Natriuretic Response to Saline Infusion in Normotensive and Hypertensive Man

The Role of Renin Suppression in Exaggerated Natriuresis

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SUMMARY Previous studies have reported an exaggerated natriuresis in hypertensive man; however, a systematic appraisal of this response in various forms of hypertension has not been made. We measured fractional excretion of sodium (FENa) during a four hour intravenous infusion of 2 liters normal saline in 162 normal subjects and 120 hypertensives. Of these, 13 had primary aldosteronism (ALDO), 19 high renin (HRH), 30 low renin (LRH), and 57 normal renin (NRH) essential hypertension. FENa for normals (1.42%), NRH (1.57%), and HRH (1.46%) was similar. That for LRH (2.56%) and ALDO (4.18%) was elevated compared to the other three subgroups ($P < 0.001$).

Although the four hour FENa during saline infusion was associated with mean arterial blood pressure (MABP) within the entire hypertensive population ($r = 0.51$), when the subgroups of the hypertensive patients were considered separately no association between FENa and MABP was identified. Moreover, the MABP of subjects with HRH was greater ($P < 0.05$) than in those with NRH, although the FENa of the two subgroups was similar.

Patients with ALDO and LRH have a greater natriuretic response to a salt load than do other subgroups of essential hypertension or normal subjects. The exaggerated natriuresis appears to be a feature of hypertension with renin suppression. The degree of exaggerated natriuresis is not solely a function of an elevated mean arterial blood pressure.

AN EXAGGERATED NATRIURETIC RESPONSE to volume expansion has been observed in essential hypertension,\textsuperscript{1,2} Cushing's syndrome,\textsuperscript{3} primary aldosteronism,\textsuperscript{4} and pheochromocytoma,\textsuperscript{5} as well as in a variety of nonhypertensive states. The site of impaired salt reabsorption along the nephron remains controversial. Buckalew et al.\textsuperscript{6} showed that volume expanded hypertensive patients had reduced abilities both to generate free water during hydration and to reabsorb free water during diuresis. The authors concluded that the ascending limb of Henle's loop was the major site of impaired salt reabsorption. Chaimovitz and associates\textsuperscript{7} presented evidence that volume expanded hypertensive patients, undergoing sustained water diuresis, had an exaggerated phosphaturia, natriuresis, and enhanced distal delivery of sodium. They found that sodium reabsorption in the diluting segment was normal, and suggested that decreased reabsorption of sodium in the proximal tubule was the most likely explanation for the exaggerated natriuretic response.

The mechanism responsible for the phenomenon is also imperfectly defined. While initial studies suggested that the degree of natriuresis was closely correlated with the level of arterial blood pressure,\textsuperscript{8} other observers found a very poor correlation.\textsuperscript{9} Krakoff et al.\textsuperscript{10} suggested a relationship between the exaggerated natriuresis and plasma renin responsiveness in certain hypertensives. Their work suggested that the level of plasma renin activity may affect the degree of natriuresis or that the natriuretic response may be a function of extracellular fluid volume expansion.

The demonstration by Krakoff et al.\textsuperscript{11} that essential hypertensive patients are not derived from a homogeneous population with respect to their natriuretic response following volume expansion prompted us to examine this response in a larger hypertensive population. The natriuretic response to intravenous isotonic saline infusion was measured in patients with essential hypertension or primary aldosteronism while they were undergoing studies to categorize them on the basis of their dynamic renin responses to standardized maneuvers.\textsuperscript{12} Relationships between renin and aldosterone responses and the degree of natriuresis were sought which might elucidate the role of the renin-angiotensin-aldosterone system in the phenomenon of exaggerated natriuresis.

Methods

Since January 1, 1974, hypertensive patients referred to Indiana University Medical Center for evaluation have been studied according to a protocol designed for the efficient diagnosis of secondary forms of hypertension and establishment of a renin profile if they are found to have essential hypertension.\textsuperscript{13} Normal values for the humoral studies and for the natriuretic response to be described were derived from observations in 162 normotensive volunteers. The normotensive subjects were obtained by advertisement and were hospitalized at the Indiana University Clinical Research Center. The protocol was approved by the Indiana University Medical Center Human Use Committee and informed consent was obtained after detailed explanation of the procedures to be performed. The 120 hypertensive subjects included in the study had no evidence of excessive catecholamine production, coarctation of the aorta, or other identifiable secondary forms of hypertension. Renal artery stenosis was excluded by arteriography. The hypertensive subjects were hospitalized in the Clinical Research Center or on a subspecialty ward of the Indiana University Hospital designated for endocrinologic or hypertensive patients. Each subject was instructed to collect a twenty-four hour urine specimen on the day prior to admission.

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Saline Infusion Day

On the morning following admission, the suppressibility of the renin-angiotensin-aldosterone system and the natriuretic response following saline infusion were determined. At 6:00 a.m., the subject was awakened and assumed an upright posture (standing or walking) until 8:00 a.m., at which time the subject was instructed to empty his bladder. Blood samples were then obtained for measurement of plasma renin activity (PRA) and plasma aldosterone (PA). The subject then assumed the recumbent position until noon while receiving an intravenous infusion of two liters of isotonic (0.9%) saline (500 ml/hr) beginning at 8:00 a.m. At noon, a four hour urine collection for electrolytes and creatinine was terminated and blood was obtained for PRA and PA, as well as sodium, potassium and plasma creatinine determinations. After completion of the infusion, the subject was permitted to move around, and received a diet of 150 mEq sodium and 70 mEq potassium. The total sodium intake on this day was 458 mEq.

Furosemide Stimulation

On the following morning at 8:00 a.m., after two hours of upright posture, blood was again obtained for PRA and PA. The diet on this day was limited to 10 mEq sodium and 25 ml/kg body weight. Furosemide (40 mg) was given orally at 10:00 a.m., 2:00 p.m., and 6:00 p.m. in order to evaluate the response of PRA to the stimulus of upright posture following sodium and volume depletion, blood was again sampled after two hours of upright posture at 8:00 a.m. on the following morning.

Twenty-four hour urine collections were obtained on each day of study and analyzed for volume, sodium, potassium and creatinine. In addition, serum was obtained for measurements of electrolytes and creatinine content and calculation of endogenous creatinine clearance. The blood pressure measurements tabulated for this study were obtained on the morning of the saline infusion with the subject resting quietly in bed prior to assuming upright posture. Measurements were made by a specially trained nurse using the indirect auscultatory technique. Mean arterial blood pressure was calculated from the summation of one-third the pulse pressure and the diastolic pressure.

Laboratory Methods

Sodium, potassium and creatinine concentrations in blood and urine were measured by IL flame photometer. The fractional excretion of sodium (FENa) and potassium (FEK) were calculated from values obtained from the four hour urine collection during the saline infusion by means of the following formula: FE_X% = (C_X/Cr) × 100 where the fractional excretion of X represents the percentage of filtered X appearing in the urine, C_X represents the clearance of X, and Cr the clearance of creatinine. Plasma renin activity and

<table>
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<th>Table 1. Characteristics of the Population Studied (mean values ± sem)</th>
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<td>Normal renin hyper tension</td>
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<td>----------------------------</td>
</tr>
<tr>
<td>Number</td>
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<tr>
<td>Age (yr)</td>
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<td>MABP (mm Hg)*</td>
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<td>Control urine Na* (mEq/24 hr)</td>
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<td>Plasma Na mEq/L</td>
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<td>Plasma K (mEq/L)</td>
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<td>Ccr (ml/min)</td>
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<td>4 hr FENa (%)**</td>
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<td>4 hr FEK (%)***</td>
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*Mean arterial blood pressure.
**Fractional excretion of sodium.
***Fractional excretion of potassium.

<table>
<thead>
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<th>Table 2. Plasma Renin-Aldosterone Profile of the Population (mean value ± sem)</th>
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<td>Normal renin control subjects</td>
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<td>Presaline*</td>
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<td>Postsaline†</td>
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<tr>
<td>Prefurosemide*</td>
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<tr>
<td>Postfurosemide*</td>
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<td>Plasma aldosterone (ng/100 ml)</td>
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<td>Presaline*</td>
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<tr>
<td>Postsaline†</td>
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<tr>
<td>Prefurosemide*</td>
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<td>Postfurosemide*</td>
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*Upright posture.
†Supine posture.
plasma aldosterone were measured by previously reported radioimmunoassay techniques. Statistical analyses were performed by means of a computerized statistical program.

Results

The general characteristics of the various groups studied are shown in table 1, whereas their plasma renin-aldosterone profiles appear in table 2.

Normotensive Subjects

The average age of the normotensive subjects was 30 years (table 1) and ranged from 14-79 years. Sixty-nine were white men, 58 white women, 19 black men and 15 black women.

PRA and PA at 8:00 a.m. before saline, at noon after saline, and on the succeeding days before and after furosemide are outlined in table 2. The 95% confidence limits for the normal population were as follows: PRA upright before saline, 0.9-12 ng/ml/3 hr; PRA supine after saline, 0.4-2.5 ng/ml/3 hr; PRA upright before furosemide, 0.7-10 ng/ml/3 hr; PRA upright after furosemide, 4-50 ng/ml/3 hr; PA upright before saline, 12-75 ng/100 ml; and PA supine after saline, 1-11 ng/100 ml.

In the normotensive population, there was an inverse association between age and renin activity before saline (r = -0.31), after saline (r = -0.28), before furosemide (r = -0.41), and after furosemide (r = -0.39). Age was weakly associated with FENA (r = 0.16), but not with FEK (r = -0.05). FENA was associated inversely with PRA before saline (r = -0.22), and PA after saline (r = -0.18). FENA was also associated weakly with FEK (r = 0.37).

Hypertensive Subjects

The 120 hypertensive subjects were subdivided on the basis of the comparative responses of their PRA and PA to the 95% confidence limits previously described for the normotensive population. Four groups were defined. Normal renin hypertensives were those individuals who demonstrated PRA activity and PA that were consistently within the normal range. Those with high renin hypertension were characterized by a failure of PRA to suppress to levels of 2.5 ng/ml/3 hr or less following saline infusion. Low renin hypertension was characterized by those individuals in whom PRA failed to stimulate to levels of 4.0 ng/ml/3 hr after furosemide administration, but in whom PA was suppressed into the normal range following sodium loading. The diagnosis of primary aldosteronism comprised those patients who demonstrated a failure of PA to suppress to less than 11 ng/100 ml after saline infusion, and in whom stimulation of PRA into the normal range after furosemide-induced volume depletion could not be attained. Such patients were studied further by means of bilateral venous catheterizations and assay of plasma aldosterone and plasma cortisol emanating from each adrenal gland. Adrenal venography and radioisotopic scans using 19 iodocholesterol were also performed in selected patients. The patients with evidence of primary aldosteronism had either documented adenomas at the time of operation with subsequent reduction in blood pressure postoperatively, or were individuals in whom bilateral venous catheterization suggested adrenal hyperplasia and in whom medical therapy, specifically spironolactone, resulted in adequate control of blood pressure.

The diagnostic protocol placed 57 subjects in the category of normal renin hypertension, 19 in the category of high renin hypertension, 30 in the category of low renin hypertension, and identified 13 with primary aldosteronism (table 2). Patients in each hypertensive subgroup had a significantly greater mean arterial blood pressure than did normotensive subjects (P < 0.05). Patients with primary aldosteronism had higher mean arterial blood pressures than patients with either normal renin or low renin hypertension (P < 0.05). Patients with high renin hypertension had significantly higher mean arterial blood pressures than patients with normal renin hypertension (P < 0.05).

The twenty-four hour outpatient urine sodium collections revealed no significant differences among the four groups of hypertensive and normotensive subjects (table 1). The four-hour FENA during saline infusion for normotensive subjects, patients with normal renin hypertension, and high renin hypertension were similar (table 1). Patients with low renin hypertension and primary aldosteronism had a FENA significantly greater than the other three groups (P < 0.001). In addition, the FENA of patients with primary aldosteronism was significantly greater than for patients with low renin hypertension (P < 0.05). Only one patient with primary aldosteronism had a FENA of less than two percent.

A positive association was observed between age and FENA in the hypertensive individuals (r = 0.50). Since an association between FENA and age was apparent in the normotensive subjects as well, and since patients with primary aldosteronism and low renin hypertension were older on the average than other hypertensives, the FENA for each of the hypertensive subgroups was compared to age matched controls (fig. 1). Nevertheless, the same significant differences were apparent.

An inverse association was found between the four hour FENA during saline infusion and PRA upright before saline infusion (fig. 2) (r = -0.27), as well as a positive association between FENA and mean arterial blood pressure (r = 0.38). However, when the individual hypertensive subgroups were

![Figure 1](https://example.com/figure1.png)

**Figure 1.** FENA (mean ± SEM) for each hypertensive subgroup studied vs age-matched control subjects. NRH = normal renin, HRH = high renin, LRH = low renin hypertension; ALDO = primary aldosteronism.
analyzed separately, no association between FENa and mean arterial blood pressure was apparent.

The four hour FEK during administration of the saline load was significantly greater in patients with primary aldosteronism than in normotensive subjects or patients with essential hypertension \((P < 0.05)\) (table 1). No significant differences were seen among the creatinine clearances of the five groups.

**Discussion**

We studied the four-hour fractional sodium excretion of hypertensive subjects who were admitted to the hospital expressly for a diagnostic evaluation to rule out secondary forms of hypertension. As normotensive controls, we chose the same subjects who served to establish normal renin and aldosterone values for the diagnostic protocol employed. The precise state of sodium balance was not determined for any of the subjects prior to the study. Neither were specific attempts made to assure an equal dietary sodium intake before the evaluation. The large numbers of hypertensive and control subjects made such precautions impractical, but the sodium contents of the twenty-four hour urine specimen brought by the patient before admission suggest that the state of sodium balance of the normotensive and hypertensive subjects was similar. Moreover, the large number of subjects studied served to minimize individual differences.

Data from the normotensive subjects demonstrate the importance of age in consideration of response to a salt load since we found that age correlated significantly with FENa in our normotensive subjects. Older subjects have been shown to conserve sodium less well than younger persons.\(^{16}\) Increasing age also affects renin responsiveness. In our normotensive subjects, PRA was associated inversely with age. Previous investigators have demonstrated the effect of age upon renin activity and aldosterone excretion.\(^{16,\ 17}\) Crane and Harris noted that PRA declined with age so that by the seventh decade PRA values were 60% of those seen in subjects between twenty and thirty years of age.\(^{18}\) A similar decrease in PA and aldosterone secretion rates were noted by Crane and Harris as well as by Flood and his colleagues.\(^{17}\) Whether or not the increase in FENa seen in our older normotensive subjects was a function of decreased PRA cannot be ascertained from the present study.

The results of the studies in subjects with essential hypertension demonstrated that following the infusion of two liters of isotonic saline, patients in the low renin subgroup exhibited a greater natriuretic response than did patients in the normal renin or high renin subgroups. The latter two groups had no greater degree of natriuresis than did normotensive subjects. Similar results were reported by Krakoff and associates.\(^{11}\) Their patients with renin-unresponsive hypertension, who seemingly correspond to our patients with low renin hypertension, exhibited a significantly greater natriuresis in response to isotonic saline than did patients with renin-responsive hypertension. The latter group corresponds to either normal renin or high renin hypertensives in our study. Whether or not the renin responsive hypertensives described by Krakoff et al. displayed a greater natriuresis than did normotensive subjects is unclear. Their study was specifically designed to compare the natriuretic responses following sodium administration in patients with different degrees of renin responsiveness. Large numbers of nonhypertensive control subjects were not included in their study. Krakoff et al.\(^{11}\) also noted an exaggerated kaliuretic response in the renin-unresponsive subjects relative to renin-responsive or normal subjects. We were able to demonstrate an exaggerated kaliuresis only in patients with primary aldosteronism. The kaliuresis evident in the remaining groups of patients was no greater than that of normotensive subjects. The reasons for the difference in kaliuretic response noted in what appear to be comparable patient groups between Krakoff et al. and ourselves are not clear.

Schalekamp et al.\(^{19}\) carried out studies on the mechanism of exaggerated natriuresis in 22 subjects with essential hypertension. Their subjects received 300 ml 5% NaCl intravenously over 30 minutes. Normotensive subjects were not included in their report since it was the authors' purpose to compare characteristics from patient to patient. They were unable to relate the enhanced excretion of sodium observed in some of their subjects to changes in cardiac output, renal blood flow, glomerular filtration rate, or mean arterial blood pressure. In their study, the natriuretic response after the salt load was greatest in older subjects whose plasma renin concentration was suppressed. These subjects also had increased renal vascular resistance and an elevated filtration fraction. The authors expressed the opinion that the exaggerated natriuresis and renin suppression were a "function of intrarenal pressure relationships," but were unable to exclude an independent age-related factor in the hypertensive patient. Our inclusion of age-matched normotensive control subjects and subsequent demonstration that the exaggerated natriuresis was not a function of advancing age per se mitigates against such an age related factor. Since renal hemodynamic measurements were not made in the present study, our results do not clarify the observations of Schalekamp et al.\(^{18}\)

Our patients with primary aldosteronism demonstrated a
significantly greater natriuretic response to saline infusion than did any other patient group. Only one patient had a FENa of less than two percent during infusion, and all had a response greater than the mean response observed in the normal population. A significant kaliuresis was observed as well. The degree of the natriuretic response exhibited by patients with primary aldosteronism suggests that it may be of some value in differentiating patients with primary aldosteronism from other forms of hypertension. A FENa below the mean value of normotensive subjects would appear to make the diagnosis of primary aldosteronism highly unlikely.

The exaggerated natriuresis observed in primary aldosteronism has been described in detail by Rovner et al. These authors observed a significantly exaggerated natriuresis in patients with primary aldosteronism which was dependent upon dietary sodium intake. A corresponding kaliuresis, as observed in our patients, was also described. Following operative removal of their adrenal adenomas, the patients of Rovner et al. exhibited natriuretic responses following sodium infusion which were no different than the responses of normotensive subjects. Studies in normotensive individuals given d-aldosterone demonstrated an exaggerated natriuresis after “escape” had fully developed. In their subjects, the exaggerated natriuresis could not be correlated with increases in extracellular fluid volume, glomerular filtration rate, plasma volume, renal plasma flow, blood pressure, or changes in aldosterone excretion. The authors suggested that a humoral mechanism evoked by chronic excess of aldosterone was responsible for the increased tubular rejection of sodium.

Our spectrum of hypertensive patients suggests that an exaggerated natriuresis is primarily a feature of hypertension with renin suppression. The design of our protocol was such that the FENa was measured over a four-hour period during which two liters of normal saline were infused. We were unable to demonstrate a natriuretic response in patients with normal renin or high renin hypertension greater than that seen in normotensive subjects. Previous authors chose to measure the natriuretic response in hypertensive subjects over a shorter time interval than was done in the present study. Such differences in methodology may serve to explain our failure to demonstrate an exaggerated natriuresis for all patients with an elevated arterial blood pressure. Differences in glomerular filtration rate among the groups were not responsible for the differences in natriuretic response. Age-matching the controls failed to alter the interpretation. Since the degree of natriuresis or FENa was associated with the mean arterial blood pressure and since patients with primary aldosteronism were the most hypertensive, it could be argued that the observed responses were merely a reflection of elevated blood pressure. However, when each hypertensive subgroup was considered separately, no association between mean arterial blood pressure and FENa was apparent. Furthermore, patients with high renin hypertension had significantly higher blood pressure than did subjects with normal renin hypertension, yet their FENa proved to be the same. Our data support the thesis that the exaggerated natriuresis observed in certain hypertensives is not a function of blood pressure elevation alone. Initial studies by Hollander and Judson suggested that the capacity to excrete sodium was significantly correlated with arterial pressure; however, the lack of a high degree of correlation suggested that additional factors were operative. The same investigators studied the effect of lowering arterial blood pressure by means of antihypertensive medication and found that such a maneuver retarded the natriuretic response. However, since the medication was not given concomitantly to normotensive subjects in that study, it is difficult to separate effects on blood pressure from other possible effects of the medication utilized on the renin-angiotensin-aldosterone system, or on extracellular fluid volume.

Studies on the spontaneously hypertensive rat serve to corroborate the viewpoint that the exaggerated natriuresis observed after salt loading is dependent upon factors other than an increased arterial blood pressure. The rats of the Okamoto strain, while normotensive at birth, develop hypertension within a few weeks after birth and have firmly established hypertension by the time they are ten to twelve weeks of age. Since they have PRA levels which are lower than normotensive Wistar-Kyoto controls, they provide a potential model for low renin essential hypertension. Willis has observed that normalization of blood pressure in the spontaneously hypertensive rat with a combination of quanethidine and hydralazine failed to alter the exaggerated natriuretic response following an oral salt load. Furthermore, Ben-Ishay et al. reported an increased sodium and water excretion in young, normotensive, but hypertensive-prone rats of the Dahl strain. These investigators demonstrated that the exaggerated natriuretic response preceded the advent of elevated arterial blood pressure. Since rats of the Dahl strain have low juxtaglomerular indices and reduced renal renin content, as well as increased secretion of 18-hydroxy-deoxycorticosterone, the authors suggested the possibility of a causal relationship between low plasma renin activity due to mineralocorticoid-induced volume expansion and the exaggerated response to saline loading. However, since rats of the spontaneously hypertensive rat strain have been shown to have lower aldosterone levels, mineralocorticoid excess may not be the only explanation for the exaggerated natriuresis in experimental hypertension with low plasma renin activity.

In summary, our results demonstrate that when considering renal sodium handling or plasma renin and aldosterone responses, the subject’s age is an important consideration. Patients with primary aldosteronism have a greater degree of natriuresis following a saline load than do essential hypertensives or normal subjects. Patients with low renin essential hypertension exhibit an exaggerated natriuresis whereas subjects with normal renin or high renin hypertension fail to do so. Low renin hypertensives have no apparent mineralocorticoid excess and consistent evidence of volume expansion has not been observed in this group. Therefore, it is conceivable that the exaggerated natriuresis in this group may be due to mechanisms or factors other than those responsible for this phenomenon in primary aldosteronism. The exaggerated natriuresis appears to be a common feature of hypertension with renin suppression. The
degree of exaggerated natriuresis is not solely a function of an elevated mean arterial blood pressure.

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