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EXAGGERATED NATRIURESIS IN CHRONIC HYPERTENSION *IN* PREGNANCY

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Summary

In this study, the way in which sodium is handled by the nephron, and the ability to excrete a salt load was investigated in five patients with chronic hypertension in pregnancy (CHP) and in five non-pregnant patients with chronic hypertension (CH) as a control group. The patients were loaded with isotonic saline (NaCl), 3mEq/kg bodyweight intravenous, in 60 minutes, during water diuresis. The increment in sodium excretion was significantly greater in CHP than in CH. In CHP, the filtered load of sodium was greater than in CH, accounting for enhanced distal sodium delivery. C_{H_2O}, however, was similar in CHP and CH. Therefore, the C_{H_2O}/Na^+ delivery was decreased in CHP. These results indicate that in CHP the exaggerated natriuresis, secondary to impaired sodium transport in the diluting segment, may be due to the transmission of increased haemodynamic pressure by the renal vasodilation of pregnancy.

Introduction

Recently, we have shown by metabolic and micropuncture studies that hypertensive pregnant rats excrete more sodium than hypertensive non-pregnant rats and that in pregnant rats with renal hypertension total arteriolar glomerular resistance is much lower than in non-pregnant rats with a similar degree of high blood pressure [1,2]. This renal vasodilation blunts renal autoregulation in pregnancy, allowing for systemic hypertension to determine profound modifications in intrarenal haemodynamics, and hence in renal sodium handling. As yet, however, to our knowledge, no adequate controlled study has been performed in man.

The aim of the present study was to investigate the way by which sodium is handled by the nephron, and the ability to excrete a salt loading in patients with chronic hypertension in pregnancy (CHP) and in non-pregnant patients with chronic hypertension (CH) as control group.

Methods

Studies were performed in five patients with essential hypertension during the last trimester of pregnancy (chronic hypertension in pregnancy: CHP) and in five female non-pregnant patients with essential hypertension (chronic hypertension: CH). These latter patients were used as control group and were matched with CHP group for age and blood pressure. All the patients selected for the study were hospitalized and received a constant sodium intake of 100mEq/day. All medications had been discontinued for at least five days before the study. Two morning urinalyses with careful sediment examination were performed. Two quantitative urine cultures from clean voided midstream collections of the first morning urine specimens were obtained. Two 24 hour urine collections were analysed for protein, sodium, and potassium. Hypertension as related to the selection and the inclusion of patients in this study is defined as an elevation of diastolic pressure to greater than 90mmHg on three separate cuff recordings with the patient in supine position.

Five hypertensive pregnant and five hypertensive non-pregnant subjects were loaded with isotonic NaCl infusion during water diuresis. The latter was induced by oral administration of 20ml/kg body weight of water in 1/2 hours and was maintained by administration of an amount of water, in part by mouth in part intravenously as 5% glucose solution, equal to urine flow plus 1ml/min to replace insensible losses. When a steady state of urine flow had been obtained (i.e. urine volume changes for three consecutive collection periods were contained within 1.5ml/min) three 20-minute control clearance periods were performed. Saline infusion (NaCl 0.9%) was then started in order to give a salt load of 3mEq NaCl/kg body weight in 60 minutes. During the salt load three consecutive 20-minute clearance periods (experimental) were carried out. Urine was collected by spontaneous voiding. Clearance of creatinine (C_{cr}), sodium, potassium and osmolar clearance (C_{osm}) were measured both in control and experimental periods.

Creatinine was determined by a creatinine autoanalyzer (Beckman Instruments, Inc, Fullerton, California, USA), sodium and potassium by a flame photometer (Beckman Instruments, Inc), and osmolality by an osmometer (Model 230D, Fiske Associates, Inc, USA).

C_{cr}, C_{osm}, free-water clearance (C_{H_2O}) and the filtered load of sodium (Na_F) were calculated from standard expressions. The rate of sodium reabsorption in diluting segments ($Na_{R,dil}$) was calculated as: $Na_{R,dil} = C_{H_2O} \times P_{Na}$ where P_{Na} is plasma sodium concentration. The delivery of sodium to diluting setments ($Na_{delivery}$) was calculated from the expression:

$$Na_{delivery} = Na_{R,dil} + (U_{Na} + U_K) \times V$$

where U_{Na} and U_K are urine concentrations of sodium and potassium, respectively. Fractional sodium reabsorption in diluting segments ($Na_{R,dil\%}$) was given by the ratio:

$$Na_{R,dil\%} = \frac{Na_{R,dil}}{Na_{delivery}} \times 100$$

Finally, fractional sodium reabsorption in the proximal tubules

$$(Na_{R,\,prox\%}) = \frac{Na_F - Na_{delivery}}{Na_F} \times 100$$

The results of clearance studies were evaluated by Student's 't' test for paired and unpaired samples.

Results

At the start of clearance experiments, mean systolic blood pressure was 159±13 SD mmHg in pregnant patients and 160±12mmHg in non-pregnant patients. Mean diastolic blood pressure (5th Korotkoff phase) was 105±6 and 107±6mmHg, respectively. These values were not significantly changed by salt loading; at the end of salt infusions, in fact, mean systolic blood pressure was 162±11 SD mmHg in pregnant patients, and 164±12mmHg in non-pregnant patients; mean diastolic blood pressure was 105±5 and 106±5mmHg, respectively. The mean age of pregnant patients, ranging from 18 to 36 years with a mean value of 25, was similar to the age of non-pregnant patients (mean: 27; range, 20 to 39 years). Both pregnant and non-pregnant subjects showed urinary excretion of protein less than 0.5g/day.

At the last day of stabilization, mean urinary sodium excretion was 91±6mEq/day in hypertensive pregnant patients and 92±5mEq/day in hypertensive non-pregnant patients, which indicates that both groups were in sodium balance.

During water diuresis, as shown in Figure 1, the increment in urinary sodium

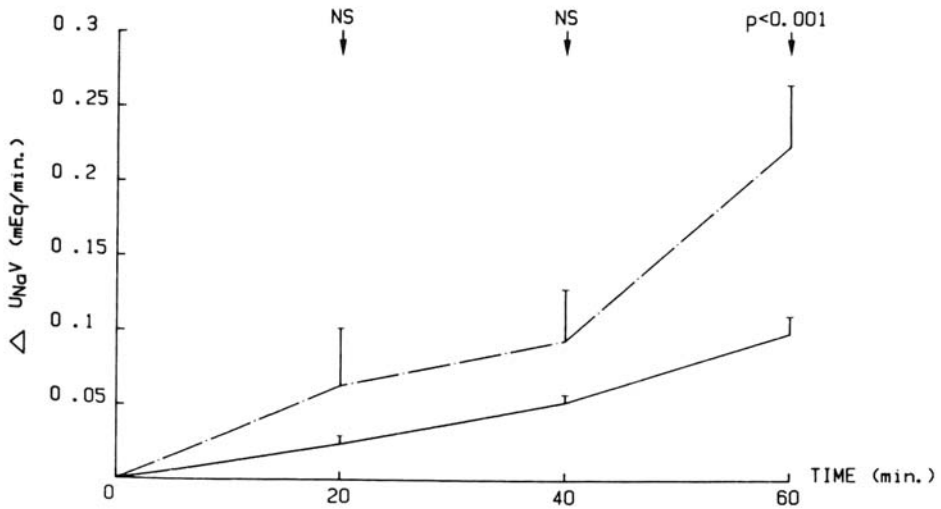

Figure 1. Increment in urinary sodium excretion ($U_{Na}V$) during saline infusion in hypertensive pregnant (– · –) and non-pregnant subjects (——)

excretion rate determined by saline infusion was more rapid in hypertensive pregnant patients than in hypertensive non-pregnant patients, the difference attaining statistical significance in the last experimental period. The latter was therefore used to compare the effects of saline infusion on renal function in hypertensive pregnant and non-pregnant patients. The results are summarized in Table I. Both C_{Cr} and Na_F were greater in CHP than in CH in control condition and during saline infusion. Fractional proximal reabsorption was the same in the two groups in control and experimental condition. $Na_{delivery}$ was, thus, higher in CHP than in CH. C_{H_2O}, however was similar in CHP as in CH. Therefore, fractional sodium reabsorption in diluting segments was significantly decreased in CHP (84.7±10% vs 75.7±1.4%, $p<0.001$). Finally, the sustained water diuresis allowed to reach minimum value in urine osmolality (range 40–81mOsm/kg) and maximum value in urine output (range 11.0–19.2ml/min) in both control and experimental condition.

TABLE I. Effects of saline infusion on renal function in non-pregnant subjects with chronic hypertension (CH) and in subjects with chronic hypertension in pregnancy (CHP) in maximal water diuresis (mean±SD)

	C_{Cr} ml/min	Na_F mEq/min	$Na_{R,prox}$ %	$Na_{delivery}$ mEq/min	C_{H_2O} ml/min	$Na_{R,dil}$ %
CH	110.2 ±7.8	14.6 ±1.1	86.7 ±0.9	1.92 ±0.06	12.3 ±0.4	84.7 ±1.0
CHP	138.2 ±3.3	18.5 ±0.4	87.3 ±0.7	2.33 ±0.09	13.2 ±0.3	75.7 ±1.4
p	0.001	0.001	NS	0.001	NS	0.001

C_{Cr}: creatinine clearance; Na_F: filtered sodium; $Na_{R,prox}$: fractional sodium reabsorption in the proximal tubule; $Na_{delivery}$: sodium delivery to diluting segments; C_{H_2O}: free-water clearance; $Na_{R,dil}$: fractional sodium reabsorption in diluting segments

Discussion

In the present study the increase in sodium excretion induced by saline loading was more rapid in hypertensive pregnant patients than in hypertensive non-pregnant patients. This exaggerated natriuresis was accounted for by a larger increase in the filtered load of sodium, due to increase in GFR in pregnant subjects, and by an impaired tubular sodium reabsorption.

Our study in water diuresis was carried out to obtain information on the site of the nephron in which a decreased tubular reabsorption of sodium occurs.

Proximal tubular reabsorption was calculated in maximally hydrated subjects, and was similar in hypertensive pregnant and non-pregnant patients, thus ruling out any possibility that the proximal tubule is the site of defective reabsorption. During maximal water diuresis, C_{H_2O}, and index of sodium reabsorption in diluting segments, was not statistically different between pregnant and non-pregnant hypertensive patients. This latter finding in conjunction with the

increased delivery of sodium to diluting segments, due to increase in GFR of pregnant patients, reflected a decrease in fractional sodium removal from diluting segments, suggesting that sodium reabsorption is impaired in the ascending limb of Henle's loop [3].

As it is known, a new salt balance is achieved in pregnancy which allows salt retention. This new equilibrium, however, appears labile, to the point that pregnancy has been compared to a condition of subtle salt wasting. It is our opinion that the renal haemodynamic changes characteristic of pregnancy contribute to the subtle salt-losing tendency in this condition and account for the increased salt excretion caused by hypertension. The defect in sodium reabsorption of Henle's loop suggests that it depends upon the transmission of an increased haemodynamic pressure to the vasa recta. This mechanism is made possible by the potent renal vasodilatory effect of pregnancy, that blunts renal autoregulation [4]. In pregnant rats with renal hypertension total arteriolar glomerular resistance is much lower than in non-pregnant rats with a similar degree of high blood pressure [1,2].

Inhibition of salt reabsorption in Henle's loop by increased haemodynamic pressure in vasa recta is considered responsible also for the exaggerated natriuresis of hypertension [5,6]. In hypertensive patients, renal vasodilation, evoked by rapid extracellular volume expansion, allows increased perfusion pressure to medullary circulation. The pregnancy intensifies the exaggerated natriuresis of hypertensive patients by the impaired autoregulation secondary to renal vasodilation.

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