Original Contributions

Contribution of the Baroreflex Afferent Nerves to the Production of Vasoconstricted Hypertension in Volume-Expanded Dogs

Atsuhiro Otsuka, Toshio Ogihara, Hiroshi Mikami, Katsuhiko Kohara, Katsutoshi Katahira, Takeshi Tsunetoshi, and Yuichi Kumahara

Dextran in lactated Ringer’s solution (20 ml/kg) was infused for 1 hour into anesthetized dogs with sinoaortic denervation and vagotomy (deafferentation; n=10) and dogs treated with hexamethonium (de-efferentation; n=13) to compare with our previous observation in dogs with an intact autonomic nervous system (control, n=34). During the infusion, increase in blood pressure associated with increase in cardiac output was observed in all three groups. The increases in blood pressure were larger in the two groups with an impaired autonomic nervous system. In the recovery period, the control dogs and the hexamethonium-treated dogs showed gradual increases in total peripheral resistance and in vasoconstricted hypertension 3 hours after stopping the infusion. In contrast, the dogs with sinoaortic denervation and vagotomy did not show any increase in total peripheral resistance. The vasoconstricted groups showed peaks of natriuresis soon after the infusion, not 3 hours after the infusion when vasoconstriction was observed, although the dogs with deafferentation did not show a significant increase in natriuresis. Norepinephrine (0.5 μg/kg) was administered intravenously before and after volume expansion, and the pressor responses in the three groups after volume expansion were enhanced similarly (143%, 128%, and 136%, respectively). These results indicate that the afferent signals from peripheral vessels to the brain contribute to the production of vasoconstricted hypertension after acute volume expansion and that the vasoconstriction is independent of pressor hypersensitivity and is dissociated in time from the natriuresis. (Circulation Research 1989;65:1467-1474)

From the hemodynamic point of view, the blood pressure is determined by the cardiac output and vascular resistance. Human essential hypertension is reported to be cardiac output-dependent in the early phase and resistance-dependent in the chronic phase, although some discrepant results have been obtained. Similar change in the predominant hemodynamic factor controlling the blood pressure elevation from cardiac output (CO) to total peripheral resistance (TPR) has also been observed in models of chronic volume expansion. The idea of systemic autoregulation, as a summation of local autoregulation, has been postulated to explain these hemodynamic changes. But this idea is controversial, and the importance of structural changes of the heart and vessels has been emphasized by Kornler.

Recently, we reported that acute volume expansion induced by infusion of dextran in lactated Ringer's solution, which has a physiologically normal concentration of sodium, also results in this hemodynamic conversion and that, in this case, any structural changes in the vasculature, the peripheral sympathetic nervous system, the renin-angiotensin system, or vasopressin are not likely to contribute to the vasoconstriction. In this study, we extended our studies to dogs with impairments of the autonomic nervous system, that is, deafferentation (sinoaortic denervation and vagotomy) or de-efferentation (hexamethonium treatment), and demonstrated the importance of afferent signals to the brain for production of vasoconstricted hypertension.

Materials and Methods

Mongrel dogs of both sexes, weighing 8–17 kg (mean body weight, 10±1 kg), were used. The dogs were housed individually and maintained with normal intakes of sodium (50 meq Na+/day) and potassium (55 meq K+/day) and tap water ad libitum for at least 1 week before experiments. Volume expa-
sion studies were performed on the following four groups: group I, normal control dogs (control); group II, dogs subjected to sinoaortic denervation and vagotomy 1 day previously; group III, dogs subjected to sham operation for sinoaortic denervation and vagotomy; and group IV, hexamethonium-treated dogs. Sham infusions were performed in three groups: group V, normal dogs; group VI, dogs subjected to sinoaortic denervation and vagotomy; and group VII, hexamethonium-treated dogs. These three sham groups were not subjected to volume expansion. The studies on groups I and V were reported previously, but here we include the results with additional data for better understanding of the hemodynamic changes in groups II and IV.

Dogs were fasted the night before experiments, and on the day of the experiments they were anesthetized at 9 AM by intravenous administration of sodium pentobarbital (a loading dose of 40 mg/kg followed by a maintenance dose of 4 mg/kg/hr). After tracheal intubation, dogs were ventilated artificially (rate, 20 times/min; inspiratory pressure, 20 cm H2O) with room air by a respirator (Mark 8, Bird Electronic, Cleveland, Ohio). We confirmed that values of arterial blood gases measured with an autoanalyzer (model ABL2, Radiometer A/S, Copenhagen, Denmark) were within the physiological range throughout the experiment, and the body temperature was maintained at 37°-39° C by external warming (Aquamatic K module, model K-20, American Hospital Supply, Cincinnati, Ohio). One catheter was placed in the abdominal aorta below the renal arteries via the right femoral artery for measurement of the arterial blood pressure and for collection of blood samples. Venous catheters were inserted for the infusions of sodium pentobarbital and lactated Ringer's solution containing 10% low molecular weight dextran (Low Molecular Dextran-L [40,000 Da, Na+ 130 meq/l, K+ 4 meq/l, Ca2+ 3 meq/l, Cl- 109 meq/l, lactate- 28 meq/l], Otsuka, Tokyo, Japan) and hexamethonium in groups IV and VII. A 5F Swan-Ganz flow-directed catheter (model 73-4045, Electro-Catheter, Rahway, New Jersey) was inserted under pressure wave monitoring via the right femoral vein for measuring CO and right atrial pressure (RAP). The hemodynamic variables were recorded with an eight-channel polygraph system (RM-6000 series, Nihonkohden, Tokyo, Japan).

Volume Expansion

At least 1 hour was allowed for stabilization of the hemodynamic variables after completion of surgical operations. Volume expansion was induced by infusing the low molecular dextran solution, warmed to 37° C, at a dose of 20 ml/kg over a period of 1 hour. Hemodynamic changes were monitored during the infusion period and during the 3-hour recovery period after infusion. Catheters were inserted into the urinary bladder of some dogs for measurement of urine volume and urinary sodium excretion during the experiment.

Sinoaortic Denervation and Vagotomy

Fourteen dogs (10 dogs from group II and four dogs from group VI) were subjected to sinoaortic denervation and vagotomy 1 day before experiments. At about 1 PM, they were anesthetized by a bolus injection of sodium thiopental (15 mg/kg i.v.) followed by supplemental administration. The carotid sinus was exposed bilaterally, and silk threads were passed around all the structures between the internal and external carotid arteries. Denervation was performed by ligating and sectioning these structures. The area of the carotid sinus was painted with 10% phenol. The vagus, including the aortic nerves, was sectioned bilaterally to eliminate the aortic arch baroreceptor reflex and cardiovascular reflex. After these surgical treatments, the skin was closed with 2-0 silk. Dogs were able to stand a few hours after the surgical treatment and were given tap water ad libitum.

Hexamethonium Administration

Seventeen dogs (13 dogs from group IV and four dogs from group VII) were given 40 mg/kg i.v. hexamethonium. From 15 minutes later, 4 mg/kg/hr of hexamethonium was infused throughout the experiment. A minimum of 60 minutes was allowed to ensure a stable blood pressure before the start of volume expansion. The effectiveness of the denervation procedure was confirmed in a separate series of dogs by demonstrating the absence of reflex changes in the HR in response to alterations in blood pressure induced by injection of phenylephrine (5 μg/kg) or nitroglycerin (10 μg/kg). In four dogs, sham denervation was done by cervical incision without sectioning the nerves (group III).

Pressor Response to Norepinephrine

The pressor response to intravenous administration of norepinephrine (0.5 μg/kg) was examined before and after volume expansion in groups I, II, IV, and V.
Statistical Analyses

The changes in the hemodynamic variables, urine volume, and urinary sodium excretion in each group during and after the infusion period were analyzed by two-way analysis of variance, followed by Dunnett’s test. For between-group comparison of these changes, two-way analysis of variance for repeated measures was used. The pressor response to noradrenaline after volume expansion was compared with that before volume expansion by Student’s t test. Probability levels of less than 0.05 were considered significant. Results are presented in the text, table, and figures as mean±SEM.

Results

Hemodynamic Changes by Volume Expansion

Table 1 shows the changes in hemodynamic variables of all groups at the control period, at 60 minutes (at the end of infusion), and at 240 minutes (3 hours after infusion). The basal levels of MBP and CO in groups II and IV were lower than those in group I. The basal TPR values of the groups were similar. The basal HR was higher in group II and lower in group IV than in control group I.

Figure 1 shows the percentage changes in the hemodynamic variables during the infusion period of 1 hour and the recovery period of 3 hours. In control dogs (group I), volume expansion resulted in increase in the MBP (from 114±2 to 128±3 mm Hg) associated with increase in the CO (from 0.15±0.01 to 0.26±0.01 l/min/kg) during infusion. Three hours after volume expansion, the MBP had returned to the basal level (80%). In three dogs observed until 6 hours after infusion, the MBP remained below the basal value, while the TPR was still lower than the basal level (80%). In dogs in group II, the MBP had returned to the basal level (88%), and the TPR did not increase from the level 3 hours after infusion (78%). Thus, no dogs in group II showed vasoconstricted hypertension. The RAP increased during infusion and

Table 1. Changes in Hemodynamic Variables During and After Volume Expansion

<table>
<thead>
<tr>
<th>Group</th>
<th>Variables</th>
<th>Control</th>
<th>60 min</th>
<th>240 min</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>MBP (mm Hg)</td>
<td>114±2</td>
<td>128±3</td>
<td>124±3</td>
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<td>RAP (mm Hg)</td>
<td>5.7±0.3</td>
<td>9.0±0.5*</td>
<td>5.6±0.5</td>
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<td>HR (beats/min)</td>
<td>143±4</td>
<td>125±4*</td>
<td>107±6*</td>
</tr>
<tr>
<td></td>
<td>CO (l/min/kg)</td>
<td>0.15±0.01</td>
<td>0.26±0.01*</td>
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<td>TPR (unit)</td>
<td>8.5±0.6</td>
<td>5.6±0.4*</td>
<td>9.7±0.7*</td>
</tr>
<tr>
<td>II</td>
<td>MBP (mm Hg)</td>
<td>93±5</td>
<td>128±5*</td>
<td>93±4</td>
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<td></td>
<td>RAP (mm Hg)</td>
<td>6.1±0.6</td>
<td>9.0±0.4*</td>
<td>6.4±0.8</td>
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<tr>
<td></td>
<td>HR (beats/min)</td>
<td>165±7†</td>
<td>157±9</td>
<td>135±10*</td>
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<tr>
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<td>CO (l/min/kg)</td>
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<td>0.16±0.02*</td>
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<tr>
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<td>TPR (unit)</td>
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<td>5.4±0.6*</td>
<td>6.9±0.8§</td>
</tr>
<tr>
<td>III</td>
<td>MBP (mm Hg)</td>
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<td>130±5*</td>
<td>118±6§</td>
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<tr>
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<td>RAP (mm Hg)</td>
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<tr>
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<td>CO (l/min/kg)</td>
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<td>TPR (unit)</td>
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<td>7.4±0.9§</td>
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<tr>
<td>IV</td>
<td>MBP (mm Hg)</td>
<td>68±4†</td>
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<td>RAP (mm Hg)</td>
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<td>HR (beats/min)</td>
<td>108±3§</td>
<td>112±4</td>
<td>99±4*</td>
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<td></td>
<td>CO (l/min/kg)</td>
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<tr>
<td>V</td>
<td>MBP (mm Hg)</td>
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</tr>
<tr>
<td>VI</td>
<td>MBP (mm Hg)</td>
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<td>88±7</td>
<td>89±4</td>
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<td></td>
<td>RAP (mm Hg)</td>
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<tr>
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<td>HR (beats/min)</td>
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<td>163±5</td>
<td>160±6</td>
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<td>CO (l/min/kg)</td>
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<tr>
<td></td>
<td>TPR (unit)</td>
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<td>5.8±1.1</td>
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<tr>
<td>VII</td>
<td>MBP (mm Hg)</td>
<td>75±8†</td>
<td>78±8</td>
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<tr>
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<td>RAP (mm Hg)</td>
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<td></td>
<td>HR (beats/min)</td>
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<td>98±10</td>
<td>99±13</td>
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<tr>
<td></td>
<td>CO (l/min/kg)</td>
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<td>0.12±0.02</td>
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<td>TPR (unit)</td>
<td>6.8±1.6</td>
<td>6.9±1.8</td>
<td>7.2±1.6</td>
</tr>
</tbody>
</table>

Values are mean±SEM. MBP, mean blood pressure; RAP, right atrial pressure; HR, heart rate; CO, cardiac output; TPR, total peripheral resistance.

*p<0.01, †p<0.05, compared with control value. *p<0.05, †p<0.01, compared with value of group I.
In group IV with de-efferentation, the MBP increased during infusion (from 68±4 to 107±5 mm Hg; 161%; p<0.01), associated with increase in the CO (from 0.11±0.01 to 0.28±0.02 l/min/kg; 261%; p<0.01). These increases were significantly larger than those in group I. In this period, the TPR decreased significantly from 8.1±1.1 to 5.1±0.7 (p<0.01), as in groups I and II. Three hours after the infusion, the MBP and CO remained high (92±6 mm Hg, p<0.01, and 0.14±0.01 l/min/kg, p<0.01, respectively). The TPR increased to 8.8±1.2 (108%; p<0.05) similar to group I. Thus, 3 hours after the volume expansion, the elevated MBP in group IV was attributable to increases in both the CO and TPR. The RAP increased during infusion and returned to the basal level in the recovery period. No significant decrease in the HR was observed until 2 hours after volume expansion.

Table 1 also shows values of the hemodynamic variables in groups V, VI, and VII, before and 4 hours after the start of sham infusion. The values for the MBP, RAP, CO, TPR, and HR at these times were not significantly different.

Urinary Excretion

Data on the urine volume and urinary sodium excretion in groups I, II, and IV are shown in Figure 2. The control values of these parameters in the three groups were not significantly different. Volume expansion resulted in increase in the urine volume in all three groups, but natriuresis increased significantly only in groups I and IV. The peaks of diuresis in the three groups and of natriuresis in groups I and IV were observed soon after the infusion, not 3 hours later when the TPR increased in groups I and IV. The total urine volume values during the experiment in groups I, II, and IV were 9.0±1.4, 5.8±1.0, and 5.2±1.6 ml/kg, respectively. The values of groups II and IV appear smaller than that of group I, but the differences were not significant. Sequential changes in the urine volume (Figure 2) were not different in the three groups (analysis of variance for repeated measures) either.

The total urinary sodium excretion values during the experiment in groups I, II, and IV were 1.04±0.15, 0.30±0.11, and 0.76±0.34 meq/kg, respectively. There was a significant difference between groups I and II (p<0.01). Also, sequential evaluation of the urinary sodium excretion (Figure 2) revealed that natriuresis was less in group II than in group I in the recovery period (analysis of variance for repeated measures followed by Student’s t test with Bonferroni correction). Natriuresis in group IV was not significantly different from that in group I.
Pressor Response to Norepinephrine

In the control period, the pressor responses to intravenous administration of norepinephrine were significantly greater in groups II and IV than in group I, and after volume expansion the pressor responses in all three groups were enhanced to similar extents (143%, 128%, and 136%, respectively, Figure 3). The pressor response was not increased in group V, which did not receive volume expansion.

Discussion

The major findings in this study were as follows: 1) Acute volume expansion with dextran produced vasoconstricted blood pressure elevation 3 hours after the infusion in normal anesthetized dogs. 2) A combination of sinoaortic denervation and vagotomy abolished this vasoconstricted blood pressure elevation. 3) Hexamethonium administration did not eliminate this vasoconstriction. 4) Changes in the CO and urine volume were similar in the two groups with autonomic nerve impairment. 5) Increases in natriuresis in normal dogs and hexamethonium-treated dogs were observed soon after volume expansion, not at the time when vasoconstriction was noted. 6) No significant increase in natriuresis was observed in dogs with sinoaortic denervation and vagotomy. 7) The pressor response to intravenous administration of norepinephrine after volume expansion was potentiated similarly in the three groups.

The fact that the dogs with deafferentation did not show vasoconstricted hypertension in response to volume loading indicates that the afferent signals from the peripheral baroreceptors to the brain are necessary for the production of the resistance-dependent hypertension in this model of volume overloading. Although there were some differences in the basal values of hemodynamic variables in the various groups, these differences probably did not contribute to the absence of vasoconstriction in group II: The basal level of the MBP in group II was...
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intermediate between those of groups I and IV; the basal CO of group II was similar to that of group IV; and the basal TPR and RAP of group II were comparable to those of group I. The stable hemodynamics of time-control groups (groups V, VI, and VII) confirmed that our experimental conditions were adequate. We also confirmed that the body temperature and blood gases were stable during experiments.

Sinoaortic denervation is known to cause labile hypertension with increases in the CO and/or TPR.12,13 However, the changes in hemodynamic variables depend on the degree of alertness and environmental stimuli.12-15 and Cowley et al14 and Norman et al15 reported that the mean level of blood pressure was not elevated. In our experiment, sinoaortic denervation with cardiopulmonary denervation caused decrease in the MBP and CO without change in the TPR. These results may be due to our experiments being performed under anesthesia.

Volume expansion, whether acute11 or chronic,5,6 has been reported to produce vasoconstricted hypertension by some as-yet unknown mechanism. The sympathetic nervous system16,17 and vasopressin18 have been shown to be involved in vasoconstriction in some models of volume expansion. The theory of systemic autoregulation as a summation of local autoregulation was proposed by Guyton et al7 and Coleman et al8 to explain the vasoconstriction after an initial increase in the CO. However, Korner13 and other investigators19-21 found two hemodynamic patterns different from that found by Guyton et al: Volume expansion produced 1) vasoconstricted hypertension without an preceding increase in the CO and 2) cardiac output-dependent hypertension without subsequent increase in the TPR. The demonstration of these two patterns throws doubt on the theory of autoregulation.

In a previous study on acute volume expansion,11 we found that all dogs showed cardiac output-dependent hypertension during volume expansion and that blood pressure 3 hours after infusion was attributed to increase in the TPR. Peripheral sympathetic activity, the renin-angiotensin system, and vasopressin18 were found to be involved in vasoconstriction in these models of volume expansion. The theory of systemic autoregulation as a summation of local autoregulation was proposed by Guyton et al7 and Coleman et al8 to explain the vasoconstriction after an initial increase in the CO. However, Korner13 and other investigators19-21 found two hemodynamic patterns different from that found by Guyton et al: Volume expansion produced 1) vasoconstricted hypertension without an preceding increase in the CO and 2) cardiac output-dependent hypertension without subsequent increase in the TPR. The demonstration of these two patterns throws doubt on the theory of autoregulation.

What is the reason for the difference between results after deafferentation and de-efferentation? One possible reason is that a humoral factor may be released from the brain. An ouabain-like natriuretic substance(s)23-25 might be responsible for resistance-dependent hypertension by inhibiting Na+,K+-ATPase in volume-expanded models, and there is considerable experimental evidence for the existence of such a factor in the brain.23-25 Although the physiological role of this substance is still controversial,28-29 a hypothesis that group II did not secrete this substance seems attractive, since the sodium excretion in group II was impaired with lowered peripheral resistance. Group II did not receive a signal from the baroreceptors and hence might not be able to secrete the natriuretic Na+,K+-ATPase inhibitor. This lack of secretion might account for the absence of vasoconstriction and for the reduced natriuresis. However, we need to evaluate in detail the renal hemodynamics. The

vasoconstriction observed in this acute volume expansion is not mediated by the autoregulatory mechanism. Thus, autoregulation may occur in other types of volume loading or human essential hypertension. Here we showed that a factor other than autoregulation can play a role in the conversion of the main factor responsible for blood pressure maintenance in acute volume expansion.

Our experiments were performed by simple volume loading without increase in serum sodium concentration or osmolality.11 Thus, the circunventricular organs, which sense changes in sodium or osmolality and have a role in a salt-excess model, did not seem to contribute to the hemodynamic changes in our experiments. The increases in the MBP or the RAP may trigger subsequent changes in hemodynamics because the elimination of the pressor information by deafferentation prevented the increase in the TPR. To our knowledge, this is the first study to demonstrate that the signals from the baroreceptors, as well as sodium concentration and osmolality, are very important.

The finding that de-efferentation by hexamethonium did not affect sequential hemodynamic changes, together with a previous finding that plasma norepinephrine decreased during similar experiments,11 suggests that volume expansion did stimulate the peripheral sympathetic nervous system directly to contribute to the vasoconstriction in the recovery period. The sudden cessation of increase in the RAP or MBP on stopping the infusion would reduce signals from baroreceptors, resulting in suppression of baroreflex activity, and would consequently induce indirect activation of the sympathetic nervous system in the recovery period. Although this possible explanation is attractive, the results in dogs treated with hexamethonium (vasoconstriction was observed despite the absence of baroreflex function from the beginning) indicate that changes in baroreflex activity were not involved in this vasoconstriction.

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The percent reductions of the TPR in groups I, II, and IV were similar. However, increase in the MBP may be partly due to decreases in the renin-angiotensin system and buffering action of the baroreflex, because decreases in vascular resistance was below its control level. Vasoconstriction was observed later, at 240 minutes. This difference in time between the natriuresis and the vasoconstriction is not consistent with the hypothesis that the vasoconstriction is attributable to the natriuretic Na⁺,K⁺-ATPase inhibitor. In addition, this ouabain-like substance is known to potentiate vascular sensitivity to vasoactive agents. In the present study, enhancement of the pressor response to intravenous administration of norepinephrine was observed in groups I, II, and IV, suggesting that this enhancement was independent of the degree of vascular resistance. The discrepancy between the hypersensitivity and the vasoconstriction is not consistent with the idea that only group II did not secrete an ouabain-like substance.

Sakamaki et al suggested from studies by a cross-circulation method that some circulatory hormonal factor was involved in pressor hyperresponsiveness after saline infusion. However, in their experiment the TPR was reduced, and we do not know whether their hormonal factor was identical with the one that might have had a role in our dogs with acute volume expansion. This hormonal factor is presumably released from, or in the vicinity of, the hypothalamus, and the pathways that stimulate its secretion should be elucidated. The central interconnections between the nucleus tractus solitarii and paraventricular nucleus of the hypothalamus may be important, because the afferent nerves from the peripheral baroreceptors are known to project to the nucleus tractus solitarii. Some efferent pathways other than the sympathetic or parasympathetic pathway (i.e., dopaminergic, histaminergic, or serotonergic neurons) might be responsible for the different results obtained with the two kinds of interception of the autonomic system. However, our results provide no data on this subject.

Our experiments showed that the decrease in TPR during infusion cannot be attributed only to the buffering action of the baroreflex, because decreases in the TPR during the volume expansion were observed in dogs in which either the afferent or the efferent pathway of the baroreflex had been destroyed. This destruction of the baroreflex was confirmed by the complete lack of bradycardia during volume expansion in groups II and IV. Decrease in the TPR may be partly due to decreases in the renin-angiotensin system and vasopressin, which would contribute to vascular relaxation. Decrease in viscosity resulting from decrease in the hematocrit would also cause reduction of the calculated TPR. The percent reductions of the TPR in groups I, II, and IV were similar. However, increase in the MBP was greater in groups II (141%) and IV (161%) than in group I (112%). Disablation of the baroreflex in groups II and IV would account for the observation that the decreases in vascular resistance were equivalent in groups I, II, and IV even though the increases in blood pressure were greater in groups II and IV than in group I.

In this study, dogs were subjected to total deafferentation by section of the cardiopulmonary, aortic, and carotid sinus nerves for comparison with dogs subjected to de-efferentation by treatment with hexamethonium. Further study is needed to determine which nerve is responsible for the production of the vasoconstricted hypertension.

Because our experiments were performed on acute volume expansion, it may not be appropriate to extrapolate our findings to chronic experiments or to human essential hypertension. However, our evaluation of the vasoconstriction in acute volume expansion will bring some new aspects for the research of chronic hypertension.

In summary, we showed that the acute volume expansion with dextran in lactated Ringer’s solution produced cardiac output-dependent hypertension followed by resistance-dependent hypertension and that this vasoconstriction was not observed in dogs with sinoaortic denervation and vagotomy. The vasoconstriction was shown to be independent of pressor hyperresponsiveness and dissociated in time from the natriuresis. We conclude from the results that afferent signals to the brain are involved in production of vasoconstricted hypertension. Further studies are required on the mechanisms of the response to afferent signals.

References

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Contribution of the baroreflex afferent nerves to the production of vasoconstricted hypertension in volume-expanded dogs.

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