Relation of Sodium Balance to Arterial Pressure During Drug-Induced Saluresis

By Frank A. Finnerty, Jr., M.D., Michael Davidov, M.D., and Nikos Kakaviatos, M.D.

SUMMARY
Serial determinations of plasma volume and urinary sodium excretion were determined during saluresis in 20 hypertensive patients. Although the diuretics produced a decrease in plasma volume and an increase in urinary sodium excretion in all patients, there was no direct relationship between the decrease in plasma volume and the fall in arterial pressure. Concomitant administration of dextran solution prevented the reduction in plasma volume but did not prevent the fall in arterial pressure. Similarly, replacement of plasma volume with dextran solution at the peak of hypotension following the diuretics had no effect on the reduced arterial pressure. Concomitant administration of hypertonic saline solution with the diuretic prevented the fall in arterial pressure, and the replacement of urinary sodium loss at the peak of hypotension returned the arterial pressure to control values when the sodium administered exceeded the urinary sodium loss. It would seem that in the hypertensive sodium depleted state a direct relationship exists between arterial pressure and sodium balance. Thus, a positive sodium balance is associated with a rise in arterial pressure, whereas a negative sodium balance is associated with a fall in arterial pressure. The data suggest also that the decreased pressor response during saluresis is due more to the production of negative sodium balance than to a decrease in plasma volume.

Additional Indexing Words:
Plasma volume  Hypertension  Hypotension
Dextran solution  Pressor response  Hydrochlorothiazide
Furosemide  Norepinephrine

RECENT STUDIES from this laboratory have shown that furosemide is a potent saluretic agent similar to thiazides, at least in its effect on plasma volume and sodium excretion.1 2 It was hoped that its rapidity of action (1 to 2 minutes) and potency (more than a thirteenfold increase in urinary output and a fourfold increase in urinary sodium excretion 15 minutes after injection) would enable its use as a tool to clarify the mechanism of the early fall of arterial pressure during saluresis. Although most investigators are in agreement that the fall of arterial pressure which accompanies the chronic administration of diuretics is due mainly to sodium depletion and has little, if anything, to do with plasma volume reduction, there is still no agreement regarding which of these parameters causes the early fall in arterial pressure.3-5 The purpose of the present study was to determine the mechanism of the early fall in arterial pressure during drug-induced saluresis.

Methods
Twenty patients were selected from the hypertensive clinic of the District of Columbia General Hospital. Nine were male and 11 were female. In addition to the elevated arterial pressure, each of the patients had objective evidence...
of vascular disease. Ophthalmoscopic examination revealed arteriovenous nicking in 10 patients and arteriovenous nicking plus retinopathy in four patients. There was electrocardiographic evidence of left ventricular hypertrophy in 17 patients and bundle-branch block in two patients. None of the patients was in congestive heart failure. All antihypertensive therapy, including diuretics, had been discontinued 1 month prior to and during the entire study period.

Patients arrived in the cardiovascular laboratory in the fasting state. A catheter was inserted into the antecubital vein and an indwelling catheter was placed in the urinary bladder. The intravenous catheter was kept patent by intermittent administration of small amounts of heparin. The arterial pressure was recorded at 10-minute intervals. After the arterial pressure had been stabilized for 1 hour, control determinations of plasma volume were performed. At the end of the control period, each patient received 100 to 200 mg of furosemide (14 patients) or 200 mg of hydrochlorothiazide intravenously (six patients). Furosemide was supplied in 2-ml ampules in a concentration of 10 mg/ml and was administered undiluted intravenously in 2 to 5 minutes. Hydrochlorothiazide was supplied in 50-mg ampules in a dry form and 5 ml of sterile water was added to each ampule to form an intravenous solution. A placebo was administered intravenously to each patient either 1 week before the diuretic (15 patients) or 1 week after the diuretic (five patients). The plasma volume determination was repeated at the previously observed peak of hypotensive action of the diuretics (2 to 3 hours after furosemide and placebo and 5 to 6 hours after hydrochlorothiazide). The amount of sodium excreted in the urine during the period was determined.

In the two subsequent phases of the experiment, each performed 1 week apart, the effects of replacing the plasma volume with dextran solution and the sodium loss with hypertonic saline on the arterial pressure were studied. Dextran was supplied as a 6% solution in normal saline and contained 77 mEq of sodium in 500 ml. The hypertonic saline was supplied as a 5% solution in water and contained 427.5 mEq of sodium in 500 ml. In 10 patients the hypertonic saline infusion was given 7 days before the dextran solution whereas, in the other 10 patients, the dextran infusion preceded the saline. Half of the patients received the infusions immediately following the diuretic; the other half received the infusions at the peak of hypotension.

The administration of the infusion lasted 30 to 60 minutes. The dextran infusion was administered at a rate of 5 to 8 ml/min. In the patients who received the hypertonic saline infusion and diuretic concomitantly, an attempt was made to maintain the arterial pressure at the control level, but in the patients who received the saline infusion at the peak of hypotension, an attempt was made to increase the arterial pressure to control levels. Thus in both instances the initial rate of the saline infusion of 1 ml/min was slowly increased according to the response or arterial pressure to an average of 15 to 20 ml/min.

In patient 20, a week after completion of the above experiment, 1,000 ml of 5% saline was administered at the peak of hypotension during a period of 144 minutes. At the end of the infusion, 200 mg of furosemide was repeated. Arterial pressure and urinary sodium excretion were measured serially.

When the dextran solution and saline infusions were given concomitantly with the diuretic, the plasma volume was repeated at the estimated (previously observed) peak of hypotension (2 to 3 hours following the dose of furosemide and 5 to 6 hours following that of hydrochlorothiazide). When the infusions were given at the peak of hypotension, a second plasma volume determination was performed just prior to the infusion and a third determination was performed one-half hour after the completion of the infusion. The urine was collected separately during each of the phases and the sodium content was measured.

The sensitivity of the arterial pressure to norepinephrine was determined in all patients before and after the placebo, before and at the peak of hypotension, following the administration of diuretics, and one-half hour after the dextran solution and saline infusions. Levarterenol bitartrate was administered as an intravenous infusion in a concentration of 4 μg/ml of 5% dextrose in water. The rate of the infusion was regulated according to the increase in arterial pressure and varied between 4 and 24 μg/min. The end point of the experiment was taken as a rise of arterial pressure in excess of 25%. During the norepinephrine infusion the arterial pressure was recorded every 30 sec.

The arterial pressure was recorded by the auscultatory method with the patient in the supine position. The mean arterial pressure was calculated as the arithmetic mean (systolic plus diastolic divided by two). The control arterial pressure represented the average of five determinations after the arterial pressure was stabilized.

The indicator for plasma volume determination was 123I-RISA (Abbott radioiodinated serum albumin). Following collection of a blank sample, 50 μc of the indicator was injected during a period of 3 seconds into the antecubital vein.
through a 14-gauge needle from an in vitro calibrated syringe. Samples were obtained at 20, 25, 30, 35, and 40 minutes after administration of the indicator from the antecubital vein of the opposite arm and collected in tubes containing dried heparin. The radioactivity of the samples was determined in a scintillation well counter. The plasma volume was calibrated by extrapolating the radioactivity to the time of injection. Appropriate corrections for background radioactivity were made consistently. Counts per second per milliliter were plotted on the ordinate and the times in minutes on the abscissa of semilogarithmic paper.

Urinary sodium was determined photometrically by the method of Berry and associates. Values were expressed as total amounts in milliequivalents.

Results

Two hours following the intravenous administration of the placebo the mean arterial pressure fell from an average of 155 ± 14 mm Hg to an average of 148 ± 12 mm Hg (−0.05 ± 4%) and the plasma volume increased an average of 22 ± 40 ml (+0.6 ± 4%). The peak of hypotension occurred 2 to 3 hours following furosemide and 5 to 6 hours following hydrochlorothiazide. The average reduction in mean arterial pressure following furosemide was 18 ± 7% (from an average of 148 ± 13 to an average of 123 ± 11 mm Hg), whereas the average reduction following hydrochlorothiazide was 11 ± 5% (from an average of 145 ± 11 to an average of 127 ± 13 mm Hg) (table 1). The average urinary sodium excretion during furosemide diuresis was 96 ± 34 mEq and was 63 ± 16 mEq during hydrochlorothiazide diuresis.

Although the plasma volume was reduced and the urinary sodium excretion increased following both diuretics in all patients, there was no direct relationship between the reduction in plasma volume and the fall in arterial pressure (table 1). Thus, a 7% reduction in mean arterial pressure in one patient

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*Chlorothiazide.

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Table 1

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*Chlorothiazide.

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*Chlorothiazide.

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*Circulation, Volume XXVII, February 1968
was associated with a 21% reduction in plasma volume. Also a 19% reduction in mean arterial pressure in another patient was associated with a 4% reduction in plasma volume. Although there seems to be no direct relationship between the fall in mean arterial pressure and urinary sodium excretion, it must be realized that the patients studied were not receiving a constant sodium intake which could greatly influence sodium excretion. Comparing the urinary sodium excretion in these patients is, therefore, meaningless.

The concomitant administration of dextran solution with the diuretic prevented the reduction in plasma volume but did not prevent the fall in mean arterial pressure (table 2). In each patient the urinary sodium excretion exceeded both the amount excreted following the diuretic alone and the additional 77 mEq of sodium contained in the 500 ml of dextran solution. Thus, the average sodium excretion in the 10 patients following the diuretic alone was 96 ± 42 mEq (table 1), whereas the average urinary sodium excretion following the diuretic plus dextran solution in the same 10 patients was 230 ± 61 mEq. When the dextran infusions were administered at the peak of hypotension following the diuretic, the plasma volume returned to control or above control values in all patients, whereas the arterial pressure remained reduced (table 3).

The concomitant administration of hypertonic saline with the diuretic did not prevent the fall in plasma volume, but did prevent the reduction in mean arterial pressure in six of 10 patients (table 4). Thus a 13 ± 5% average reduction in plasma volume followed the concomitant administration of the diuretic plus hypertonic saline. The same patients, however, had a 16 ± 10% average reduction in plasma volume following the diuretic alone. Following the concomitant administration of diuretic plus hypertonic saline there was a 3 ± 15% average increase in mean arterial pressure, whereas after the diuretic alone there was a 16 ± 9% average decrease in mean arterial pressure. The urinary sodium excretion of patients 3, 5, 6, 8, 12, 14, and 15 averaged 282 mEq and that of each patient did not exceed the 428 mEq of sodium administered. However, in patients 1, 7, and 9, the average urinary sodium excretion was 478 mEq (table 4). The mean arterial pressure in patients 1, 7, and 9 fell from an average of 162 mm Hg to an average of 136 mm Hg (a 15% average reduction as compared with a 25% average reduction in the same patients when the diuretic was given alone). In six of the seven

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**Table 2**

*Effect of Concomitant Administration of Diuretic and Dextran on Plasma Volume, Mean Arterial Pressure, and Urinary Sodium Excretion*

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*Circulation, Volume XXXVII, February 1968*
Table 3
Effect of Dextran Infusion Administered at the Peak of Hypotensive Action of Diuretic on Plasma Volume, Mean Arterial Pressure, and Urinary Sodium Excretion

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Table 4
Effect of Concomitant Administration of Diuretic and 5% NaCl on Plasma Volume, Mean Arterial Pressure, and Urinary Sodium Excretion

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patients (nos. 3, 5, 6, 8, 14, and 15) whose urinary sodium excretion did not exceed the amount of sodium administered, the mean arterial pressure increased from an average of 141 ± 14 mm Hg to an average of 160 ± 14 mm Hg (14 ± 6%). In patient 12, although the urinary sodium excretion was 217 mEq (211 mEq less than the amount administered), there was a 10% fall in mean arterial pressure.

Although the administration of hypertonic saline at the peak of hypotension did not alter the reduced plasma volume in any patients, it promptly increased the arterial pressure to control or above control values in eight of the 10 patients (table 5). The mean arterial pressure in patients 2, 4, 10, 13, and 16 to 19 rose from an average of 141 ± 16 to 152 ± 14 mm Hg (an 18 ± 6% increase). The mean arterial pressure at the peak of hypotension in these eight patients was 117 ± 15 mm Hg, which represented a 17 ± 6% reduction from the control. The actual increase in mean arterial pressure after the sodium infusion was, therefore, 32 ± 7%. In these eight patients the urinary sodium excretion.
Table 5

Effect of 5% NaCl Administered at the Peak of Hypotensive Action of Diuretic on Plasma Volume, Mean Arterial Pressure, and Urinary Sodium Excretion

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<td>200</td>
<td>3694</td>
<td>-510</td>
<td>-14</td>
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</tbody>
</table>

In two patients (nos. 11 and 20) the mean arterial pressure did not begin to rise above control values until the sodium intake exceeded the sodium loss (table 6, fig. 1). Repeating the furosemide produced a negative sodium balance and a fall in mean arterial pressure. During the control period, norepinephrine produced a 29 ± 9% average increase in mean arterial pressure (from 148 ± 12 to 190 ± 23 mm Hg) (table 7). Following the placebo, the same rate of infusion produced a 28 ± 11% average increase in mean arterial pressure (from 148 ± 12 to 190 ± 24 mm Hg), whereas after the diuretic and during the infusion, norepinephrine produced a 30.4 ± 4.7% average increase in mean arterial pressure (from 156 ± 15 to 183 ± 21 mm Hg) (table 7).
Table 6
Effect of 1,000 ml of 5% NaCl Administered at the Peak of Hypotensive Action of Diuretic on Urinary Sodium Excretion and Arterial Pressure in Patient 20

<table>
<thead>
<tr>
<th>Time interval (min)</th>
<th>Diuresis during</th>
<th>Sodium balance (mEq)</th>
<th>Arterial pressure</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Intake</td>
<td>Output</td>
<td>Total output</td>
</tr>
<tr>
<td>49</td>
<td>Control</td>
<td>0.22</td>
<td>250</td>
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<tr>
<td>86</td>
<td>Furosemide 200 mg IV</td>
<td>250</td>
<td>250</td>
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<tr>
<td>50</td>
<td>5% NaCl 260 ml</td>
<td>222</td>
<td>135</td>
</tr>
<tr>
<td>33</td>
<td>5% NaCl 500 ml</td>
<td>428</td>
<td>109</td>
</tr>
<tr>
<td>17</td>
<td>5% NaCl 600 ml</td>
<td>513</td>
<td>48</td>
</tr>
<tr>
<td>44</td>
<td>5% NaCl 1,000 ml</td>
<td>855</td>
<td>191</td>
</tr>
<tr>
<td>91</td>
<td>Furosemide 200 mg IV</td>
<td>229</td>
<td>920</td>
</tr>
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</table>

Table 7
Effect of Changes in Plasma Volume and Sodium Balance on Arterial Pressure During Norepinephrine Infusion

<table>
<thead>
<tr>
<th>Case</th>
<th>Placebo</th>
<th>Diuretic</th>
<th>Diuretic + dextran</th>
<th>Diuretic + 5% NaCl</th>
<th>% changes in mean arterial pressure following:</th>
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<tbody>
<tr>
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<td>+15</td>
<td>+20*</td>
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<td>+4*</td>
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<td>+12</td>
<td>+12</td>
<td>+8*</td>
<td></td>
</tr>
</tbody>
</table>

*Negative sodium balance.

14 to 204 ± 21 mm Hg) (table 7). In patients 1, 7, 9, 11, 12, and 20 in whom the administration of hypertonic saline did not produce positive sodium balance, the same rate of norepinephrine infusion was followed by a 9.0 ± 5.7% increase in mean arterial pressure (from 130 ± 8 to 171 ± 10 mm Hg).

Discussion

The immediate fall in arterial pressure following both furosemide and hydrochlorothiazide was consistently followed by a decrease in plasma volume and an increase in urinary sodium excretion. Although the diuretics produced a decrease in plasma volume and an increase in urinary sodium excretion in each patient, there was no direct relationship between the decrease in plasma volume and the fall in arterial pressure. Thus, the fall in arterial pressure was as great following a 1% reduction in plasma volume as that following a 24% reduction. The fact that the concomitant administration of dextran solution with the diuretics prevented the reduction in plasma volume but did not prevent the fall in arterial pressure further attests to the lack of importance of plasma volume reduction in the early fall of arterial pressure during saluresis. The average reduction in mean arterial pressure following the administration of dextran solution and the diuretic was actually greater than after the diuretic alone. Finally in this regard it should be noted that replacement of the plasma volume
with dextran solution at the peak of hypotension following the diuretics had no effect on the reduced arterial pressure (table 3).

Although these findings are in agreement with those of Hollander and associates, they are not in agreement with those of Wilson and Freis and Dustan and associates. The fact that the patients studied here had all antihypertensive therapy discontinued for at least 1 month prior to the study and never received ganglion-blocking agents and the fact that the patients of Wilson and Freis and Dustan and associates had been receiving blocking agents might account for the difference in the response of the arterial pressure to dextran infusions. The response of the arterial pressure to changes in plasma volume may be altered by antihypertensive drugs, particularly blocking agents. Thus, Freis and associates reported that under control conditions withdrawal of small amounts of blood had no effect on the arterial pressure, whereas following administration of hexamethonium, withdrawal of small amounts of blood was immediately reflected by a decrease in arterial pressure, and replacing the blood loss was promptly reflected by an increase in arterial pressure.

The administration of dextran solution, either concomitantly with or at the peak of hypotension following the diuretic, was consistently followed by excessive increases in urinary sodium excretion far above the expected amount (tables 2 and 3). The average urinary sodium excretion following the diuretic alone was 96 ± 42 mEq (table 1), whereas the average urinary sodium excretion following the diuretic plus dextran solution, which contained 77 mEq of sodium, was 236 ± 61 mEq. It would seem that, if the urinary sodium loss is to be replaced adequately, actual measurements of the sodium loss in the urine must be determined and not estimated. Failure to measure urinary sodium loss could readily result in inadequate replacement of sodium and might explain the lack of change in arterial pressure following the infusion of normal saline reported by Hollander and associates. Since parenteral administration of saline, dextran solution, or water can each greatly increase urinary sodium excretion, particularly in the hypertensive subject, adequate replacement of sodium loss following a diuretic seemed best accomplished by hypertonic saline.

The concomitant administration of hypertonic saline with a diuretic prevented the fall in arterial pressure, and the replacement of urinary sodium loss at the peak of hypotension returned the arterial pressure to control values only when adequate amounts of sodium were administered (tables 4 and 5).

Thus hypertonic saline administered concomitantly with the diuretic prevented the fall in arterial pressure in six of seven patients when the sodium excretion did not exceed the amount administered (patients 3, 5, 6, 8, 12, 14, and 15, table 4), and did not prevent the fall in arterial pressure when the urinary sodium loss exceeded the amount given (patients 1, 7, and 9, table 4). Similarly hypertonic saline administered at the peak of hypotension following the diuretic caused an increase in arterial pressure in patients 2, 4, 10, 13, 16, 17, 18, and 19 (table 5) in whom the administered amount of sodium exceeded the sodium loss. Hypertonic saline did not increase the arterial pressure in those two patients (11 and 20) whose loss of urinary sodium exceeded the amount administered. These data suggest that the fall in arterial pressure during saline infusion is due to the production of a state of negative sodium balance and also that in the sodium depleted state in the hypertensive subject there is a direct relationship between arterial pressure and sodium balance. This relationship can be clearly visualized in the separate experiment performed on patient 20 (table 6, fig. 1). The arterial pressure was not increased until positive sodium balance was established (which necessitated the administration of an additional 428 mEq of sodium). Repeating the dose of furosemide was followed by an increase in sodium excretion, production of negative sodium balance, and a fall in arterial pressure.

The data presented also indicate that the
decreased response of the arterial pressure during norepinephrine infusion following the diuretics depends more on the production of a negative sodium balance than on the decrease in plasma volume (table 7). Replacement of the plasma volume with dextran or administration of the saline infusions which were associated with a negative sodium balance did not alter the reduced pressor response during saluresis (patients 1, 7, 9, 11, 12, and 20). Only when the saline infusions produced a positive sodium balance did the sensitivity of the arterial pressure to norepinephrine return to control or above control values. Raab and associates, Tobian, and Hollander and associates attributed the diminished pressor response following saluresis to sodium depletion. On the other hand, Wilson and Freis and Dustan and associates attributed these changes to a decrease in plasma volume. The fact that the patients studied by these latter two groups of investigators were also receiving ganglion-blocking agents might explain the discrepancy.

Finally, it should be emphasized that the relationship between arterial pressure and sodium balance was observed only in hypertensive patients in the sodium depleted state. It is not known whether this relationship exists in hypertensive subjects in normal sodium balance or in normotensive or hypotensive subjects. It is also not clear how changes in cardiac output, red cell blood volume or, particularly, extracellular fluid volume affect this relationship. Such studies are currently being carried out.

References
Relation of Sodium Balance to Arterial Pressure During Drug-Induced Saluresis
FRANK A. FINNERTY, JR., MICHAEL DAVIDOV and NIKOS KAJAVIATOS

Circulation. 1968;37:175-183
doi: 10.1161/01.CIR.37.2.175

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Print ISSN: 0009-7322. Online ISSN: 1524-4539

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