Regulation of Sodium Balance in Hypertension

PER OMVIK, M.D., ROBERT C. TARAZI, M.D., AND EMMANUEL L. BRAVO, M.D.

SUMMARY Pressure natriuresis, defined as the relationship between sodium excretion and mean arterial pressure (MAP), was assessed during graded reduction of arterial pressure with nitroprusside in 12 uncomplicated essential hypertensives. In all patients, sodium excretion fell linearly with reductions in arterial pressure ($r > 0.71; p < 0.05$). The percent change of sodium excretion from control per mm Hg change in MAP ($\Delta U_{\text{Na}}/\Delta MAP$) was less in patients with resting MAP above 120 mm Hg than in those with lower BP ($1.4\% \pm 0.1\%$ versus $3.2\% \pm 0.3\%; p < 0.001$), but the pressure at which urine flow extrapolated to zero ($77 \pm 4$ mm Hg) was not significantly different in the two groups. Further, there was a significant correlation between $\Delta U_{\text{Na}}/\Delta MAP$ and resting MAP ($r = -0.65, p < 0.05$), suggesting that the sensitivity of pressure natriuresis was, in part, determined by the level of resting arterial pressure. This attenuation of pressure natriuresis might reduce sodium loss and thereby preserve body fluid volume in the face of persistent hypertension.

The slope of the relationship between sodium excretion and arterial pressure was also significantly correlated ($r = 0.70; p < 0.05$) with plasma volume (PV). Thus, two mechanisms might be activated in essential hypertension to avoid dangerous sodium and volume depletion: 1) attenuation of pressure natriuresis at higher levels of arterial pressure, and 2) blunting of pressure natriuresis by volume contraction. Therefore, hypovolemia might be, at the same time, the consequence of hypertension and a limiting factor for pressure natriuresis. By this hypothesis, the lower slope of pressure natriuresis is secondary to hypertension rather than its cause. (Hypertension 2: 515-523, 1980)

KEY WORDS pressure natriuresis • nitroprusside • sodium excretion • mean arterial pressure • hypovolemia • plasma volume

ESSENTIAL hypertensives with widely different levels of blood pressure (BP) are usually in sodium balance, excreting the same amount of sodium for the same level of sodium intake. The current hypothesis postulates that they maintain sodium balance in the face of subtle defects in renal function because of higher BP, implying a shift of the relationship between sodium excretion and arterial pressure. However, both clinical and experimental studies have shown that hypertensive subjects eliminate a sodium load more rapidly than normotensives, suggesting that kidneys of essential hypertensives behave just like normal kidneys exposed to high perfusion pressure.

If an initial impairment of renal function was the true mechanism for development of essential hypertension, one would expect either normal fluid volumes or a tendency to hypervolemia because correcting mechanisms are more likely to undercorrect the disturbance than overcompensate for it. Experimentally it has been shown that there is no need for plasma volume (PV) to increase to develop hypertension. Moreover, PV was found to be reduced in essential hypertension. These discrepancies led to an alternate explanation for the maintenance of sodium balance at different levels of arterial pressure, namely, that a secondary adjustment in renal function develops precisely to prevent excessive sodium and volume depletion from pressure natriuresis.

To test this model, it was necessary first to examine to what extent the relationship between sodium excretion and arterial pressure (pressure natriuresis) is altered in essential hypertensives. Most studies of regulation of sodium excretion in hypertension have been designed to explore the effect of volume-loading. However, the natriuresis resulting from volume expansion is not the same as that resulting from increases in arterial pressure; in fact, these two stimuli increase sodium excretion by different mechanisms. Hence, modulation of pressure natriuresis in hypertension can only be established by examining the effect on sodium excretion of alterations in arterial pressure per se. We, therefore, examined the rela-
The relationship between arterial pressure and sodium excretion duringgraded reduction of arterial pressure by infusion of nitroprusside in 12essential hypertensive patients with different levels of resting mean arterialpressure (MAP) and with normal renal function. Furthermore, to explore a possible interrelationship between volume and pressure in the control of sodiumbalance, pressure natriuresis was related to body fluid volumes and resting arterial pressure. It was found that the slope of the relationship between sodiumexcretion and arterial pressure was reduced in patients with more severe hypertension and that this attenuation of pressure natriuresis was related both to BP level and to body fluid volume.

Methods

Patients

Eight male and four female patients with essential hypertension were studied. Age ranged between 42 and 66 years, with an average of 51 ± 2 years. Patients were selected with serum creatinines of less than 1.5 mg/dl, and usual criteria were used to exclude secondary hypertension. None of the patients had clinical history of renal disease, and there were no clinical or radiological signs of heart failure. All antihypertensive medications had been discontinued for at least 3 weeks prior to hospitalization. Patients were given standard hospital diet, and daily sodium output was monitored in 24-hour urine samples for 3 days prior to the test. Free sodium intake allowed us to study patients with different levels of body fluid volume expansion. The study was approved by the institutional Review Committee of the Cleveland Clinic Foundation, and all patients gave their informed consent to the procedures.

Experimental Protocol

Patients fasted overnight but were given 1000 ml of water by mouth 1 hour before, and 500 ml each hour during the study to assure high urine flow. The study was performed between 9 a.m. and 12 noon, with the patient in the supine position. The BP was measured by arm cuff; urine was collected by bladder catheter. A needle was placed in a cubital vein on each arm for infusion and withdrawal of blood specimens. Following a priming dose of 0.5 μCi per kg body weight of 131I-iodohippurate and 125I-Hippuran respectively, Iothalamate was infused at a constant rate of 0.25 μCi/min and Hippuran at 0.5 μCi/min throughout the study. The isotope concentrations were dissolved in 5% dextrose, and the volume of infusion ranged between 0.5 and 2.0 ml/min. To avoid radioiodine uptake by the thyroid gland, 10 drops of Lugol's solution were given by mouth at least 2 hours before the test. Control measurements of BP and sodium excretion were made after an equilibration period of 30 minutes. Urine was collected in two periods of 10-15 minutes each, and blood samples were drawn in the middle of each period for clearance measurements and for determination of hematocrit (Hct) and plasma renin activity (PRA).
Statistics

Results are presented as means ± 1 standard error of the mean (SEM). Statistical probability (p) of differences between means was tested by Student's t test. Slopes and correlation coefficients (r) of regression curves were calculated by the method of least squares, and multiple correlations were analyzed according to Snedecor and Cochran.

Results

Effects on Sodium Excretion and Blood Pressure of Nitroprusside Infusion

Daily sodium excretion averaged 120 ± 13 (range, 55 to 179) mEq/24 hr before the study; the day-to-day variation of sodium excretion was significantly correlated with the fall in pressure (r = 0.71; p < 0.05). This significant inverse correlation (r = -0.65, p < 0.05) between the slope and resting MAP, with an index of determination of 42%. In the calculation of that correlation, the data of one patient (No. 5) were not included; he had marked hypervolemia (PV 123% of normal) and high control rate of sodium excretion (430 μEq/min), and the slope obtained exceeded the value expected from his control MAP (fig. 3).

To compare the effect of a fall in arterial pressure on sodium excretion among patients with different levels of sodium balance, changes in sodium excretion were normalized and expressed as percent of control. It was found that, in the group as a whole, sodium excretion was halved by a mean reduction in arterial pressure of 24.1 ± 3.0 mm Hg. By subdividing the patients in two subgroups on the basis of resting control MAP (seven with mean arterial pressure below 120 mm Hg and five with higher MAP), it could be shown that a larger fall in arterial pressure was needed to reduce sodium excretion by 50% in patients with more severe hypertension than in those with moderate hypertension (35.3 ± 1.4 vs 16.1 ± 1.3 mm Hg; p < 0.001) (fig. 2). Change in sodium excretion (in percent of control) per mm Hg change in MAP averaged 1.4% ± 0.1% per mm Hg in patients with a resting MAP above 120 mm Hg and 3.2% ± 0.3% per mm Hg in the group with lower resting BP. This

| Pt no. | MAP (mm Hg) | UNaV (μEq min⁻¹) | ΔUNaV/ΔMAP (μEq min⁻¹ per mm Hg) | PV (% of normal) | ECF* (% bwt) | PRA (ng/ml) | Endogenous GFR (ml/m²/1.73 M²) | Lower normal range of GFR
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MAP = mean arterial pressure; UNaV = sodium excretion; PV = plasma volume; ECF = extracellular fluid volume; PRA = plasma renin activity.

*Normal range 16.5%–21.2% bwt.

†From Slack and Wilson. (ref. 25.)
difference was not only apparent between two arbitrary subgroups of patients, but was also evident as a continuum over the range of MAP investigated: a highly significant \((r = -0.84; \ p < 0.01)\) inverse correlation was found between \(\Delta U_{Na^+}V/\Delta MAP\) and resting MAP (fig. 4).

**Pressure Natriuresis and Body Fluid Volumes**

Plasma volume ranged among the 12 patients from 82% to 123% of normal, with an average of 101.0% ± 3.7% (table 1). There were no significant correlations in this group of essential hypertensives between PV and either resting BP or sodium excretion. However, the ratio \(\Delta U_{Na^+}V/\Delta MAP\) was significantly \((p < 0.02)\) higher in the group of patients with a PV 10% or more above normal than in the patients with normal or low PV (7.39 ± 2.61 vs 3.30 ± 0.36 \(\mu\)Eq/min/mm Hg). Furthermore, a significant relationship was found between PV and the ratio \(\Delta U_{Na^+}V/\Delta MAP\); the relationship fitted much better as an exponential line \((r = 0.946, \ p < 0.01)\) (fig. 5) than a linear equation \((r = 0.70, \ p < 0.05)\). Multiple correlation analysis revealed that the index of determination was increased to 71% \((r = 0.84; \ p < 0.005)\) when pressure natriuresis was related to both PV and resting BP.
MAP: \( \Delta U_{NaV}/\Delta MAP = -0.082 \text{ MAP} + 0.171 \text{ PV} - 2.434 \).

A similar improvement of correlation \((r = 0.71)\) was found when ECF, measured as radiosulfate space, was substituted for PV \((\Delta U_{NaV}/\Delta MAP = -0.074 \text{ MAP} + 1.395 \text{ ECF} - 11.142)\), but this correlation did not attain a level of statistical significance \((p = 0.08)\), possibly because of fewer observations (Table 1). There was no significant correlation between control sodium excretion and either MAP or ECF.

The PRA averaged \(1.17 \pm 0.27 \text{ ng/ml/hr}\). There were no significant correlations between PRA and either MAP, PV, or the ratio \(AU_{NaV}/AMAP\). During BP lowering with nitroprusside, PRA rose by an average of \(53\% \pm 23\%\), but the change was not statistically significant.

Renal Hemodynamics

Control RBF averaged \(696 \pm 75 \text{ ml/min/1.73 m}\), and GFR (six patients) averaged \(88 \pm 19 \text{ ml/min/1.73 m}\). The endogenous creatinine clearance for the group averaged \(90 \pm 14.6 \text{ ml/min/1.73 m}\). Compared to the age-corrected lower limit of normal range given by Slack and Wilson, only one of our patients (No. 10) had a GFR well below that range. Both RBF and GFR remained virtually unchanged when MAP was lowered to about \(100 \text{ mm Hg}\) by nitroprusside infusion (Fig. 6); below that level there was a linear fall in both flow rates with MAP. Renal blood flow was, in patients with more severe hypertension, maintained unchanged down to the same level of arterial pressure as in the group of patients with MAP below \(120 \text{ mm Hg}\) (Table 2). Neither RBF nor GFR were significantly

![Figure 4. Sensitivity of pressure natriuresis expressed as percent fall in sodium excretion per mm Hg reduction in BP in relation to resting MAP in 12 hypertensive patients \((r = -0.84, p < 0.01)\).](image)

![Figure 5. Relation of pressure natriuresis \((\Delta U_{NaV}/\Delta MAP)\) with plasma volume \((PV)\) in 12 hypertensive patients (see text).](image)

### Table 2. Renal Hemodynamic Characteristics of Twelve Hypertensive Patients Before and During Nitroprusside Infusion

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RBF = renal blood flow; GFR = glomerular filtration rate; FF = filtration fraction.

*GFR and FF measured in only three patients of each group.
correlated to the ratio \( \Delta U_{\text{Na}} / \Delta MAP \) or control sodium excretion. In the six patients in whom it was measured, filtration fraction remained virtually unchanged during lowering of arterial pressure.

**Discussion**

**Sensitivity of Pressure Natriuresis in Essential Hypertension**

This investigation showed that the fall in sodium excretion induced by a reduction in arterial pressure in essential hypertensives was dependent on initial level of arterial pressure: the slope of the relationship between change in sodium excretion and arterial pressure \( \Delta U_{\text{Na}} / \Delta MAP \) during nitroprusside infusion was significantly less in patients with more severe hypertension than in others (fig. 2). However, the average fall in sodium excretion, about 50% per 25 mm Hg drop in arterial pressure, was similar to that previously reported by Kaneko et al.

The effect on sodium excretion of a rise in arterial pressure is usually described as pressure natriuresis, but the same relationship between sodium excretion and arterial pressure is found whether arterial pressure rises or falls. The pressure natriuresis mechanism enables the kidneys to increase sodium excretion when arterial pressure rises and to retain sodium and water when BP falls. Intrarenal hydrostatic pressure, a mediator of pressure-induced changes in sodium excretion, has been found to be raised not only under experimental conditions with acute elevation of arterial pressure but also in patients with essential hypertension. Yet, it is a clinical paradox that essential hypertensives with widely different BP levels may be in sodium balance, excreting the same amount of sodium for the same level of sodium intake. The reduction of the ratio \( \Delta U_{\text{Na}} / \Delta MAP \) at higher levels of arterial pressure indicates a fall in sensitivity of the pressure natriuresis mechanism; in patients with more severe hypertension, the change in sodium excretion induced by a given variation in BP was less than in patients with mild hypertension.

A fall in sensitivity of the pressure natriuresis mechanism at higher levels of BP can also be calculated from data of Onesti et al. in their study on hemodynamic effects of clonidine. By plotting sodium excretion against MAP before and after oral administration of clonidine, it may be seen that the pressure natriuresis was less steep in patients with more severe hypertension. Hence, with two different hypotensive drugs it was possible to demonstrate that the slope of the relationship between sodium excretion and arterial pressure in hypertensive patients was determined, in part, by the level of resting BP. This attenuation of the pressure natriuresis mechanism might serve the purpose of reducing sodium loss and thereby preserve body fluid volume in the face of persistent hypertension. Conversely, hypertensive patients might tolerate a larger drop in arterial pressure than normotensives without seriously impairing the capacity for sodium excretion. Body fluid volume, although somewhat reduced in hypertension, therefore appears to be more efficiently protected from fluctuations due to acute changes of arterial pressure.

The second important observation of our present study is that the arterial pressure at which sodium excretion extrapolates to zero was not raised as much as control pressure before nitroprusside administration; in fact, urine flow approached zero at approximately the same pressure level independent of degree of initial hypertension. Normotensive subjects were not examined, but resting MAP ranged from near normal to clearly hypertensive levels (from 103 to 166 mm Hg). Hence, the lack of correlation between resting BP level and the pressure at which sodium excretion stops argues against "resetting" of sodium excretion in essential hypertension in the sense that the pressure threshold for sodium excretion be raised.

It is generally accepted that changes in sodium excretion associated with changes in BP are caused by changes in tubular sodium reabsorption because of autoregulation of glomerular filtration. In this and other studies from our laboratory, it was shown that GFR and RBF both in hypertensive man and in animals remain constant over a wide range of BP during nitroprusside infusion, implying that the fall in sodium excretion was due to enhanced tubular reabsorption. Onesti et al. came to similar con-
clonidine in hypertensive patients and in anesthetized dogs. As discussed by Page et al. and Pagani et al., the direct vasodilating effect of nitroprusside is probably small in the kidney compared to other vascular beds. Thus, the constancy of RBF and GFR down to the same level of arterial pressure, independent of initial pressure or flow characteristics, indicates that renal autoregulation is maintained in essential hypertension. Similar results were recently found in spontaneously hypertensive rats. These observations show that the reduction in the slope of the relationship between sodium excretion and arterial pressure in patients with higher arterial pressure was not dependent upon changes in renal autoregulation.

Relationship Between Pressure Natriuresis and Body Fluid Volumes

It is recognized that a majority of essential hypertensives have reduced PV and that there is an inverse curvilinear relationship between resting BP and PV. Since renal handling of sodium and water is closely linked to the control of body fluid volumes, it was possible that the change in pressure natriuresis in patients with more severe hypertension could be associated with alterations in body fluid volumes. From animal experiments there is ample evidence of such an association between body fluid volume and pressure natriuresis. In dogs the relationship between sodium excretion and arterial pressure gradually rises during saline infusion, and data from acute loading experiments show a direct relationship between loading of salt and rise in pressure natriuresis. Conversely, it is known that sodium excretion may fall with volume contraction even before any BP change. Furthermore, in dogs kept on low sodium intake, it was found that an acute elevation of arterial pressure increased sodium excretion less (i.e., less steep pressure natriuresis) before than after volume repletion. From such experiments, it may be concluded that sensitivity of the pressure natriuresis is modified by degree of volume expansion. Thus, a whole family of curves relating BP and sodium excretion can be obtained depending on the degree of spontaneous or induced volume status.

This study shows that at least two mechanisms are influencing sodium excretion in essential hypertension, both with the net effect that excessive natriuresis is avoided in hypertensive patients: 1) fall in sensitivity of pressure natriuresis at higher levels of arterial pressure, and 2) blunting of pressure natriuresis by volume contraction. The interrelationship between these mechanisms may be depicted by figure 7. Arbitrary units along the ordinate represent intake and output of sodium, and the state of equilibration with sodium balance is indicated by the dotted line. Normotensive and hypertensive pressure levels are indicated by N and H respectively. First, a clear distinction must be made between a natriuresis produced by an increase in arterial pressure (pressure natriuresis) and a natriuresis induced by volume expansion. A moderate rise in sodium excretion is achieved by raising MAP from a normotensive to a hypertensive level (pressure natriuresis; line A). Saline loading raises sodium excretion at both pressure levels but the increase in sodium excretion at a high arterial pressure by far exceeds that at a normal pressure (exaggerated natriuresis). Hence, volume expansion modifies pressure natriuresis by making the relationship between sodium excretion and arterial pressure steeper (line B). The opposite effect with a fall in sensitivity of pressure natriuresis is induced by volume depletion as indicated in line C. Thus, the challenge of an acute saline loading, the usual test for exaggerated natriuresis of hypertension, explores volume natriuresis at a given level of BP rather than pressure natriuresis. After volume expansion has been accomplished, however, pressure natriuresis may be enhanced, as shown by the larger increases in sodium excretion with rise in arterial pressure.

It is usually held that essential hypertension is secondary to subtle defects in renal function. Nephrosclerosis is common among hypertensive patients so that an alteration in pressure natriuresis could conceivably be ascribed to this complication of hypertension. It is very difficult, short of biopsy, to exclude nephrosclerosis from patients with hypertension of various duration; however, all our patients, with the exception of one, had GFRs well within the normal values for their age. Furthermore, one would expect that reduced renal function would shift the curve of pressure natriuresis to the right rather than alter its slope without changing the point of origin.

An alternative explanation is possible on the basis of the relationship outlined in our results between arterial pressure, body fluid volume, and sodium balance, namely, that in essential hypertension, to avoid dangerous sodium and volume depletion from uncontrolled natriuresis and to maintain sodium balance, the sensitivity of pressure natriuresis is reduced.
This could be achieved by activating at least two mechanisms: 1) attenuation of pressure natriuresis at higher levels of arterial pressure, and 2) blunting of pressure natriuresis by volume contraction. By this hypothesis, therefore, the lower slope of pressure natriuresis is secondary to hypertension rather than its cause. More studies in a larger group of patients, particularly younger people with minimal BP elevation, might help decide the argument although a complete exclusion of nephrosclerosis in any patient with hypertension would remain a difficult undertaking in man.

Our present study has presented some evidence in favor of our hypothesis. The slope of the relationship between sodium excretion and arterial pressure was higher in patients with PV expansion than in normo- or hypovolemic patients. However, the association between body fluid volumes and slope of the relationship between sodium excretion and arterial pressure was weak, as shown by an index of determination of about 50%, so that it is obvious that other factors might also influence the sensitivity of the pressure natriuresis.

It is known that activation of the sympathetic nervous system might induce changes in sodium excretion, and that the renal handling of salt is closely linked to the renin-angiotensin system. However, PRA did not influence the slope of the relationship between sodium excretion and arterial pressure during nitroprusside infusion. Differences in baroreceptor activity among patients could play some role, but a possible relationship between activation of the sympathetic nervous system and pressure natriuresis was not systematically explored in this study.

Divergent responses of cardiac output to nitroprusside infusion could account for impairment of pressure natriuresis in some patients but, as reviewed by Earley and Schrier, changes in cardiac output were not found to be associated with changes in renal sodium excretion. Furthermore, in our study the renal hemodynamic response to nitroprusside was similar in all patients.

Conclusions

In summary, pressure natriuresis is blunted in essential hypertensives with no gross abnormalities of renal function. The fall in sensitivity of the pressure natriuresis mechanism is related to BP level and body fluid volumes. These findings suggest a self-regulating mechanism whereby hypovolemia might at the same time be the consequence of hypertension and a limiting factor for pressure natriuresis, thereby preventing excessive sodium and fluid losses.

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