.30 ± 0.17 ml/mm Hg per kg at an intrasinus pressure of 175 mm Hg. However, after carefully rechecking these previously published data (Shoukas and Sagawa, 1973), we have found that there is a statistically significant difference, 13%, of compliance values obtained at these two extremes of intrasinus pressure by t-test of the difference of mean values. Therefore we conclude that the baroreceptor reflex affects vascular capacity not only by shifting the pressure-volume relationship, the “unstressed vascular volume,” but also by changing the slope of the pressure-volume relationship, namely, the compliance. At the same intrasinus pressure we saw no significant difference between compliances before or after splenectomy. Rubin et al. (1979) obtained similar results. Although the spleen is capable of mobilizing significant quantities of blood in response to the carotid sinus baroreceptor reflex, the spleen’s compliance is only 4–7% of the total systemic vascular compliance (Donald and Aarhus, 1974).

In series I experiments, the changes in arterial pressure before and after splenectomy were found to be 49.9 and 51.1 mm Hg, respectively. In series II experiments, the arterial pressure change average of 67.3 mm Hg was significantly larger than the value from series I experiments. The lack of increases in time-dependent arterial pressure despite the time-dependent increase in reservoir volume change in four dogs from series II experiment would indicate that capacitance vessels may be more active to various stimuli than resistance vessels. There is supportive evidence for such a hypothesis. Recently Shoukas and Brunner (1980) have shown that, when epinephrine was given at 1.0 µg/min per kg, the reflex changes in reservoir blood volume were greatly attenuated and changes in vascular compliance were totally abolished. Higher doses of epinephrine, 2.0 µg/min per kg, totally abolished the changes in reservoir blood volume caused by the reflex, whereas the reflex changes in resistance were greatly attenuated but not abolished. Karim and Hainsworth (1976), using splanchnic nerve stimulation, found the capacitance vessel response to be much more sensitive than resistance vessel response at low frequencies of stimulation. Therefore, it is not unlikely that the increases in blood volume changes with time would precede any changes in arterial pressure if the anesthetic state of the dog were diminishing. It might well be that a more sensitive indicator of physiological state of the cardiovascular system may be in capacitance vessel responses rather than resistance vessel responses. Other studies on isolated vascular beds do support this contention (Mellander, 1960; Folkow and Mellander, 1964; Hadjiminas and Oberg, 1968).

The fact that sodium pentobarbital and constant cardiac output were used makes extrapolation of these findings to the intact dog difficult. Hausner et al. (1938) and Hahn et al. (1942) have shown that the spleen size is significantly larger in barbiturate-anesthetized dogs than in unanesthetized dogs. Nevertheless, the results of our study do show that the spleen does significantly contribute to the blood volume mobilization caused by the carotid sinus baroreceptor reflex mechanism. However, we must emphasize that the spleen is not the major contributor to the total blood volume shifts caused by the reflex. Therefore, other organs and/or venous vascular beds play an important role in blood volume mobilization which may make a significant contribution to the maintenance of right heart filling pressure and cardiac output.

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The importance of the spleen in blood volume shifts of the systemic vascular bed caused by the carotid sinus baroreceptor reflex in the dog.
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doi: 10.1161/01.RES.49.3.759

Circulation Research is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7330. Online ISSN: 1524-4571

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