Vasoconstriction and Hypersensitivity to Vasoactive Substances After Acute Volume Expansion in Dogs

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SUMMARY In a search for factors contributing to the sustained blood pressure (BP) elevation in acutely volume-loaded animals, dextran dissolved in lactated Ringer's solution (20 ml/kg) was infused into 34 mongrel dogs over a period of 1 hour under pentobarbital anesthesia and changes in hemodynamic and humoral variables were monitored during its infusion and for 3 hours after its infusion. BP elevation during volume loading (from 114 ± 3 to 128 ± 3 [SEM] mm Hg) was attributed to an increase in cardiac output. After volume loading, some dogs maintained BP elevation whereas others did not. The former group showed an increase in total peripheral resistance, demonstrating a transformation of cardiac output to total peripheral resistance as a responsible factor in maintenance of the elevated BP. The plasma levels of norepinephrine, vasopressin, and plasma renin activity were not elevated, indicating that these vasoactive factors were not responsible for elevation of the BP or total peripheral resistance. The changes in the hematocrit, atrial natriuretic factor, urine volume, and urinary sodium excretion were identical in the two groups, and natriuresis was not prominent when total peripheral resistance was high. Pressor responses to norepinephrine and angiotensin II were potentiated 3 hours after stopping infusion in both groups, but this potentiation was not correlated with the increase in total peripheral resistance or mean BP. Thus, acute volume expansion produced resistance-dependent hypertension following the initial volume-dependent hypertension. It is unlikely that a vascular sensitizing natriuretic factor plays a role in the resistance-dependent BP elevation. The mechanism and physiological importance of hypersensitivity to vasoactive substances remain to be elucidated. (Hypertension 12: 59-66, 1988)

KEY WORDS • volume expansion • vasoconstriction • hypersensitivity • natriuretic factor • autoregulation

As demonstrated by Ledingham and Cohen1 and Borst and Borst-de Geus,2 volume expansion, which itself influences cardiac output (CO), increases the total peripheral resistance (TPR). Guyton et al.3-4 explained this conversion of the predominant factor responsible for blood pressure (BP) elevation from CO to TPR as a result of a summation of local autoregulation. However, Korner3 emphasized the importance of structural changes, especially in chronic hypertension, and questioned the concept of autoregulation; he and others demonstrated some hemodynamic patterns that were not consistent with autoregulation.6-8 On the other hand, a natriuretic factor9-11 that inhibits Na⁺,K⁺-adenosine triphosphatase (ATPase) is reported to be increased in volume-loaded hypertension and postulated to be a contributory factor in resistance-dependent hypertension induced by volume loading. This factor is suggested12, 13 to potentiate the pressor responses to norepinephrine and angiotensin II, which are also observed in deoxycorticosterone acetate (DOCA)-salt hypertension14, 15 and in animals infused with saline.16 Thus, this vassosensitizing natriuretic factor may have a role in the change from the predominance of CO to that of TPR, but there has been no report on the relationship of the increase in the TPR with vascular sensitivity and urine output in the volume-expanded state.

In this experiment we demonstrated that acute volume expansion, a condition in which an effect of structural changes could be neglected, caused TPR to increase. As in previous studies on chronic volume expansion,6-8 we also observed two different hemodynamic patterns in dogs in the present study. In an attempt to determine the factors con-
contributing to the high BP, we compared the hemodynamic and hormonal variables, urinary excretion, and pressor responsiveness in the two groups and evaluated whether the natriuretic factor plays a role in the vasoconstrictive hypertension induced by acute volume expansion.

Materials and Methods

Animal Preparation

Experiments were performed on 38 mongrel dogs of both sexes, weighing 7 to 17 kg (mean body weight, 10 ± 1 kg; Keari, Japan). Dogs were housed individually, placed on a normal intake of Na⁺ (50 mEq/day) and K⁺ (55 mEq/day), and given tap water ad libitum at least 1 week before the experiments. They were anesthetized with pentobarbital sodium (a loading dose of 40 mg/kg body weight followed by a maintenance dose of 4 mg/kg/hr) and ventilated with room air by a respirator (Mark 8, Bird, Palm Springs, CA, USA). The arterial blood gas value was kept within the physiological range throughout the experiment, and the body temperature was maintained by external warming (Aquromatic K module, Model K-20, American Hospital Supply, Cincinnati, OH, USA). One catheter was placed in the abdominal aorta below the renal arteries through the right femoral artery, for measurement of arterial BP and collection of blood samples. Two venous catheters were inserted for the infusions of sodium pentobarbital and lactated Ringer’s solution containing 10% dextan (molecular weight, 40,000; Low Molecular Dextran-L, Otsuka, Tokyo, Japan). A Swan-Ganz flow-directed catheter (5F, Model 73-4045, Electro-Catheter, Rahway, NJ, USA) was inserted under pressure-wave monitoring through the right femoral vein to measure CO and right atrial pressure (RAP). Hemodynamic variables were obtained with an eight-channel polygraph system (RM-6000 series, Nihon Kohden, Tokyo, Japan). The heart rate (HR) was determined by continuous recording of the electrocardiogram, using an electrocardiographic amplifier (Model AC-600G, Nihon Kohden) and an HR counter (Model AT-600G, Nihon Kohden). The systemic BP and RAP were measured using pressure transducers (Model TP-300T, Nihon Kohden). CO was measured in triplicate by a thermodilution method (Model TP-300T, Nihon Kohden) and a CO computer (Model EQ-611V, Nihon Kohden) and was expressed in liters per minute per kilogram of body weight. TPR was calculated as mean BP (MBP) minus mean RAP (mm Hg) divided by CO (L/min/kg body weight) and expressed in arbitrary units.

Experimental Protocol

After completion of the surgical procedures, at least 1 hour was allowed for stabilization of hemodynamic variables. Volume expansion was achieved (n = 34) by infusion of dextran 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 a 3-hour recovery period after the infusion was stopped. Blood samples were obtained for measurements of the hematocrit, plasma renin activity (PRA), plasma aldosterone, norepinephrine, epinephrine, atrial natriuretic factor (ANF), vasopressin, and serum Na⁺ and K⁺ before infusion, at 30-minute intervals during the infusion period, and at 60-minute intervals during the recovery period. To evaluate the influence of pentobarbital sodium on hemodynamics, we also performed sham-infusion studies in four dogs. These controls were prepared like test animals, and their hemodynamic changes were monitored by the same experimental protocol, but without volume expansion. Urine was collected every 30 minutes throughout the experiment through a catheter inserted into the urinary bladder (n = 10).

In some dogs (n = 23), pressor responses to norepinephrine (1 µg/kg) and angiotensin II (0.1 µg/kg) were examined before and 3 hours after the infusion was stopped.

Assays

Na⁺ and K⁺ were measured with an autoanalyzer (Model 736-60, Hitachi, Tokyo, Japan). Plasma osmolality was measured with an osmometer (Model OM-6, Kyoto-Daichi Kogaku, Kyoto, Japan). PRA, aldosterone, and vasopressin were measured with commercially available kits (Dainabot, Tokyo, Japan). Norepinephrine and epinephrine were measured by the trihydroxyindole method after high performance liquid chromatographic separation. Immunoreactive ANF was measured by the sensitive radioimmunoassay described previously.

Data Analysis

First, sequential changes in the MBP, CO, and calculated TPR were evaluated in each dog. When we analyzed all the dogs as a whole, we observed volume-dependent hypertension during volume expansion and resistance-dependent hypertension during the postinfusion period (see Results). However, these hemodynamic changes were variable, and we classified the dogs into two groups by the following criteria: those whose high BP (>110% of control) was maintained 3 hours after stopping the infusion were classified as Group 1, and those whose BP was at control levels (within 110% of control) was maintained 3 hours after stopping the infusion were classified as Group 2. The sequential changes were analyzed by two-way analysis of variance followed by Dunnett’s test for within-group comparison or a whole comparison. For between-group comparison, two-way analysis of variance for repeated measures was used. Pressor responses were compared using Student’s t test, and the relationship between the changes in hemodynamic variables and the change in vascular sensitivity was examined. Statistical
significance was defined as a p level of less than 0.05. All values in the text and figures are expressed as means ± SE.

Results

Sequential Hemodynamic Changes

Acute volume expansion induced by dextran resulted in MBP elevation (from 114 ± 3 to 128 ± 3 mm Hg), and this elevation was attributable to an increase in the CO (from 0.15 ± 0.01 to 0.26 ± 0.01 L/min/kg) in all dogs. No dogs showed an increase in the TPR during volume expansion (from 8.9 ± 0.6 to 5.6 ± 0.4 units). The MBP, CO, and TPR 3 hours after stopping the infusion were 124 ± 3 mm Hg (108%, p < 0.01, compared with control), 0.16 ± 0.01 L/min/kg (p = NS), and 9.7 ± 0.7 units (109%; p < 0.01, compared with control), respectively. However, the changes in these hemodynamic parameters were variable. Classification of all the dogs into two groups showed the apparent maintenance of BP 3 hours after volume expansion in Group 1 and recovery of BP in Group 2 (see Data Analysis). The basal values of hemodynamic variables were similar in the two groups (Table 1). The hemodynamic changes in these two groups are compared in Figure 1. During infusion, increases in the MBP, RAP, and CO and decreases in the TPR and HR were similar in the two groups, but the MBPs of Groups 1 and 2 at 240 minutes (i.e., 3 hours after stopping the infusion) were 131 ± 4 and 116 ± 4 mm Hg, respectively. In both groups the CO returned to the basal level in the postinfusion period. In Group 1 the TPR increased to 127 ± 10% 3 hours after the infusion was stopped, whereas in Group 2 it returned to the basal level (103 ± 3%). The increases in MBP and TPR in the first group 3 hours after volume expansion were significantly different from control values (by two-way analysis of variance followed by Dunnett's test). The sequential changes in the MBP and TPR of Group 1 were significantly different (p < 0.01) from the changes in those of Group 2 or sham-infusion dogs (by two-way analysis of variance for repeated measures). Student's t test also showed that 3 hours after volume expansion the MBP and TPR of Group 1 were higher than those of sham-infusion dogs (p < 0.01 and p < 0.05, respectively). HR decreased gradually during infusion and in the postinfusion period, and in both groups the RAP returned to the basal level in the postinfusion period.

The changes in hemodynamic variables in the sham-infusion group are also shown in Figure 1. Possible influences of anesthesia on the hemodynamics must be taken into consideration when anesthetized animals are used, but a 4-hour infusion of pentobarbital sodium at the dose and by the route used in this study had no further cumulative effect on any of these variables except the HR; it caused only slight changes in the MBP, CO, TPR, and RAP. The pressor response to norepinephrine and the reactive decrease in HR in the sham-infusion group decreased.

### Table 1. Basal Values of Hemodynamic Variables in Three Groups of Dogs

<table>
<thead>
<tr>
<th>Variable</th>
<th>Group 1 (n = 17)</th>
<th>Group 2 (n = 17)</th>
<th>Sham-infusion (n = 4)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Body weight (kg)</td>
<td>9 ± 2</td>
<td>10 ± 2</td>
<td>10 ± 1</td>
</tr>
<tr>
<td>MBP (mm Hg)</td>
<td>113 ± 3</td>
<td>116 ± 3</td>
<td>115 ± 7</td>
</tr>
<tr>
<td>RAP (mm Hg)</td>
<td>5.8 ± 0.5</td>
<td>5.7 ± 0.5</td>
<td>5.7 ± 1.5</td>
</tr>
<tr>
<td>HR (beats/min)</td>
<td>143 ± 5</td>
<td>144 ± 6</td>
<td>135 ± 5</td>
</tr>
<tr>
<td>CO (L/min/kg)</td>
<td>0.16 ± 0.01</td>
<td>0.15 ± 0.01</td>
<td>0.12 ± 0.02</td>
</tr>
<tr>
<td>TPR (units)</td>
<td>8.6 ± 0.7</td>
<td>9.2 ± 1.1</td>
<td>10.2 ± 0.2</td>
</tr>
</tbody>
</table>

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

FIGURE 1. Effects of dextran infusion on the mean BP (MBP), right atrial pressure (RAP), heart rate (HR), cardiac output (CO), and total peripheral resistance (TPR) in Group 1 (•), Group 2 (○), and the sham-infusion group (□). The stippled areas represent the 1-hour infusion period. Single (p < 0.05) and double asterisks (p < 0.01) indicate significant difference compared with control values.
TABLE 2. Sequential Changes in Hormonal Factors Following Volume Expansion

<table>
<thead>
<tr>
<th>Variable</th>
<th>Control</th>
<th>30 min</th>
<th>60 min</th>
<th>120 min</th>
<th>180 min</th>
<th>240 min</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hct (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Group 1 (n=13)</td>
<td>41 ± 2</td>
<td>32 ± 2*</td>
<td>27 ± 2*</td>
<td>29 ± 2*</td>
<td>31 ± 2*</td>
<td>32 ± 2*</td>
</tr>
<tr>
<td>Group 2 (n=15)</td>
<td>37 ± 2</td>
<td>28 ± 2*</td>
<td>24 ± 1*</td>
<td>25 ± 2*</td>
<td>26 ± 2*</td>
<td>28 ± 2*</td>
</tr>
<tr>
<td>PRA (ng Ang I/ml/hr)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Group 1 (n=8)</td>
<td>3.3 ± 0.5</td>
<td>2.7 ± 0.8</td>
<td>2.4 ± 0.9</td>
<td>2.0 ± 0.5†</td>
<td>1.6 ± 0.4*</td>
<td>1.7 ± 0.5*</td>
</tr>
<tr>
<td>Group 2 (n=7)</td>
<td>3.9 ± 1.0</td>
<td>2.8 ± 1.0</td>
<td>3.5 ± 0.4</td>
<td>2.6 ± 0.5†</td>
<td>2.7 ± 0.4†</td>
<td>2.3 ± 0.4†</td>
</tr>
<tr>
<td>PAC (pg/ml)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Group 1 (n=8)</td>
<td>237 ± 52</td>
<td>135 ± 25*</td>
<td>90 ± 13*</td>
<td>76 ± 17*</td>
<td>68 ± 12*</td>
<td>55 ± 14*</td>
</tr>
<tr>
<td>Group 2 (n=7)</td>
<td>289 ± 55</td>
<td>190 ± 24</td>
<td>114 ± 10</td>
<td>89 ± 12†</td>
<td>64 ± 10†</td>
<td>89 ± 20</td>
</tr>
<tr>
<td>ANF (pg/ml)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Group 1 (n=7)</td>
<td>33 ± 9</td>
<td>73 ± 18*</td>
<td>91 ± 13*</td>
<td>76 ± 17*</td>
<td>68 ± 12*</td>
<td>55 ± 14*</td>
</tr>
<tr>
<td>Group 2 (n=10)</td>
<td>56 ± 10</td>
<td>79 ± 12</td>
<td>132 ± 39†</td>
<td>97 ± 20†</td>
<td>68 ± 10</td>
<td>65 ± 13</td>
</tr>
<tr>
<td>NE (pg/ml)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Group 1 (n=7)</td>
<td>111 ± 25</td>
<td>62 ± 11*</td>
<td>33 ± 11*</td>
<td>52 ± 17*</td>
<td>65 ± 17*</td>
<td>74 ± 26†</td>
</tr>
<tr>
<td>Group 2 (n=10)</td>
<td>160 ± 32</td>
<td>102 ± 21</td>
<td>75 ± 19†</td>
<td>76 ± 24†</td>
<td>84 ± 32†</td>
<td>96 ± 24†</td>
</tr>
<tr>
<td>EPI (pg/ml)</td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Group 1 (n=7)</td>
<td>28 ± 12</td>
<td>12 ± 5</td>
<td>12 ± 3</td>
<td>11 ± 3†</td>
<td>8 ± 2†</td>
<td>9 ± 1†</td>
</tr>
<tr>
<td>Group 2 (n=10)</td>
<td>49 ± 20</td>
<td>16 ± 5</td>
<td>17 ± 6</td>
<td>8 ± 2</td>
<td>11 ± 4†</td>
<td>10 ± 1†</td>
</tr>
<tr>
<td>AVP (pg/ml)</td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Group 1 (n=6)</td>
<td>8.7 ± 4.3</td>
<td>—</td>
<td>2.3 ± 0.3*</td>
<td>—</td>
<td>—</td>
<td>1.9 ± 0.4*</td>
</tr>
<tr>
<td>Group 2 (n=4)</td>
<td>9.9 ± 4.4</td>
<td>—</td>
<td>1.4 ± 0.4*</td>
<td>—</td>
<td>—</td>
<td>2.4 ± 0.6*</td>
</tr>
</tbody>
</table>

Values are means ± SEM. Hct = hematocrit; PRA = plasma renin activity; Ang I = angiotensin I; PAC = plasma aldosterone concentration; ANF = atrial natriuretic factor; NE = norepinephrine; EPI = epinephrine; AVP = arginine vasopressin.

*p < 0.01, †p < 0.05, compared with control values.

The changes in humoral variables in the two groups during and after infusion are shown in Table 2. The changes of these factors were similar in the two groups. As expected, volume loading reduced the PRA and plasma aldosterone concentration. The levels of norepinephrine and epinephrine decreased during the infusion; the level of norepinephrine was lowest at the end of the infusion, whereas that of epinephrine was lowest 2 hours after stopping the infusion. The ANF level increased during the infusion and returned to nearly the control value in the postinfusion period. The level of vasopressin decreased. The osmolality and levels of Na⁺ and K⁺ did not change throughout the experiment.

Urinalysis

Data on the urine volume and urinary sodium excretion are shown in Figure 2. In Group 1, these variables increased to maxima in the period just after the infusion, and then decreased during the postinfusion period. The patterns of change in the two groups were similar (by two-way analysis of variance for repeated measures). Although the diuresis and natriuresis of Group 1 (4.7 ± 3.1 ml/kg and 0.54 ± 0.40 mEq/kg, respectively) in the first hour look greater on average than those of Group 2 (2.8 ± 2.5 ml/kg and 0.29 ± 0.02 mEq/kg, respectively), there were no significant differences. Those of Group 1 in the third hour, when TPR was increased, were quite similar to those of Group 2.

Vascular Sensitivity

The pressor responses to norepinephrine and angiotensin II before and 3 hours after volume expansion were compared in 23 dogs (12 in Group 1 and 11 in Group 2). In both groups, these responses were potentiated by volume expansion, and the
increases in the pressor responses in the two groups were similar (Figure 3). To examine the role of this increased pressor response in the increases in TPR and MBP, we compared the enhanced pressor responses and percent values of the TPR and MBP 3 hours after volume expansion with the control values. No positive correlation was found between the increase in the pressor response to norepinephrine and the change in the TPR or MBP in Group 1 or 2 or in all the dogs (Figure 4). The enhanced response to angiotensin II was also not correlated with changes in the TPR or MBP.

To evaluate the effect of the endogenous norepinephrine level on the pressor response, we injected norepinephrine into a set of six dogs (5 in Group 1 and 1 in Group 2) just after volume expansion in addition to the two occasions just described. The increases in BP in these six dogs were 28.2 ± 5.4, 45.5 ± 8.9, and 64.3 ± 12.0 mm Hg, before, just after, and 3 hours after volume expansion, respectively. The increase in pressor response 3 hours after volume expansion was significantly greater than that of the control value and that just after volume expansion.

**Discussion**

In chronic volume-loaded hypertension, an increase in TPR is known to be preceded by an increase in CO.\textsuperscript{1-2} and Guyton et al.\textsuperscript{3-4} proposed that the increase in TPR is due to systemic autoregulation as a summation of local autoregulation. However, in chronic experiments, other investigators have observed sequential hemodynamic changes that are not consistent with the hemodynamic pattern of autoregulation (i.e., vasoconstriction was observed without a preceding increase in the CO).\textsuperscript{6-8} In contrast to chronic volume expansion, there have been few studies on acute volume expansion. In this work, we demonstrated that acute volume expansion produced resistance-dependent hypertension following initial volume-dependent hypertension. In our study, infusion of dextran initially caused an increase in the CO associated with a decrease in the TPR in all dogs. The reason why our results, unlike those of other studies,\textsuperscript{6-8} were consistent with the hemodynamic pattern of autoregulation may be mainly attributable to the experimental design. First, an increase in the circulatory volume, which increases the CO, may be more prominent in acute volume expansion than in chronic volume expansion, and acute activation of cardiopulmonary baroreceptors may decrease the TPR through a reactive baroreceptor reflex. Another possible explanation is related to the hypertensive model. Fletcher et al.\textsuperscript{6} used renal wrap hypertension, in which the renin-angiotensin system is thought to be one of the main contributory factors.\textsuperscript{19} Kim et al.\textsuperscript{7} studied hemodynamic pattern in end-stage renal disease and the anephric state during volume expansion. In these states, the activity of the sympathetic nervous system has been reported to be elevated.\textsuperscript{20} Thus, increased activities of the renin-angiotensin system and sympathetic nervous system could have contributed to the increase in the TPR from the beginning in their experiment.

The increase in TPR occurred despite the decrease in hematocrit. Therefore, if the resistance had been corrected for the decrease in viscosity, the actual total resistance would have been much more increased. However, because the decrease in the
hematocrit was almost the same in the two groups, the difference in the actual vascular resistance between the two groups must have been unchanged.

We do not think that our hemodynamic results are due to the pharmacological effects of dextran. Although dextran reportedly can change renal vascular resistance by altering renal function, we observed the resistance-dependent hypertension 3 hours after volume expansion in nephrectomized dogs (unpublished observation, 1988).

In our study all dogs showed similar patterns of hemodynamic change during volume expansion, but during the recovery period they showed one of two different patterns. Kim et al. and Bravo et al. reported differences in responses to volume loading similar to those observed in our work, but they did not provide a detailed explanation for the differences. We could not find any factors responsible for these different hemodynamic patterns. The finding that the reductions of the hematocrit and increases in the RAP were similar in the two groups indicated that the volume loading was the same. Moreover, the similar increases in the levels of plasma ANF and decreases in those of norepinephrine in the two groups during infusion suggested a similar extent of mechanical stretching of the right atrium and cardiopulmonary nerve activation in response to volume loading. Furthermore, the similar restorations of hematocrit and CO in the two groups during the postinfusion period, together with the result that diuresis and natriuresis occurred similarly in the two groups, would exclude the possibility that a difference in the capacity for urine excretion, which has been reported to be impaired in Dahl salt-sensitive rats, was responsible for the different hemodynamic responses of the two groups. Therefore, the BP 3 hours after infusion did not depend on a volume factor.

The sympathetic nervous system has been reported to be involved in DOCA-salt hypertension and chronic sodium loading. Elevation of the plasma level of norepinephrine has been reported in the former, and intracerebroventricular administration of 6-hydroxydopamine prevented the DOCA-induced hypertension and increase in plasma norepinephrine. On the contrary, our observations are consistent with reports of no increase in norepinephrine in saline-loaded Wistar rats and of a decrease in norepinephrine in metyrapone-induced hypertensive dogs. The discrepancy between these findings may be due to differences in the species used and the rapidity of volume expansion. In addition, we infused isosmotic dextran in lactated Ringer’s solution instead of normal saline. Oral sodium loading or infusion of saline could stimulate the central nervous system. Another possible factor is vasopressin, which is postulated to be involved in DOCA hypertension and sodium-loaded rats. But we did not observe any increase in vasopressin. Moreover, our dogs showed no elevation of plasma osmolality or Na+, which would stimulate vasopressin secretion.

The decrease in plasma norepinephrine does not directly indicate a decrease in the sympathetic activity, because diuresis may increase the clearance of norepinephrine. However, even when clearance may be changed, the changes in clearance would not be different between the two groups, because urine volume was similar in the two groups. Thus, the change in peripheral sympathetic nerve activity likely did not contribute to the vasoconstriction in Group 1. However, we cannot exclude the contribution of the central nervous system to the production of resistance-dependent hypertension. Ishizuka et al. reported that nucleus tractus solitarii contribute to the cerebral autoregulation and that this contribution is mediated by the baroreceptor reflex. We examined the effects of volume expansion of the same degree on the hemodynamics in hexamethonium-treated dogs. As these dogs showed an increase in TPR with sustained hypertension 3 hours after volume expansion (unpublished observation, 1988), the vasoconstriction is not likely to have resulted from changes in the buffering action of the baroreceptor reflex control. The precise role of the autonomic nervous system remains to be elucidated.

Na+,K+-ATPase inhibitors could cause an increase in peripheral resistance. Extensive studies by de Wardener, Haddy, Blaustein, and others have resulted in a new concept of the mechanism of the maintenance of hypertension. Na+,K+-ATPase inhibitors released by volume loading would restore the circulatory volume by increasing the urine output and induce peripheral vasoconstriction associated with hyperresponsiveness to vasoactive substances. Unfortunately, the present study provided no positive evidence for the role of Na+,K+-ATPase inhibitors, as will be described.

To our knowledge, this is the first study to report urinary output simultaneously with the hemodynamic changes. Before the experiments, all the dogs were given the same amount of dietary sodium to minimize the differences in their condition. However, the possibility remains that some difference in sodium or fluid status was present, as the initial urine output following the infusion appeared greater, although it was not significant, in the dogs of Group 1 compared with those of Group 2. There was no second peak in the late phase of the recovery period. Since the increase in the TPR did not coincide with natriuresis or diuresis, our results provide no evidence for the contribution of a natriuretic factor to this vasoconstriction.

Another interesting finding in this study was that of hyperresponsiveness to vasoactive substances. To our knowledge, this is the first study of the relationship between vascular hyperresponsiveness and increased peripheral resistance in acute volume-loaded hypertension. Although hyperresponsiveness and its contribution to the pathogenesis of
Vasoconstriction in Volume Expansion/Otsuka et al.

Hypertension have been postulated from studies on volume-loaded hypertension\(^{16,32}\) and the DOCA model of hypertension,\(^{14,15}\) hemodynamic components were not evaluated in these studies. The characteristics of this hypersensitivity are not known. The role of vasopressin has again been postulated in this potentiation of the pressor response to vasoactive substances,\(^{15}\) but vasopressin was not increased in our acute volume expansion studies. Berecek et al.\(^{27}\) reported that intravenous administration of 6-hydroxydopamine prevented the development of enhanced vascular reactivity, suggesting the importance of the central sympathetic nervous system. The absence of an increase in norepinephrine in our dogs does not rule out the possibility of integrated control of the BP by the central nervous system. On the other hand, in 1972 Mizukoshi and Michelakis\(^{33}\) reported a vasosensitizing factor in volume-loaded animals, and in 1984, Sakamaki et al.,\(^{16}\) using a cross-circulating method, showed that this factor could be transferred to recipient animals. Recently, Jandhyala and Hom\(^{32,34}\) suggested that this factor inhibited Na\(^+\),K\(^+\)-ATPase. However, Pedrinelli et al.\(^{33}\) obtained no evidence of a role for an endogenous Na\(^+\),K\(^+\)-ATPase inhibitor. Thus, despite extensive investigations, no conclusive results have yet been obtained.

Alteration in the plasma level of vasoactive substances affects the pressor responsiveness to the substances,\(^{36-37}\) and a negative correlation between the two has been reported.\(^{38}\) Cowley and Lohmeier\(^{39}\) emphasized the importance of this endogenous hormone level in the interpretation of vascular reactivity, and they did not find "real" enhancement of the pressor response to angiotensin II in acute volume expansion. Indeed, in our experiment, the levels of norepinephrine and PRA were decreased when hypertension was lowest at the end of the infusion, and more prominent enhancement of the response to exogenous norepinephrine was demonstrated 3 hours after volume expansion. This result indicates the existence of "real" hypersensitivity that cannot be explained by "receptor occupancy." The reason that Cowley and Lohmeier\(^{39}\) did not observe potentiation of the pressor response is not clear. They also used mongrel dogs, and the conditions of anesthesia were almost identical to those in our work. The time of pressor examination is presumably important. The hypersensitivity mechanism would probably not be fully operative during or soon after volume expansion. This may also be why we observed more potentiation 3 hours after stopping the infusion associated with vasoconstriction.

We found that the pressor responses to norepinephrine and angiotensin II were potentiated not only in the vasoconstricted group but also in the other group, whose TPR and MBP had returned to nearly basal values, and that vascular hypersensitivity showed no correlation with increases in the TPR or MBP. These findings suggest the possible contribution of some factors that induce vascular hypersensitivity, but they also indicate that hypersensitivity cannot be the sole factor responsible for resistance-dependent hypertension. This finding is consistent with the recent report by Soltis and Bohr\(^{40}\) of dissociation of the BP and vascular sensitivity before and after treatment of hypertension. Because these experiments were performed on anesthetized animals, there is some limitation in interpreting the results, and it may not be appropriate to extrapolate our findings directly to conscious or chronic experiments. However, the series of hemodynamic events did occur in this acute condition.

In summary, we demonstrated that acute isosmotic volume expansion in anesthetized dogs produced resistance-dependent hypertension after an initial increase in the CO, without activation of the peripheral sympathetic nervous system, the renin-angiotensin system, or vasopressin secretion. Hypersensitivity to vasoactive substances was observed after volume expansion. However, the mechanism of this hypersensitivity and its contribution to resistance-dependent hypertension remain to be elucidated.

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Vasoconstriction and hypersensitivity to vasoactive substances after acute volume expansion in dogs.
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