Contribution of Intravascular Receptors to the Renal Responses Following Intravascular Volume Expansion

By Joseph P. Gilmore, M.S., Ph.D., and Myron L. Weisfeldt, B.A.

During the past three decades considerable effort has been made to elucidate the mechanisms which contribute to the diuretic and natriuretic response to iso-oncotic, isotonic, intravascular volume expansion. The suggestion made by Peters, that the fullness of the intravascular space was "sensed" by the organism, directed attention towards a search for receptors which might respond to changes of intravascular volume or some variable influenced by volume. From consideration of earlier work and analysis of the pressure-volume relationships of the intravascular space, Henry and associates undertook studies to determine if volume receptors were present in the thoracic area. They observed that distention of the left atrium was associated with an increase in urine flow whereas diuresis was not seen when the pulmonary veins, pulmonary artery or right atrium were distended. Subsequent studies indicated that the diuretic response was blocked by vagotomy. Although Henry et al. suggested that the diuresis was the result of inhibition of ADH secretion it has been shown that there is both a hormonal and neural efferent component; the former appears to increase free water excretion and the latter glomerular filtration rate and sodium excretion. The possibility that the hormonal component is ADH has, however, been challenged by Ledsome et al.

As a natural consequence of the studies of Gauer and associates, Atkins and Pearce and Pearce undertook experiments to determine the influence of vagotomy on the renal response to intravascular volume expansion. They observed that vagotomy decreased both diuresis and natriuresis following the infusion of plasma but that neither vagotomy nor carotid sinus denervation influenced the diuretic response to 6% bovine albumin. These authors, however, did not present data which permitted an evaluation of the extent to which changes in free water clearance contributed to the attenuating influence of vagotomy upon the diuresis which resulted from plasma infusion.

Preliminary experiments indicated that in response to dextran infusion, normally innervated dogs often produced hypotonic urine. It was of interest, therefore, to compare the renal responses of these animals with those in which the vagi or carotid sinus nerves were sectioned with the objective of assessing the extent to which these afferent pathways contribute to the production of hypotonic urine under conditions of acute intravascular volume expansion.

Methods

All experiments were performed on mongrel dogs (9.0 to 21.5 kg) anesthetized with intravenous pentobarbital sodium (30 mg/kg). Following tracheal intubation, a femoral or jugular vein was cannulated for administering infusions and blood sampling and a femoral artery cannulated for recording blood pressure. Urine was collected by direct catheterization of the ureters through a low midline abdominal incision. Left atrial pressure was measured in several experiments by the transbronchial approach using the left atrium as the zero reference. Arterial and atrial pressures were recorded using Sanborn transducers. Heart rate was recorded using a Waters cardiotachometer. All recordings were continuous and were done on a Sanborn multichannel recorder.

Endogenous creatinine clearance was used as an index of glomerular filtration rate with urine and blood creatinine determined by the method of Edwards and Whyte. Osmolality was determined by freezing point depression, chloride

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by automatic titration,\textsuperscript{11} and sodium and potassium by either a Patwin flame photometer or Technicon autoanalyzer. Hematocrit was determined by the Drummond microhematocrit.

Six per cent dextran in normal saline (Cutter or Baxter) was used to increase intravascular volume. It is described by the manufacturer as having an average molecular weight approximately that of serum albumin with 5 to 10\% having a molecular weight as low as 25,000 and as high as 250,000. The solution was found to have an osmolality of approximately 290 milliosmols/liter. The dextran did not interfere with creatinine analysis but did give erroneously high inulin values using either standard inulin method.\textsuperscript{12, 13}

The animals were divided into four groups. Group 1 (Control Dilution Experiments) consisted of animals in which dilution was produced by infusing dextran intravenously in an amount equal to 2.5\% body weight at a rate of 35 ml/min while withdrawing blood from an artery at the same rate. The bleeding followed the infusion by two minutes. Group 2 (Control Expansion Experiments) consisted of animals which were given dextran intravenously, in an amount equal to 3\% body weight at a rate of 35 ml/min. Group 3 (Vagotomy Experiments) consisted of animals in which bilateral section of the vagosympathetic trunks was done prior to the intravenous infusion of dextran in the same amount and at the same rate as Group 2. Group 4 (Carotid Sinus Denervation Experiments) consisted of animals in which the carotid sinuses were denervated by ligation and section of the sinus nerves and then clearing the sinus of all tissue. Adequacy of carotid sinus denervation was demonstrated by the lack of a blood pressure and heart rate response to pinching of the sinus. Dextran was administered intravenously following denervation in the same amount and at the same rate as Group 2. Some animals of Groups 2, 3, and 4 were maintained on a positive-negative respirator. This, however, did not influence the results obtained in any given group. The animals in the various groups were studied in a random manner and when more than one animal was done on the same day it was paired with an animal from another group.

The general experimental procedure was the following. After completion of the surgical preparations, urine was collected in graduated cylinders for periods of 20 to 30 minutes or until at least 2 ml of urine were obtained. A blood sample was obtained between two such successive periods with two urine samples that showed similar urine flows. Dextran was then infused. Urine was collected continuously for 20 minute periods until a steady diuresis was achieved after which time urine collections were made continuously for 10 minute periods. A second sample of blood was taken at the time of steady diuresis. Urine collections were again extended to continuous 20 minute periods when urine flow began to decline. The experiment was continued until urine flow declined to at least one-half the maximum diuresis value and, in most experiments, until urine flow was one-fourth the maximum value. A third blood sample was usually drawn when the last urine sample was recorded. In some experiments the blood samples were replaced with dextran.

**Results**

**GROUP 1: CONTROL DILUTION EXPERIMENTS**

The results of the five experiments done in this series are shown in table 1. All animals showed a small but significant increase in urine flow (0.011 to 0.025 ml/kg/min). The three animals in which urine sodium was determined showed also a small but significant increase in sodium excretion (1.43 to 3.37 μEq/kg/min). The changes in urine flow and sodium excretion reached their peak at approximately 34 minutes following the end of infusion. In all animals in which it was determined, Uosm/Posm showed a significant decrease (6.01 to 4.54). Plasma osmolality did not change significantly following dextran infusion in this or the other groups presented below. The exchange procedure had no significant effect upon arterial pressure and produced a significant decline in hematocrit (38.3 to 26.1), values similar to those found in the control expansion experiments in which both dilution and intravascular volume expansion were produced. The dogs in the control dilution experiments had a significantly lower hematocrit than those in the control expansion experiments; however, the hematocrits were within the normal range.

**GROUP 2: CONTROL EXPANSION EXPERIMENTS**

Eleven animals were studied in this series, the results of which are shown in table 2. Following dextran infusion every animal showed a substantial increase in urine flow, sodium and osmolar excretion and a decline of Uosm/Posm. In five of the ten animals in which data were obtained for the calculations, Uosm/Posm declined below 1.0 (0.37, 0.38, 0.39, 0.40, 0.41) which is approximately that of serum albumin.
TABLE 1
Average Data from the Control Dilution Experiments: Exchange Experiments

<table>
<thead>
<tr>
<th></th>
<th>N*</th>
<th>C**</th>
<th>D†</th>
<th>± SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Volume, ml/kg/min</td>
<td>(5)</td>
<td>.011</td>
<td>.025</td>
<td>.014 ± .006</td>
</tr>
<tr>
<td>VUNa, μEq/kg/min</td>
<td>(3)</td>
<td>1.43</td>
<td>3.37</td>
<td>1.94 ± 2.12</td>
</tr>
<tr>
<td>VUosm, μOsm/kg/min</td>
<td>(4)</td>
<td>23.2</td>
<td>37.5</td>
<td>14.3 ± 6.4</td>
</tr>
<tr>
<td>Uosm/Posm</td>
<td>(4)</td>
<td>6.01</td>
<td>4.54</td>
<td>1.47 ± .66</td>
</tr>
<tr>
<td>Mean arterial pressure, mm Hg</td>
<td>(5)</td>
<td>124</td>
<td>121</td>
<td>2.6 ± 9.8</td>
</tr>
<tr>
<td>Hematocrit, %</td>
<td>(5)</td>
<td>38.2</td>
<td>26.1</td>
<td>12.1 ± .9</td>
</tr>
<tr>
<td>Time to maximum diuresis, min ± SD</td>
<td>(5)</td>
<td>33.8 ± 10.6</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Time to maximum natriuresis, min ± SD</td>
<td>(5)</td>
<td>37.8 ± 14.3</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*N: number of animals.
**C: control period.
†D: value at maximum diuresis.
VUNa: sodium excretion. VUosm: total solute excretion.

0.63, 0.87, 0.93, and 0.94) and three others declined to 1.0. There was no correlation between urine osmolality and the change in urine flow or the change in arterial blood pressure. No significant difference was found between the time to peak diuresis (50 min) and natriuresis (50 min). Urine flow fell to one-half the peak diuresis value 74 minutes after reaching the peak, at which time 52% of the infused volume had been excreted. Mean arterial pressure showed no average significant change from the preinfusion value at peak diuresis, increasing in six animals, decreasing in four and showing no change in one. The greatest increase was 31 mm Hg and the largest decrease 10 mm Hg. The largest increase occurred in the animal that had the lowest control arterial pressure (101 mm Hg). Endogenous creatinine clearance increased in seven of eight animals following infusion (P < 0.01). There was no correlation between the change in clearance and arterial pressure. In each animal the hematocrit showed a substantial decline (P < 0.01). Figure 1 shows a representative experiment from this series.

GROUP 3: VAGOTOMY EXPERIMENTS

The ten animals in this series responded to dextran infusion with an increase in urine flow, sodium and solute excretion, and a decline of Uosm/Posm (table 2). The increase in urine flow was, however, significantly less than in the control expansion experiments (P < 0.003), but no significant difference obtained between these two groups with respect to the change in sodium excretion (P > 0.2). Two of the animals had a Uosm/Posm of less than 1.0 (0.64 and 0.91), and in one animal the ratio declined to 1.0. The time to peak diuresis and natriuresis was approximately 64 min, a value not significantly different from that observed in the control expansion experiments (P > 0.2). Urine flow fell to one-half the peak diuresis value 79 minutes after reaching maximal diuresis. At this time 32% of the infused volume was recovered compared with 52% in the control expansion experiments (P > 0.2). Urine flow fell to one-half the peak diuresis value 79 minutes after reaching maximal diuresis. At this time 32% of the infused volume was recovered compared with 52% in the control expansion experiments. Arterial blood pressure was not significantly different from that of the control expansion experiments prior to infusion (P > 0.2), nor at the time of peak diuresis (P > 0.2), although the average increase in
TABLE 2

Average Data from the Control Expansion, Vagotomy and Carotid Denervation Experiments

<table>
<thead>
<tr>
<th></th>
<th>Control expansion</th>
<th>Vagotomy</th>
<th>Carotid denervation</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N*</td>
<td>C**</td>
<td>D† Δ ± SD</td>
</tr>
<tr>
<td>Volume, ml/kg/min</td>
<td>(11)</td>
<td>.012</td>
<td>.22 ± .084</td>
</tr>
<tr>
<td>VUNa μEq/kg/min</td>
<td>(10)</td>
<td>1.73</td>
<td>23.1</td>
</tr>
<tr>
<td>VUosm μOsm/kg/min</td>
<td>(10)</td>
<td>14.1</td>
<td>73.7</td>
</tr>
<tr>
<td>Uosm/Posm</td>
<td>(10)</td>
<td>4.46</td>
<td>1.08</td>
</tr>
<tr>
<td>C creatinine ml/kg/min</td>
<td>(8)</td>
<td>2.57</td>
<td>3.79</td>
</tr>
<tr>
<td>Mean art. press., mm Hg</td>
<td>(11)</td>
<td>127</td>
<td>136</td>
</tr>
<tr>
<td>Hematocrit, %</td>
<td>(9)</td>
<td>45.6</td>
<td>29.4</td>
</tr>
<tr>
<td>Time to max diuresis, min</td>
<td>(11)</td>
<td>49.8 ± 15.9</td>
<td>(10)</td>
</tr>
<tr>
<td>Time to max natriuresis, min</td>
<td>(11)</td>
<td>49.9 ± 11.7</td>
<td>(10)</td>
</tr>
<tr>
<td>% infused vol excreted to % diuresis</td>
<td>(11)</td>
<td>52.1 ± 29.6</td>
<td>(10)</td>
</tr>
</tbody>
</table>

*N: number of animals. **C: control period. Δ: value at maximum diuresis. ΔΔ: change between control period and time of maximal diuresis. ± SD. VUNa: sodium excretion. VUosm: total solute excretion. % infused volume excreted to % diuresis: per cent of the volume of dextran infused that was recovered as urine at the time urine flow had declined to a value approximating one-half that found during maximum diuresis.
Representative control expansion experiment showing the renal responses to dextran infusion. Dose and duration of infusion at top of figure. AP: arterial pressure; HR: heart rate; C\textsubscript{cr}: endogenous creatinine clearance; Uv: urine volume; Na\textsuperscript{+}: urine sodium; K\textsuperscript{+}: urine potassium; Uosm: total solute excretion; Uosm/Posm: ratio of urine osmolality to plasma osmolality.

Blood pressure was highest in this group. Creatinine clearance (P < 0.05) and hematocrit (P < 0.01) changed significantly in response to infusion but these changes were not significantly different from those of the control expansion experiments. A representative experiment from this series is shown in figure 2.

GROUP 4: CAROTID SINUS DENERVATION EXPERIMENTS

Twelve animals were studied in this series, nine of which are reported. Two of the three animals not reported showed little diuretic and natriuretic responses associated with little change in hematocrit. The blood pressure of the third dog did not show an elevation following what appeared to be an adequate denervation. Also, it showed the greatest change in urine flow of any of the animals in any of the series and expired when a blood sample was replaced with dextran.

The data from the nine acceptable animals are shown in table 2. As in the control expansion and vagotomy experiments, this
group responded to dextran infusion with an increase in urine flow, sodium and solute excretion, and a decline of Uosm/Posm. The increase in urine flow, however, was significantly less than that in the control expansion experiments ($P < 0.025$). There was no significant difference between these two groups with respect to the change in sodium excretion. Only one of the nine animals showed a Uosm/Posm of less than 1.0 (0.76). The time to peak diuresis and natriuresis was not significantly different from the control expansion experiments. Urine flow fell to one-half the peak diuresis value 73 min after achieving the peak, at which time 31% of the infused volume was recovered. Although the blood pressure in this group of animals was significantly higher than in the control expansion experiments.

**FIGURE 2**

Representative experiment showing renal responses of vagotomized dog to dextran infusion. Dose and duration of infusion at top of figure. Symbols as in figure 1.
experiments before infusion \((P < 0.005)\), the change in pressure following infusion was not significantly different. Following infusion, blood pressure increased in five animals, decreased in four, and showed no change in one. Neither the change in creatinine clearance nor hematocrit was significantly different from that found in the control expansion experiments.

**Discussion**

The experiments presented above demonstrate that either carotid sinus denervation or vagotomy attenuates the diuretic response to intravascular expansion with no significant influence upon sodium excretion. These results are in contrast to those of Atkins and Pearce\(^7\) who reported that vagotomy decreased both the diuretic and natriuretic response to the intravenous infusion of plasma, and to the experiments of Pearce\(^8\) who reported that neither vagotomy nor carotid sinus denervation influenced the diuretic response to bovine albumin solutions. Also, in contrast to the findings of these workers, no significant temporal dissociation was found between the maximum values for natriuresis or diuresis. The present study indicates, however, that there may be different effector mechanisms for these two responses.

In the albumin infusion experiments of Pearce\(^8\) the onset of diuresis was rapid suggesting that a significant amount of the volume infused was lost rapidly from the intravascular space, thereby increasing interstitial fluid volume, a situation similar to that which would obtain if the animal was prehydrated. Since it is established that prehydration will potentiate the diuretic response to volume expansion\(^14\) it is possible that in the experiments of Atkins and Pearce\(^7\) an attenuating influence of vagotomy did obtain but was cancelled by the change in the state of hydration caused by the first infusion of albumin. This same consideration would apply to the carotid denervation experiments of Pearce.\(^8\) That dextran was not lost rapidly from the intravascular space in the present experiments is indicated by the failure to show any substantial solute diuresis in the control dilution experiments (Group 1) and the maintenance of hemoconcentration as indicated by the decline in hematocrit following dextran infusion.\(^15\)

Certain conclusions may be made concerning the natriuretic response following the administration of dextran. The control dilution experiments (Group 1) suggest that the natriuresis is not secondary to dilation of a circulating hormone or secondary to a change in renal blood flow distribution resulting from the decline in hematocrit. The denervation experiments indicate that the natriuresis is independent of the integrity of the vagi or carotid sinus nerves. The similar increases in endogenous creatinine clearance, however, in both the control expansion and denervated groups suggest that an increase in filtered sodium does contribute to the natriuresis. The increase in glomerular filtration rate may be secondary to a withdrawal of renal sympathetic tone.\(^16\) At the same time, the recent findings of Dirks, Cirksena, and Berliner (personal communication) in the dog that the systemic infusion of sodium chloride decreases the proximal tubule/plasma inulin ratio and increases sodium excretion independent of changes in glomerular filtration rate must be considered. The consistent increase in the Na/K of urine observed in these experiments (figs. 1, 2, 3) does not necessarily indicate that a decrease in circulating aldosterone contributed to the natriuresis because this ratio can increase when glomerular filtration rate is increased.\(^17\)

The status of left atrial receptors has been reviewed recently by Gauer and Henry\(^18\) who have concluded that the diuretic response to atrial distension is due, in part, to a decreased blood titer of ADH. It is to be noted, however, that Ledsome and associates\(^6\) concluded that ADH may not play a role in atrial distention diuresis since the diuresis was not blocked by Pitressin. It does appear nevertheless that distention of the left atrium is associated with an increase in free water clearance which is dependent upon an intact vagus. With respect to the influence of vagal pathways on ADH secretion, both Share and Levy\(^19\)
and Usami and co-workers\textsuperscript{20} observed an elevation of blood ADH following vagotomy. Also, Perlmutt has recently reported that bilateral cervical vagotomy produces a prolonged inhibition of water diuresis.\textsuperscript{21}

While the available data suggest the existence of receptors in the carotid arteries which influence ADH secretion there is no consensus concerning their location. Usami and associates,\textsuperscript{20, 22} and Share and Levy\textsuperscript{19} observed that carotid occlusion in vagotomized dogs increased circulating ADH. No effect was seen when the vagi were intact and the response occurred whether occlusion was done below the thyroid carotid junction or between this junction and the carotid sinus. The response was blocked by carotid denervation. Perlmutt\textsuperscript{23} observed that free water excretion in the dog decreased when the carotid arteries were occluded below the thyroid carotid junction but not when done between this junction and the carotid sinus. In Perlmutt's experiments the vagi were intact. Similar results were obtained by Lemaire and associates.\textsuperscript{24}

The results of the present experiments are consistent with the view that both carotid sinus and vagal afferents contribute to the diuretic response produced by intravascular expansion by a mechanism which influences the excretion of free water. There are three mechanisms which can explain the appearance of hypotonic urine. The first is an increase in medullary blood flow,\textsuperscript{25} the second, an increase in solute load,\textsuperscript{26} and the third a decrease in circulating ADH. With respect to the first, it ap-

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pears that renal artery perfusion pressure is a primary determinant of medullary blood flow. In the present experiments, however, there was no correlation between arterial pressure and urine osmolality following dextran infusion. With respect to the second mechanism, there was no significant difference in the change in solute excretion between the control expansion group and the two denervated groups of animals.

That the denervated groups of animals may have had a higher circulating level of ADH following dextran than the control animals is indicated by the studies discussed above. It is of interest that carotid sinus denervation had the same influence as vagotomy upon diuresis. This is consonant with the observation of Perlmutt but not consonant with the experiments of Usami and associates or Share and Levy. To explain these apparent inconsistencies the following hypothesis is suggested: Neurons in both the carotid sinus nerves and vagi serve as part of the afferent limb of a reflex which modulates the secretion of the antidiuretic hormone. The neurons in the sinus nerve originate from a single type of receptor (perhaps pressure receptors), while the neurons in the vagi originate from receptors in both the left atrium, aortic arch, and perhaps ventricle. With respect to the aortic arch, one might expect to find in this area a counterpart analogous to receptors contained in the carotid artery. Section of the carotid sinus nerves would then either increase or have no effect on circulating ADH depending on the degree to which vagal afferents are modulating ADH secretion. In contrast, section of the vagi would be more likely to increase circulating ADH since two of at least three afferent pathways are interrupted. In the carotid denervated dog only one pathway controlling ADH secretion is not intact. Thus, in this preparation the absence of carotid sinus afferents continues to exert a positive effect on ADH secretion following infusion while the vagus pathway, secondary to atrial distension, tends to influence secretion negatively. The influence of aortic afferents is constant since no significant change in aortic pressure occurs following infusion. The net effect of these influences would be an elevated level of circulating ADH compared to the normal, intact animal. Following vagotomy, at least two pathways influencing ADH are interrupted so that the base line levels of ADH are elevated. Following infusion these levels are maintained since the remaining intact reflex pathway receives no stimulus to a change in its afferent neuron activity, i.e., no change in arterial pressure.

As Gauer has pointed out, the distensibility of the arterial system is such that it
would not be as appropriate an area for sensing volume changes as would be the low pressure system, i.e., left atrial receptors. At the same time, however, substantial changes in blood volume can occur in the normovolemic animal with little change in left atrial pressure (fig. 4), and only with large volume changes do large atrial pressure changes occur. Also, with substantial decreases in volume, small decreases of left atrial pressure occur at the lower portion of the pressure volume curve. In contrast, large increases in intravascular volume are associated with little or no increase in arterial pressure (table 1), while large volume reductions are associated with substantial decreases in aortic pressure. Thus, with respect to the control of ADH, the atrial receptors would appear to play a primary role under conditions of isotonic, iso-oncotic hypervolemia whereas arterial receptors would play a role primarily under conditions of hypovolemia. The possibility that ventricular receptors influence ADH secretion must also be considered.

There is no reason to believe that extravascular receptors played a role in the responses observed in this study. Several investigators have noted, however, that the diuretic response to intravascular volume expansion is potentiated by hydration\(^1^5\),\(^2^7\) leading them to believe that extravascular or interstitial receptors play a role under such conditions. The search to find these receptors has thus far been unproductive. It is possible that the efficacy of hydration in potentiating diuresis can be explained, at least in part, by the following mechanism. Since the hydrating fluid moves into the interstitial space it would be expected that it would move into the interstitial spaces of the kidney and thereby effect a "dilution" of the renal medullary interstitial solutes. It is possible that, secondary to this diuresis, less water is removed from the permeable portion of Henle's loop\(^2^8\) resulting in a larger volume of tubular fluid being delivered to more distal portions of the nephron. This in turn may lead to an interference of sodium reabsorption secondary to an increased velocity of flow.

Summary

The renal responses to acute isotonic, iso-oncotic intravascular volume expansion have been studied in the normal dog, the vagotomized dog, and the dog with carotid sinus denervation. It was observed that either vagotomy or carotid sinus denervation attenuates significantly the diuretic response to intravascular volume expansion without influencing significantly the natriuretic response. The results indicated that carotid sinus receptors and receptors which have afferent fibers in the vagus nerves contribute substantially to the control of plasma volume by a mechanism which influences free water excretion. The receptors of the low pressure system probably play a primary role under conditions of hypervolemia while receptors of the high pressure system appear to play a primary role under conditions of hypovolemia.

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