# Suppression of renin release by intravascular volume expansion during chronic diuretic treatment

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Circulating renin is influenced by many factors. In the clinical setting, alterations in body water and sodium balance influence plasma renin activity (PRA) significantly. Thus, with dietary sodium deprivation,<sup>1-3</sup> rapid diuresis with furosemide,4 and water deprivation5 PRA increases as it does also in association with the modest oligemia that accompanies long-term hydrochlorothiazide or spironolactone treatment of hypertension.<sup>6, 7</sup> Conversely, lowered PRA has been observed following high sodium diet,<sup>1, 3</sup> overhydration,<sup>3</sup> in primary aldosteronism,8,9 and following rapid intravascular volume expansion.<sup>10, 11</sup> In such states of altered intravascular volume and serum sodium concentration there is disagreement as to the factors (volume or sodium) controlling renin release and how they become sensory signals to the juxtaglomerular apparatus.

To investigate the relative importance of intravascular volume and serum sodium concentration on PRA we have studied diuretic-treated hypertensive patients before and after rapid expansion with solutions that caused similar changes in intravascular volume, but dissimilar changes in serum sodium concentration. We selected diuretic-treated patients because they have been found to have elevated PRA in association with diminished intravascular volume.<sup>6, 7</sup>

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#### Methods

Intravascular volume was rapidly expanded in the 21 patients by administering either 6% dextran in 5% glucose (6DG), or 6% dextran in normal saline solution (6DS). The age, sex, diagnosis, and therapy is presented in Table 1. All hypertensive patients had had complete investigative studies, including renal arteriography. Nineteen were considered to have essential hypertension; in one, hypertension was thought to be secondary to renal artery disease, and in another, to chronic pyelonephritis. One patient (No. 15) had significant impairment of renal excretory function with a creatinine clearance of 27 ml/min. Twenty had been receiving hydrochlorothiazide (50 to 150 mg per day) and/or spironolactone (50 to 150 mg per day) for varying periods at the time of this study, and one was untreated.

All patients were studied in the fasting state, usually in the morning. Following a 30- to 45-minute period of supine rest, plasma volume was measured directly with human serum albumin labeled with 2.5 microcuries of <sup>125</sup>I using a 10-minute equilibration period.<sup>12</sup> At the same time, blood samples were obtained without stasis for determination of hematocrit values by capillary microcentrifugation, of serum sodium, potassium, and chloride

| Detiont        |     | Sex          | Diagnosis               | Treatment    |          |
|----------------|-----|--------------|-------------------------|--------------|----------|
| Patient<br>no. | Age |              |                         | Туре         | Duration |
|                |     |              | 6DG                     |              |          |
| 1              | 52  | М            | Essential hypertension  | S            | 2 yr     |
| 2              | 40  | Μ            | Essential hypertension  | None         |          |
| 3              | 41  | Μ            | Essential hypertension  | H, S         | l wk     |
| 4              | 53  | М            | Essential hypertension  | H            | 3 wk     |
| 5              | 59  | F            | Essential hypertension  | S            | 6 mo     |
| 6              | 69  | F            | Essential hypertension  | Н            | 2 wk     |
| 7              | 50  | $\mathbf{F}$ | Essential hypertension  | H, S         | 4 mo     |
| 8              | 51  | Μ            | Essential hypertension  | Н            | 6 mo     |
| 9              | 44  | м            | Essential hypertension  | S            | 9 mo     |
| 10             | 62  | F            | Essential hypertension  | н            | 2 mo     |
| 11             | 56  | F            | Essential hypertension  | S            | 11 mo    |
| 12             | 52  | М            | Essential hypertension  | Н            | 3 mo     |
| 13             | 52  | $\mathbf{F}$ | Renal artery disease    | H, S         | 12 mo    |
|                |     |              | 6DS                     |              |          |
| 14             | 55  | м            | Chronic pyelonephritis  | Н            | 5 mo     |
| 15             | 45  | м            | Essential hypertension* | H, G, Hy     | 9 mo     |
| 16             | 59  | м            | Essential hypertension  | н            | 24 mo    |
| 17             | 66  | м            | Essential hypertension  | $\mathbf{H}$ | 9 mo     |
| 18             | 52  | м            | Essential hypertension  | S            | 2 yr     |
| 19             | 27  | F            | Essential hypertension  | $\mathbf{H}$ | 3 days   |
| 20             | 53  | м            | Essential hypertension  | S            | 2 yr     |
| 21             | 46  | м            | Essential hypertension  | H, G         | 2 yr     |

Table 1. Twenty-one patients studied with volume expansion

S = spironolactone, H = hydrochlorothiazide, Hy = hydralazine, G = guanethidine.

\* Moderately impaired renal excretory function.

concentrations and carbon dioxide content by Technicon<sup>®</sup> method, and of peripheral renin activity.

Plasma renin activity could not be measured by the standard Pickens<sup>13</sup> method because dextran was carried through the entire procedure, and on bioassay produced such depressor responses that they obscured the plasma pressor activity. This effect in rats is presumably due to an allergic reaction to dextran.14 To eliminate dextran from the final test solution, angiotensin released during the 4-hour incubation was adsorbed onto Dowex 50 resin and subsequently eluted as in the Boucher method.<sup>15</sup> To provide uniformity of measurement, both control and test samples were handled in this fashion, even though the control specimen did not contain dextran.

To test the validity of this method. a comparison was made of the amount of angiotensin obtained by the Pickens method with the amount obtained by this modification. Duplicate plasma samples to which .001 Goldblatt unit of renin had been added (to assure angiotensin for reliable adequate assay) were carried through each type of procedure and amounts of angiotensin measured were found to differ by less than 5%, which is well within the variance of the bioassay. To establish that dextran had not interfered with generation of angiotensin, .001 Goldblatt unit of renin was incubated with plasma in the absence and presence of dextran added in the same proportion as occurred during this study. No difference in angiotensin formation was found.

Rapid intravascular volume expansion was accomplished by infusing an amount of either 6DG or 6DS equal to 20% of the total blood volume as calculated from the plasma volume radioiodinated serum albumin (RISA) and hematocrit value. This amount of fluid was given at a rate of 15 ml/min/ M<sup>2</sup> body surface area using an infusion pump. After 25%, 50%, 75%, and 100% of the infusion volume had been administered, heart rate and blood pressure were measured and blood was obtained for determination of the hematocrit value, serum sodium, potassium, carbon dioxide, and chloride concentrations. Also, PRA and plasma volume were again measured after completion of the infusion. Plasma osmolality was measured during 6DG expansion but not 6DS, as previous reports<sup>16</sup> had indicated that no change in osmolality occurred with infusion of 3% dextran in isotonic saline.

Thirteen patients were given 6DG solution and eight received 6DS; all but one patient of the former group were receiving hydrochlorothiazide and /or spironolactone. Although amounts of the two solutions used were similar, 6DG produced significantly less plasma volume expansion than did 6DS (22% vs 38%, p < .01) (Table 2). There are at least two possible explanations for this difference: (1) patients given 6DG may have had a greater diuresis than those receiving 6DS, but since urine volume was not measured we have no information on this; (2) the 6DG, while isotonic in vitro, became hypotonic in vivo due to metabolism of glucose. We did not measure any significant change in plasma osmolality with 6DG infusion, but Schrier et al<sup>16</sup> have. They observed decreases in plasma osmolality and interstitial fluid volume with 3% dextran in 5% glucose infusion and attributed these to metabolism of glu-

|                                 | Preexpansion      | Postexpansion       | % change     |
|---------------------------------|-------------------|---------------------|--------------|
| 6DG                             |                   |                     |              |
| Total blood volume (ml)         |                   |                     |              |
| Mean $\pm$ S.D.                 | $4593 \pm 956$    | $5042 \pm 1048$     | +10          |
| q                               |                   | <.001               | ·            |
| Plasma volume (ml)              |                   |                     |              |
| Mean $\pm$ S.D.                 | $2772 \pm 523$    | $3387 \pm 614$      | +22          |
| α                               |                   | <.001               |              |
| Serum sodium (mEg/liter)        |                   |                     |              |
| Mean $+$ S.D.                   | 139 + 3.1         | 132 + 4.3           | -5           |
| D                               |                   | < .001              | -            |
| Plasma renin activity (ng/ml)   |                   | (100)               |              |
| Mean $+$ S.D.                   | 4.0 + 4.0         | $1.5 \pm 1.1$       | 62           |
| p                               | -1010             | < . 025             | ° <b>-</b>   |
| Hematocrit $(\%)$               |                   | 21020               |              |
| Mean $+$ S D                    | 43 + 50           | 35 + 41             | 19           |
| n                               | 10 ± 010          | < 001               | 10           |
| 6DS                             |                   | 1.001               |              |
| Total blood volume (ml)*        |                   |                     |              |
| Mean $\pm$ S D                  | 4678 + 316        | 5702 + 672          | <b>1</b> -22 |
| nican ± 0.D.                    | 10/0 1 010        | < 01                | 1 44         |
| P<br>Plasma volume (ml)t        |                   | <.01                |              |
| $M_{eop} \pm SD$                | <u>9710 ⊥ 905</u> | 8757 - 419          | 1.38         |
| Mean $\pm$ 5.D.                 | 2110 1 203        | 5757 ± 415<br>< 001 | 7-50         |
| P<br>Somum andium (mEa /liter)† |                   | <b>1.001</b>        |              |
| Marg + S D                      | 141 + 9.5         | 120 + 9.9           | 1.4          |
| Mean $\pm$ S.D.                 | 141 ± 2.5         | $139 \pm 2.2$       | -1.4         |
| $\mathbf{p}$                    |                   | < .02               |              |
| Plasma renin activity (ng/ml)   | 0.0 + 1.6         | 14110               | 5.9          |
| Mean $\pm$ S.D.                 | $2.9 \pm 1.0$     | $1.4 \pm 1.2$       | 55           |
| $\mathbf{p}$                    |                   | < .01               |              |
| Hematocrit (%)                  | 47 1 9 0          | 20 1 0 0            | 10           |
| Mean $\pm$ 5.D.                 | 4/ ± 2.6          | $38 \pm 2.2$        | -19          |
| р                               |                   | < .001              |              |

Table 2. Paired data analysis of average changes in total blood volume, plasmavolume, serum sodium, PRA, and hematocrit following intravascularvolume expansion with 6DG (13 patients) and 6DS (8 patients)

\* Based on six subjects.

† Based on seven subjects.

‡ Based on eight subjects.

cose which rendered the fluid hypotonic, resulting in the diffusion of extracellular water intracellularly.

Results obtained were analyzed statistically using conventional methods for calculating the significance of standard t tests and correlation coefficients.<sup>17</sup>

#### Results

**Preexpansion.** Before volume expansion, serum sodium concentration and PRA averaged 140 mEq/liter and 3.6 ng/ml respectively. In accord with findings of another study,<sup>7</sup> a significant inverse correlation between serum sodium concentration and PRA was

found in patients treated with spironolactone only or in combination with hydrochlorothiazide (r = -.701, p < .05) but not for those taking only hydrochlorothiazide (r = -.115, p n.s.). In contrast, there was no relationship between PRA and plasma volume.

# Volume expansion (Table 2).

Rapid infusion of 6DG. This resulted in an average plasma volume expansion of 22% (p < .001) which was accompanied by a significant average decline in hematocrit value of 19% (p < .001), in PRA of 62% (p < .025), and in serum sodium concentration of 5% (p < .001). There was no significant change in heart rate, mean arterial pressure, or plasma osmolality with infusion.

In three patients the initial level of PRA was less than 1 ng/ml and changed little with volume expansion, the values being less than 1 ng/ml. Omitting these, there was a significant correlation between percentile changes in plasma volume and PRA (r =-.694, p < .025) with expansion, and in the men only, a significant inverse correlation between actual levels of PRA and plasma volume (r = -.700, p < .05). No relationship was found between actual values for PRA and serum sodium concentration nor between percentile reductions accompanying the infusion.

Infusion of 6DS. This resulted in an increase in plasma volume of 38% (p < .001), a fall in hematocrit value of 19% (p < .001), in PRA of 53% (p < .005), and in serum sodium concentration of 1.4% (p < .02). There was no significant change in heart rate or mean arterial pressure. A relationship between percentile changes in

plasma volume and PRA was suggested by a correlation coefficient of r = -.569, but because of the small number of patients studied it was not statistically significant (p < .2). The relationship between actual values of PRA and plasma volume had a correlation coefficient of -.496, but p < .2. There was no significant relationship between PRA and serum sodium concentration.

Comparison of effects of the two solutions. Although both produced a marked increase in plasma volume, 6DS was more effective than 6DG (38% vs 22% respectively, p < .01) while 6DG lowered serum sodium concentration more than did 6DS (4.5% vs 1.4% respectively, p < .001). Despite these marked group differences in sodium concentration, decreases in PRA were not significantly different (p < .25).

Taking both groups together postexpansion, there was a significant inverse correlation between actual values of PRA and plasma volume (expressed as percent of normal) for the 15 males (r = -.653, p. < .01) (Fig.) but not for the men and women combined. There was no correlation between actual values of PRA and serum sodium concentration nor between percentile changes in PRA and serum sodium.

### Discussion

The individual effects of intravascular volume and serum sodium concentration upon PRA are difficult to define because of the close relationship between body sodium and extracellular fluid volume. However, results of this study suggest that in hypertensive patients receiving diuretic



Fig. Relationship between plasma renin activity and plasma volume expressed as percent of normal in diuretic-treated hypertensive men following rapid intravascular volume expansion with either 6DS in saline or 6DG in glucose solution.

treatment: (1) there is a significant inverse relationship between PRA and serum sodium concentration during treatment with spironolactone; (2) rapid intravascular volume expansion suppresses renin release and results in a significant decline in PRA; and (3) that this suppression is a function of the change in intravascular volume but not in serum sodium concentration.

Although these results indicate a dominance of intravascular volume over plasma sodium concentration as a determinant of renin release during rapid volume expansion, they do not

eliminate sodium concentration as one of the factors influencing PRA in more stable situations. In this regard, Brown et al<sup>18</sup> have reported an inverse relationship between PRA and serum sodium concentration in a heterogeneous group of hypertensive patients. The same relationship was found in untreated patients with renovascular hypertension<sup>19</sup> and in patients with essential hypertension during long-term treatment with spironolactone.7 Similarly, in the present study there was a significant inverse association between serum sodium concentration in the spironolactone-treated patients.

Clinically, hypokalemia or potassium depletion is known to increase PRA in some subjects, whereas potassium administration suppresses PRA.20 In rats potassium administration suppresses the plasma renin stimulating effect of hyponatremia, suggesting an important influence of potassium upon PRA.<sup>21, 22</sup> In the present study there were small decreases in serum potassium with both expansion Such changes may studies. have blunted the degree of fall in PRA which we observed, but certainly should not have enhanced them.

There is also ample evidence of a close, ongoing relationship between PRA and intravascular volume. Thus, Dustan et al<sup>19</sup> found a significant inverse correlation between PRA and plasma volume in normal and untreated men with essential hypertension and in women with renovascular hypertension. Also, Acchiardo et al<sup>7</sup> reported that during chronic treatment with hydrochlorothiazide or spironolactone an inverse relationship was found between the rise in PRA and reduction in PV produced by these drugs. Conversely, Tarazi et al<sup>6</sup> found following discontinuance that of chronic thiazide treatment, PRA fell as PV rose. In short-term studies in normotensive and hypertensive patients, Newsome and Bartter<sup>3</sup> demonstrated a strong inverse relationship between changes in body weight (presumed to reflect changes in intravascular volume) and PRA. This relationship was maintained even when serum sodium concentration was altered in a direction opposite to change in body weight, thus suggesting that a change in intravascular volume was the more potent modifier of PRA. Similarly, inverse relationships between PRA and

intravascular fluid volume have been inferred from observations made of the clinical states of dehydration and inappropriate ADH secretion,<sup>23, 24</sup> from studies of water deprivation in man,<sup>5</sup> and administration of small doses of furosemide to dogs.<sup>25</sup>

It might be questioned whether the fall in PRA in our experiments was simply a result of dilution by increasing the volume of distribution for renin. That this is not the case is shown by calculating "total circulating renin" from the PRA (ng/ml) and plasma volume (ml). In all but one instance, there was a significant decline in total circulating renin (average 9,565 ng preexpansion and 4,517 ng postexpansion [p < .01]).

Another question is whether our study provides any insight into the mechanism whereby intravascular volume influences PRA. Previously Nash et al<sup>26</sup> clearly demonstrated in dogs that renin release could be dissociated from renal and systemic hemodynamics and from sodium and water balance, but that there existed a reciprocal relationship between renin release and the rate of delivery of sodium to the tubules. Vander<sup>27</sup> proposed that the final common pathway for renin control is the macula densa sodium load. According to this hypothesis, when there is an increased sodium load to the macula densa site, there is increased reabsorption of sodium by macula densa cells and inhibition of renin release. When there is decreased distal tubular sodium load, there is decreased macula densa sodium reabsorption and a stimulus to renin release. Therefore, on the basis of the "macula densa sodium hypothesis," the influence of intravascular volume and serum sodium concentration upon

PRA must finally be understood in terms of the effect of these factors upon distal tubular sodium load and macula densa sodium reabsorptive capacity.

In attempting to understand our data in relationship to the "macula densa" theory we must consider how the infusion of solutions such as 6DG and 6DS influence sodium excretion and distal tubular sodium load. Volume expansion with hypotonic, isotonic, and hypertonic saline in animals results in a natriuresis (hence increased distal tubular sodium load) which is independent of measurable changes of renal blood flow or glomerular filtration rate and is due to diminished proximal tubular sodium reabsorption,28-31 although diminished distal tubular reabsorption may also occur.32, 33 Volume expansion with nonsaline-containing colloidal solutions, i.e., dextran in glucose, salt poor albumin, whole blood, or reconstituted human plasma, produces no significant natriuresis.<sup>16, 29, 31, 34</sup> Volume expansion with saline-containing colloidal solutions such as 6% dextran or albumin in isotonic saline produce a definite natriuresis, the magnitude of which is less than during isotonic saline infusion alone.16, 30, 31, 35-37 In our two study groups a similar degree of lowering of PRA was observed following expansion with 6DG which should not increase natriuresis and 6DS which does. These observations suggest that intravascular volume may at times influence PRA by a sensory signal other than distal tubular sodium load and macula densa transfer.

Plasma volume variations could affect the juxtaglomerular apparatus via renal nerves or circulating catecholamines, since it has been shown that direct stimulation of renal nerves increased renin release,<sup>38</sup> that interruption of the renal nerves reduced the renin stimulating effect of mercuhydrin,<sup>39, 40</sup> and that infusion of epinephrine and norepinephrine were potent stimuli of renin.<sup>38</sup>

Tobian<sup>41</sup> proposed that the final common pathway for renin control is via the afferent arteriolar juxtaglomerular cells acting as stretch receptors which are sensitive to changes in intraarterial pressure or volume or both. In this view, chronic diuretics which are known to produce oligemia<sup>6</sup> would decrease the stretch of the afferent arteriole and stimulate renin. Conversely, rapid intravascular volume expansion would increase the stretch of the afferent arteriole and decrease renin production. We observed no change in mean arterial pressure with volume expansion, but the afferent arteriole may have been influenced by volume changes alone.

In a recent review by Davis<sup>42</sup> the multiple stimuli known to signal renin release are summarized. The predominance of any one signal is seen as being variable, depending upon the physiologic or pathophysiologic state of the whole organism. Davis concludes by noting the failure, as yet, to discover a final common pathway from the various sensory stimuli to the macula densa.

### Summary

The influence of rapid intravascular volume expansion upon PRA, PV, and serum sodium concentration was studied in 21 diuretic-treated hypertensive patients. PRA was suppressed 53% in eight subjects receiving 6DS which elevated PV 38%, while slightly lowering serum sodium concentration by 1.4%. Similarly PRA

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was suppressed 62% in 13 subjects receiving 6DS which elevated PV 22% and significantly lowered serum sodium concentration 4.5%. Plasma renin suppression by administration of intravenous fluid was thus most clearly related to intravascular volume expansion, suggesting that whatever may have been the importance of sodium concentration as a determinant of PRA, intravascular volume played a dominant role in renin release during these experiments of brief duration.

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