Effects of Baroreceptor Denervation on Volume Loading Hypertension in Anephric Dogs

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SUMMARY The role of the baroreceptor mechanism in determining the relationship between fluid volume and arterial pressure is not clear. Therefore, the effects of the baroreflex on the arterial pressure and fluid volume of conscious, anephric dogs were studied after a sustained 10% increase in blood volume. The animals were equipped with long-term indwelling arterial and venous catheters, and arterial pressure was monitored 24 hours a day. The increase in blood volume was achieved by intravenous infusion of 50 ml/kg of lactated Ringer’s solution in 30 minutes. After volume loading arterial pressure increased rapidly to hypertensive levels (130.8 ± 7.5% of control) in a baroreceptor denervated group. The initial increase in arterial pressure in a group of normally innervated dogs was smaller (118.8 ± 1.8% of control), but by 24 hours postinfusion the arterial pressure of both groups had reached the same level. The innervated group had probably experienced baroreceptor resetting by this time. Blood volume both before and after infusion was not different in the denervated and innervated groups; however, sodium space was markedly higher before the infusion in the denervated dogs (431.8 ± 13.8 ml/kg vs 344.8 ± 19.0 ml/kg in the innervated dogs), and the volume load caused parallel increases in this space in the denervated and innervated groups. The present study shows that the blood volume of anephric dogs was unchanged after baroreceptor denervation while the extracellular fluid volume of denervated dogs was elevated. Furthermore, a small sustained increase in blood volume in either conscious, innervated dogs or conscious, baroreceptor denervated dogs, in contradiction to the effects in anesthetized dogs, resulted in significant increases in arterial pressure (p < 0.05). (Hypertension 7: 562-568, 1985)

KEY WORDS • blood volume • extracellular fluid volume • central venous pressure

Although several investigators have studied the effects of volume loading on the arterial pressure of either intact or baroreceptor denervated animals,1,2 little information is available about the effects of the arterial baroreceptors on the arterial pressure response to a step change in blood volume in conscious animals. The effects of the arterial baroreflex on fluid volume distribution also are poorly understood.

When excess volume in the form of saline is infused continuously into dogs with reduced renal mass, blood volume progressively increases for a few days and then decreases to near control values after 1 week.3,4 The peak increase in blood volume usually occurs after 2 to 3 days of infusion.4 Because of the transient nature of the hypervolemia in these studies, it has been difficult to establish the relationship between blood volume and arterial pressure; however, the excess blood volume consistently resulted in an elevated right atrial pressure. Other studies have shown that when the increase in mean arterial pressure after volume loading hypertension is accompanied by an increase in right atrial pressure, the gain of the baroreceptor mechanism is severely attenuated5; thus, the decrease in heart rate is smaller than expected, and the correction of the increase in systemic arterial pressure is smaller than expected.

In addition to the effects of excess fluid volume on arterial pressure, the baroreceptor reflex may also affect the blood volume and extracellular fluid volume. Aortic denervated rats have been shown to have a decrease in plasma volume but no change in extracellular fluid volume.7,8 Other studies have found no long-term change in plasma volume but an increase in blood volume in sinoaortic denervated dogs and rats9,10 and an increased tendency to become edematous.1
These observations indicate that the relation between fluid volumes and arterial pressure after baroreceptor deafferentation is not clear. Therefore, this study was designed to answer two questions: What are the effects of the baroreceptor mechanon on arterial pressure during a sustained increase in blood volume? What are the effects of baroreceptor denervation on blood volume and extracellular fluid volume? To answer these questions, 50 ml/kg of lactated Ringer’s solution was intravenously infused into two groups of anephric, conscious dogs in 30 minutes. The first group had intact baroreflexes, and the second group had received extensive baroreflex deafferentation. Serial measurements of a number of cardiovascular variables were made both before and after the infusion.

Materials and Methods

Animal Preparation

Studies were performed on 16 conscious, anephric adult dogs with an average weight of 19.6 ± 0.7 kg (mean ± SEM). The dogs were divided into three groups: 1) a sinoaortic baroreceptor denervated group of five dogs that received an intravenous infusion of 50 ml/kg of lactated Ringer’s solution, 2) an innervated group of six dogs with normal arterial baroreceptor reflexes that also received 50 ml/kg of Ringer’s solution, and 3) a control group consisting of five normally innervated dogs that received no infusion.

All surgical preparations were performed using aseptic techniques. Anesthesia was induced with sodium thiopental (25 mg/kg i.v.; Abbott Laboratories, North Chicago, IL, USA) and maintained with an inspired mixture of methoxyflurane (Penthrane) and oxygen or a mixture of halothane (Fluothane), nitrous oxide, and oxygen. The gas mixture was delivered from an anesthesia machine (Ohio Chemical and Surgical Equipment, Madison, WI, USA) to the animal through an endotracheal tube. The first operation involved surgically removing the spleen and the left kidney through a flank incision. Tygon catheters (Norton Plastics and Synthetics, Akron, OH, USA) were implanted in the aorta and the thoracic inferior vena cava through the femoral artery and vein, and the external ends of the catheters were exteriorized between the animals’ shoulders for protection. After at least a 2-week recovery period, the baroreceptor denervated group underwent sinoaortic denervation. At this time, one of the dogs in this group had its aortic arch surgically denervated as previously described. After another 2-week recovery period, all five dogs in this group underwent bilateral denervation of the carotid sinus areas and the common carotid arteries. The left cervical vagus also was completely severed, and the right aortic–sympathetic nerve portion of the right vagus was dissected out and cut. If the line of demarcation separating the right vagus and the aortic sympathetic bundle was not identifiable, the entire medial third of the right cervical vagus was dissected out and cut. No difference was noted between the dog that received the separate aortic arch denervation and the other dogs in this group. Completeness of denervation was checked by determining the 24-hour standard deviation of the arterial pressure and by testing the heart rate response to an intravenous bolus injection of 160 mg of phenylephrine. The phenylephrine caused a 48 mm Hg increase in arterial pressure although heart rate only decreased 1%. Also, the standard deviation of the arterial blood pressure was markedly increased. It is likely that the peripheral chemoreceptors were also denervated during these surgical procedures; however, these receptors are mainly active during hypotension or low arterial oxygen tension. Since we studied normoxic hypertension in this experiment, chemoreceptor denervation probably had no major effects.

During an additional 10-day recovery period, the dogs were familiarized with the laboratory environment and trained to lie quietly in their cages. An 8-day control period followed the recovery period. During this time mean arterial pressure was measured 24 hours per day. On the last day of this control period the remaining kidney was removed through a flank incision. The dogs recovered rapidly from operation because gas anesthesia was used. Anesthesia was induced and maintained as previously described except approximately 8 mg/kg i.v. of sodium pentothal was used to induce anesthesia in the baroreceptor denervated group. On the day after operation, control measurements were made from 0800 to 1100 hours and 50 ml/kg of lactated Ringer’s solution warmed to body temperature was then intravenously infused in 30 minutes in the baroreceptor denervated group and the innervated group. The control group received no infusion. Serial measurements of fluid volumes, arterial pressure, plasma protein concentration, and plasma electrolytes were made for 25 hours following the infusion. The animals were maintained on a dietary intake of 30 mEq/day of sodium and water ad libitum. On the day of the infusion, the dogs were fed just after the fifth hour of the postinfusion period. The viability of this preparation was attested to by the fact that the dogs continued to drink and eat voluntarily on the experimental day. For example, the denervated group ate 97.5 ± 2.5% of its normal food intake on that day.

Experimental Measurements and Instrumentation

The dogs were equipped with a backpack housing a Statham P23AC transducer (Statham Instruments Inc., Oxnard, CA, USA) at the level of the heart. The infusion tubes and transducer wires were brought out of the dog pen through protective tubing. The transducer wires were connected to a Grass model 7D recorder (Grass Instrument Co., Quincy, MA, USA), which was used to record arterial pressure 24 hours a day. The transducers were zeroed to the level of the right atrium. Because of the increased variability of the arterial pressure of the denervated dogs, the pressure data of this group were sampled by a DEC PDP 11/70 computer (Digital Equipment Corporation, Maynard, MA, USA). Each minute 500 samples were taken in a period of 3 seconds, the average mean arterial pressure for this time was stored on the computer disk.
The dilution principle was used to measure blood volume and sodium space in each group. Blood volume was measured by the dilution of sodium chromate $^{51}$Cr (New England Nuclear, Boston, MA, USA) tagged red blood cells. Blood volume was considered to be the volume of distribution of the labeled red blood cells. The dogs' cells were tagged with 100 mCi of $^{51}$Cr the day before the infusion. To determine background radioactivity, 7-ml arterial blood samples were withdrawn before 10 ml of radiomabeled red cells and 2 ml (5 mCi of $^{22}$Na as sodium chloride; New England Nuclear) were injected through the venous catheter. Seven-milliliter blood samples were withdrawn through the arterial catheter 5, 20, and 40 minutes, and 1, 2, 3, 4, and 5 hours after the infusion for determination of dilution volumes. The control values for blood volume and sodium space were determined from the sample withdrawn 3 hours after injection. Plasma volume was calculated from consideration of the blood volume and the large vessel hematocrit. Just after the 2-hour-postinfusion sample was obtained, 20 ml of arterial blood was labeled with 200 mCi of $^{51}$Cr. These cells were reinjected after the 24-hour-postinfusion sample had been obtained. Arterial blood samples were then withdrawn 20 minutes and 1 hour later for determination of the blood volume. A Searle (model 1185; Searle Analytic Inc., Des Plaines, IL, USA) solid crystal scintillation counter was used for radioactive counting procedures, and corrections were made for the overlapping gamma energy spectrums of the isotopes.

Plasma sodium and potassium concentrations were measured on an Instrumentation Laboratory flame photometer (Instrumentation Laboratory Inc., Lexington, MA, USA). An American Optical refractometer (American Optical Corp., Buffalo, NY, USA) was used to determine plasma protein concentration. Total intravascular protein was calculated by multiplying plasma protein concentration and plasma volume. Statistical analysis of the data was performed using Dunnett's test for multiple comparisons. The overall mean of the data for the denervated group was compared statistically with that of the innervated group or, when appropriate, with that of the anephric control group during the same period. The data were considered statistically different if $p$ was less than 0.05. The measurements made 3 hours into the control period were considered to be the control values and were used to calculate percent of control data.

We have previously published the data in Figures 3, 4, 5, 6, and 7 on the innervated group, and it is included so that direct comparison between the innervated and denervated groups can be made without constantly referring to numerical data in the text.

**Results**

**Volume Loading**

**Arterial Pressure Responses**

Figure 1 illustrates the changes in mean arterial pressure in the denervated, innervated, and control groups on the experimental day. The control group received no infusion, while the denervated and innervated groups received 50 ml/kg of lactated Ringer's solution in 30 minutes.

The arterial pressure of the control group stayed extremely close to its control value throughout the postinfusion period, which indicates that removing both kidneys caused no increase in pressure during the experiment. The denervated group exhibited a marked initial increase in arterial pressure to 130.8 ± 7.5% of control by 5 minutes postinfusion, while the mean arterial pressure of the innervated group increased to only 118.8 ± 1.8% of control. In general, the arterial pressure of the denervated group was higher than that of the innervated group for the first 5 postinfusion hours. Both the denervated and innervated groups experienced a secondary rise in pressure during the postinfusion period. The pressure increase in the denervated group began 3 hours after the infusion ended; in the innervated group the increase occurred between 5 and 24 hours postinfusion, which could have been due to resetting of the arterial baroreceptors. The average values for the mean arterial pressure of the denervated, innervated, and control groups during the 3-hour control period were not significantly different (100.1 ± 4.3, 100.8 ± 4.3, and 104.8 ± 2.4 mm Hg respectively). The standard deviations of the normalized mean arterial pressures for this period were 10.4, 3.9, and 3.1 for the denervated, innervated, and control groups respectively.

Mean arterial pressure was measured the week before operation to ensure that the control pressures taken on the morning of the experiment were accurate. The average mean arterial pressures for the 2 days before operation were 97.3% of the control value taken on the morning of the experiment for the control group, 98.5% of control for the innervated group, and 106.7% of control for the denervated group. None of these values were statistically different from their control values.
Effects on Central Venous Pressure

Both the denervated and innervated groups exhibited a marked increase in central venous pressure following the infusion of lactated Ringer's solution while the venous pressure of the control group stayed close to its control value throughout the experiment (Figure 2). The increase in venous pressure was greatest in the denervated group 5 minutes postinfusion. Thereafter, the pressure of this group decreased toward its control value. By 24 hours postinfusion, however, the central venous pressure was still increased more than 3 mm Hg above its control value. The central venous pressure of the innervated group remained significantly elevated above that of the control group throughout the experiment (p < 0.05).

Effects on Blood Volume

Figure 3 shows the changes in blood volume of the denervated and innervated groups following infusion of lactated Ringer's solution. Blood volume initially increased 20% in both groups, but by 3 hours postinfusion the average increase in volume was approximately 10%. The responses of blood volume were not significantly different in the two groups throughout the experiment. Control blood volumes in the denervated and innervated groups were 71.5 ± 4.1 ml/kg and 71.0 ± 3.8 ml/kg respectively. The blood volume of the control group stayed within approximately 2% of its control value of 67.8 ± 5.1 ml/kg for the first 4 hours postinfusion. Because this group continued to eat and drink normally, by 24 hours postinfusion, the blood volume had increased to 108.4 ± 2.9% of control.

Effects on Sodium Space

Figure 4 illustrates the changes in sodium space caused by infusion of lactated Ringer's solution in the denervated and innervated groups. The control value of sodium space was decidedly higher in the denervated group and was maintained throughout the postinfusion period (p < 0.05). The sodium space of the control group slowly increased during the experimental period from a control value of 344.8 ± 19.0 ml/kg to 109.9 ± 2.6% of control at 5 hours postinfusion and 116.4 ± 0.7% of control at 25 hours postinfusion.

Effects on the Distribution of Extracellular Fluid Volume

The blood volume/sodium space ratio of the denervated and innervated groups is shown in Figure 5. This ratio is an index of the distribution of fluids between the extracellular fluid volume and the vascular compartment. Because of an increased sodium space, the blood volume/sodium space ratio of the denervated group was significantly lower during the control and postinfusion periods (p < 0.05).
Effects on Plasma Protein Concentration

Plasma protein concentration can have marked effects on the distribution of extracellular fluid volume. Figure 6 illustrates the changes that occurred in protein concentration after infusion of lactated Ringer’s solution into the denervated and innervated groups. The control values were 5.8 ± 0.3 g/dl and 6.2 ± 0.1 g/dl in the denervated and innervated groups respectively. By 5 minutes postinfusion the plasma protein concentration of both groups had decreased significantly (p < 0.05). Although the protein concentrations of both groups subsequently returned toward their control values, they were still decreased at the end of the experiment.

Effects on Total Intravascular Protein

Figure 7 shows the effects of infusing lactated Ringer’s solution on the total intravascular protein mass in the denervated and innervated groups. Protein mass of each group had increased approximately 8% above their respective control values by 24 hours postinfusion, which presumably was due to an increased lymphatic return of protein from the interstitial space. The control values of intravascular protein were 3.1 ± 0.3 g/kg and 2.7 ± 0.1 g/kg in the denervated and innervated groups respectively. There was no significant difference in the response of protein mass of the two groups to volume loading.

Responses of Electrolyte Concentrations

Plasma sodium concentration was unchanged throughout the experimental period in the baroreceptor denervated group; however, this group did have a progressive increase in plasma potassium concentration. By 25 hours postinfusion, the plasma potassium concentration had increased to 121.2 ± 5.4% of its control value of 5.6 ± 0.2 mEq/L.

Discussion

The purpose of this study was to determine 1) the relationship between blood volume and arterial pressure in normal and baroreceptor-denervated dogs and 2) the effect of baroreceptor denervation on fluid volume.

Responses of Arterial Pressure to Volume Loading

Figure 1 shows that arterial pressure increased markedly in both baroreceptor denervated and innervated dogs after intravenous infusion of 50 ml/kg of lactated Ringer’s solution. This hypertension was sustained, in contradistinction to the transient elevations of arterial pressure that occurred after volume loading of anesthetized dogs by Prather et al. They intravenously infused 500 ml of either whole blood, 6% dextran-saline solution, or Tyrode’s solution during a 4-minute period. Blood volume acutely increased in all groups but returned to normal within 80 minutes in the
group infused with Tyrode’s solution. However, the blood-infused and dextran-infused groups showed 25% and 70% retention of the increase in blood volume, respectively, after 2 hours. In spite of the hypervolemia, the mean circulatory filling pressure of all groups returned to their control levels within 90 to 120 minutes, and the arterial pressure was elevated very little after the infusion in any of the groups. After 2 hours the arterial pressure of all groups was no higher than their respective control values. Therefore, according to the results of the present experiment, anesthesia in the experiment of Prather et al.6 caused the expected increase in arterial pressure after an increase in fluid volume to be markedly attenuated. Nephrectomy seems to have had no effect on the pressure data in the present experiment, since the arterial pressure of the control group did not change during the postinfusion period.

Immediately after the infusion, the denervated group’s arterial pressure increased substantially more than did the pressure of the innervated group. Between 1 and 3 hours postinfusion, however, the arterial pressure of the denervated group had decreased to approximately the same level as that attained by the innervated group. The pressure of the denervated group again increased, but by 24 hours postinfusion, the arterial pressure of the innervated group had increased to approximately the same level. The secondary increase in arterial pressure of the innervated group occurred between 5 and 24 hours and may have been due to a resetting of the arterial baroreceptors. 17, 18

Estimation of baroreceptor gain in this study, which was determined by comparing the arterial pressure responses immediately after the infusion in the denervated and innervated groups, gave no evidence of a severe attenuation in the baroreflex gain as has previously been found. 5 In the present study, however, the increase in central venous pressure was not nearly as large as that produced by Vatner et al., 5 who found a large decrease in the ratio of cardiac pulse interval to systolic arterial pressure after volume infusion. Because we did not measure heart rate continuously in our present study, our results cannot be directly compared with those of Vatner et al.5 In addition, Chen et al. 6 found that volume infusion into anesthetized rabbits increased right atrial pressure by 10 cm H2O, which is close to the increase we observed. They found that baroreceptor gain, measured by the ratio of the change in intrasinus pressure to the change in mean arterial pressure, decreased markedly when arterial pressure was in the 50 to 100, but not in the 100 to 150, mm Hg range. Since the arterial pressure in our experiment was in the upper range, our results seem to be in accord with those of Chen et al.6

In all groups the mean arterial pressure measured during the control period was close to the value of arterial pressure determined during a week of control measurements before the final nephrectomy. Therefore, the validity of the control values determined on the morning of the infusion seems to be substantiated. Since the control values for mean arterial pressure in the denervated, innervated, and control groups were all between 100 and 105 mm Hg, we found no evidence that baroreceptor denervation causes hypertension. This finding is in direct agreement with previous studies on sinoaortic denervated dogs and rats. 11–19

The stability of several values at 48 hours postinfusion in two control and two innervated dogs provides strong evidence that the values during the 24 hours following the infusion are credible. Mean arterial pressure in the control group was 102.0 and 104.6% of control at 24 hours and 48 hours postinfusion. 14 Blood volume was 108.4% of control at 24 hours and 109.1% of control at 48 hours. 14 Plasma protein concentration was 99.9% of control at 24 hours and 96.0% of control at 48 hours. Plasma sodium concentration was unchanged, and central venous pressure increased slightly from –0.4 mm Hg to 0.2 mm Hg. In the innervated group, mean arterial pressure remained at 131.7% of control at both 24 and 48 hours postinfusion. 14 Blood volume decreased slightly from 107.5% to 105.2% of control. 14 Sodium space and plasma protein concentration were unchanged, and central venous pressure increased slightly from 1.9 mm Hg to 2.2 mm Hg at 24 and 48 hours respectively.

Although the metabolic retention of waste products caused by nephrectomy could have affected the data, several findings seem to disavow this possibility. First, the data taken at 48 hours postinfusion agreed well with the 24-hour-postinfusion data, which indicates that a steady state situation existed on the experimental day. Second, the arterial pressures taken the week before nephrectomy agreed well with the postnephrectomy data. Third, another study performed in our laboratory compared the effects of intravenous infusion of lactated Ringer’s solution in dogs with intact kidneys with the effects in the same dogs 1 day after nephrectomy. 20 The same surgical-experimental schedule was followed as that used in the present study. During the control period, no statistical difference in the intact kidney and anephric groups was found in mean arterial pressure, blood volume, sodium space, blood volume to sodium space ratio, plasma protein concentration, body weight, and central venous pressure. Also, linear regressions relating blood volume to sodium space before and after the infusion, blood volume to central venous pressure, and blood volume to mean arterial pressure were not statistically different for the two groups.

The amount of volume infused into the dogs in this experiment was modest compared with the amount infused in a typical volume loading experiment. 1, 3, 4 The result was a moderate but sustained 10% increase in blood volume. During previous volume loading experiments, we have shown that blood volume exhibits a maximum increase of 25% when approximately 4 L/day of isotonic saline is infused into dogs with 30% renal mass. 4 Even though the degree of hypervolemia in the present experiment was mild, arterial pressure still increased markedly in both the denervated and innervated groups. In fact, the degree of hypertension was nearly the same as that achieved in the dogs with
30% renal mass even though their blood volume increased much more.4

Responses of Fluid Volumes and Sodium Space to Baroreceptor Denervation and Volume Loading

Blood volume during the control period was not significantly different in the denervated and innervated groups. This finding agrees with studies in sinoaortic denervated rats.10 However, another study by Schafer showed that plasma volume was unchanged but blood volume was slightly increased because of an increase in hematocrit in sinoaortic denervated dogs. As our dogs were splenectomized to prevent neurogenic increases in hematocrit, our data seem to be in accord with those of Schafer.9 On the other hand, our data do not agree totally with two studies on rats that received only aortic baroreceptor deafferentation.7 After denervation these rats experienced a decrease in plasma volume and extracellular fluid volume; however, the decrease in fluid volumes was due to a decrease in thirst, which we did not find in our dogs.8

The control blood volume as well as the blood volume response to volume loading was very similar in the denervated and innervated groups. Therefore, we found no evidence for any effect of baroreceptor denervation on blood volume.

On the other hand, 3-hour sodium space, which is an index of extracellular fluid volume, was markedly higher in the denervated group. This supports the previous finding by Cowley and Guyton that partially nephrectomized sinoaortic denervated dogs have an increased tendency to become edematous. Why the sodium space increased after sinoaortic denervation in the present study is not clear; however, one explanation can be offered. The denervated dogs experienced large minute by minute perturbations in arterial pressure that most likely caused large perturbations in capillary hydrostatic pressure. The increases in capillary pressure have been shown to cause a "stretched pore" phenomenon in the capillary bed,21 thus, the net fluid flux out of the vascular compartment could increase in a nonlinear fashion during high capillary pressure. It is possible that this extra increase in outward transcapillary flux will more than negate the inward flux owing to large downward swings in arterial pressure and capillary pressure in denervated dogs. If this phenomenon does occur, the initial result during a transient increase in arterial pressure would be a decrease in blood volume and a resultant decrease in arterial pressure. The kidney then would tend to retain sodium and water until blood volume (and arterial pressure) returned to normal. The end result would be a normal blood volume but an increased interstitial volume, which is what we found in this study.

In conclusion, our results indicate that a sustained 10% increase in blood volume will cause an increase in arterial pressure to hypertensive levels in both denervated and innervated anephric dogs in the conscious state. In addition, blood volume was not affected by baroreceptor denervation in either the normovolemic or hypervolemic states. However, sodium space was increased significantly in the sinoaortic denervated dogs before the infusion of lactated Ringer’s solution, and the volume load caused parallel increases in this space in the denervated and innervated dogs.

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