SALT SENSITIVITY IN NORMOTENSIVES WITH AND SALT RESISTANCE IN NORMOTENSIVES WITHOUT HEREDITY of HYPERTENSION

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SUMMARY

We have studied blood pressure responses to moderate sodium restriction from 200 to 50 mmol/day over 2 weeks in 62 normotensive subjects with and without a family history of hypertension by continuous automatic blood pressure recording. Based on the average of the blood pressure of 1 hour continuous monitoring under basal conditions, we have been able to demonstrate a significant fall of blood pressure in 28 young subjects with a heredity of hypertension after moderate sodium restriction from 200 to 50 mmol over 2 weeks (fall in systolic blood pressure 5.4 $\pm$ 1.1, diastolic 2.5 $\pm$ 0.8, mean blood pressure 2.9 $\pm$ 0.7 mmHg, mean $\pm$ SEM), whereas blood pressure remained unchanged in a group of 34 subjects without heredity of hypertension after moderate sodium restriction (change in systolic blood pressure -1.0 $\pm$ 0.6, diastolic blood pressure -0.6 $\pm$ 0.7 and mean blood pressure -0.93 $\pm$ 0.67 mmHg). 29 of the subjects were studied a third time 2 weeks after having returned to their usual high sodium diet and in those in whom a blood pressure fall was observed during sodium restriction it returned to pre-intervention values. This demonstrates that normotensives with a heredity of hypertension are salt sensitive and adds further evidence that a high sodium intake may be of critical importance for the initiation of essential hypertension.

INTRODUCTION

Although most workers in the field of hypertension are probably convinced that a high sodium intake is involved in the pathogenesis of essential hypertension, the effect of sodium restriction in established hypertension is very small[1-3]. Furthermore, it has not been possible to demonstrate a fall in blood pressure in normotensive subjects after sodium restriction[4-7]. Without this being demonstrated, all the epidemiological and experimental studies in animals will remain unconvincing. Since the effect of sodium intake on blood pressure is expected to be very small in short term studies, the design of the previous studies[4-7] to detect these small blood pressure changes was probably insufficient because in all these studies blood pressure was measured with sphygmomanometric methods. If one considers that with this method the blood pressure of only a single heart beat is measured, and with the given spontaneous variation of blood pressure (e.g. even by breathing) it is not surprising that any possible change of blood pressure could not have been detected in the past. Furthermore, in the previous studies cited[4-7] it was not considered that intra-individual differences of susceptibility to changes in sodium intake may exist, masking blood pressure changes in a minority of subjects by the unchanged blood pressure in a majority of subjects. In the present study, we have averaged the blood pressure of at least 1 hour continuous blood pressure recording, measured under basal conditions by an oscillometric method and have compared the blood pressure changes induced by a low sodium intake in subjects with and without a heredity of hypertension.

MATERIAL AND METHODS

We studied 62 normotensive volunteers, all medical students aged 20 to 25, during their usual diet containing 200 mmol of sodium and 80 mmol of potassium, and after two weeks on a diet moderately low in sodium (50 mmol/day) leaving potassium intake unchanged. The sequence of the diets was randomized. 29 of the subjects (11 with a positive and 18 with a negative family history of hypertension) were studied 3 times: on the usual high sodium diet, after two weeks of moderate sodium restriction and again after two weeks on the high sodium diet. Moderate sodium restriction was achieved by eliminating any salted

food products and by eliminating slat in the kitchen and at the table, except in bread. The diets were prepared and consumed in the dietetic department of the hospital, but the subjects were not kept at a metabolic ward. The family history of hypertension was obtained by questionaire administered to each subject and given to the family doctor. Those with established hypertension in grandparents or parents before the age of 65 were considered positive; those with normotensive parents and grandparents, negative.

Study protocol

After a 24-hour urine collection and after an overnight fast, the subjects were studied in a recumbent position. In each subject blood pressure was measured every minute for 90 minutes with an oscillometric method (Dinamap 845 with recorder 950), which was connected on line with a HP87 computer. The readings of the first 10 minutes were discarded, since during this time a continuous decline of blood pressure is usually observed and blood pressure only then starts to fluctuate around its basal value. From the remaining 60-70 measurements the average basal systolic, diastolic and mean blood pressure and mean pulse rate was calculated by the computer.

Statistical methods were student's paired and unpaired t-test and U test of Mann-Whitney for comparison of groups.

RESULTS

Average systolic, diastolic and mean blood pressure, pulse rate and 24-hour urinary sodium and potassium excretion on the high and low sodium diet are given in Table 1. As can be seen, subjects with a positive family history of hypertension had significantly higher systolic, diastolic and mean blood pressures at a high sodium intake. After a low sodium diet blood pressure decreased significantly only in the group of subjects with a positive family history of hypertension by between 3 and 5 mmHg (Table 1). It remained unchanged in the group of subjects with a negative family history of hypertension. 24-hour urinary sodium and potassium were not significantly different in the two groups on the high sodium intake and decreased significantly to the same extent on the low sodium intake (Table 1, Fig. 1).

Figure 2 shows an original protocol of the continuous blood pressure recording in one of the normal subjects (upper part). Figure 2 (lower part) also shows the basal blood pressure average measured during the first visit and during the third visit on a high sodium intake in those 29 normotensive subjects in whom blood pressure measurements were performed three times. As can be seen the basal blood pressure average is a highly reproducible way of blood pressure assessment. Although between the first and the third visit there had been the therapeutic intervention of sodium restriction there is no systematic fall of blood pressure from the 1st to the 3rd visit, which is usually seen with sphygmomanometric blood pressure measurements[10].

Figure 3 shows the frequency distribution of blood pressure change after sodium restriction in subjects with a negative family history of hypertension and those with a positive family history of hypertension. As can be seen, the distribution of blood pressure change is clearly different between subjects with a positive and a negative family history of hypertension, in the former a marked skewness to the left is observed. The frequency distribution of blood pressure change is significantly different in both groups ($p < 0.01$).

DISCUSSION

Although hypertensive subjects respond to sodium restriction with a fall of blood pressure, if this is measured carefully enough[1-3], it has not been possible in the past to show a fall of blood pressure in normotensive subjects after restriction of sodium intake[4-7]. All the cited studies, however, used sphygmomanometric blood pressure measurements, in effect utilizing the blood pressure of a single heart beat to estimate systolic and diastolic blood pressure. With the given spontaneous variation of blood pressure as exemplified in figure 2 the small fall of blood pressure of between 3 and 5 mmHg observed in the present study in subjects with a positive heredity of hypertension certainly must have gone unnoticed in all previous studies. In fact, the example of the variation of blood pressure recorded under basal conditions and shown in figure 2 had a standard deviation of 4.8 mmHg and was one of the lowest of all subjects (range 4.2 to 9.8 mmHg), which exemplifies the inadequate way of measuring blood pressure of a single heart beat by the usual sphygmomanometric methods. To our knowledge,

this and our previous study[8] are the first which demonstrate that subjects with a positive family history of hypertension are salt sensitive, whereas subjects with a negative family history of hypertension are (relatively?) salt resistant. This provides further evidence that a high sodium intake might be of great relevance in the initiation of essential hypertension. It will be noticed from figure 3 that not all subjects with a family history of hypertension show a fall of blood pressure, and some patients with a negative family history of hypertension show a fall of blood pressure. This could be explained by the fact that not all subjects with a heredity of hypertension develop hypertension themselves and salt sensitivity might not be due to possible inaccuracies in classifying subjects according to heredity of hypertension, although the medical students were probably better suited for that purpose than the general population. If one considers that such inaccuracies are unpreventable, and some of the small blood pressure changes may be related even to other uncontrollable factors, such as different levels of emotion or stress, the difference in blood pressure response to sodium restriction between subjects with a positive and negative family history demonstrated in Table 1 and Fig. 3 becomes even more striking. Salt sensitivity in normotensive subjects with a heredity of hypertension might be the initiating event for the development of essential hypertension. A concept for the possible biochemical mechanisms of salt sensitivity has been proposed[8,9].

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FIGURE LEGENDS

Fig. 1: 24-hour urinary sodium excretion in subjects with and without a positive family history of hypertension during high and low sodium intakes. A comparable degree of sodium restriction was achieved in both groups.

Fig. 2: Example of original 1-hour basal blood pressure monitoring. In this particular subject the standard deviation was 4.8 mmHg under strictly basal conditions. In the whole group, the standard deviation of mean blood pressure ranged between 4.2 and 9.8 mmHg.

In the lower part of the figure the mean blood pressure at the first and third visit is shown in those 29 normotensive subjects, who were investigated a third time, when again on a high sodium intake after sodium restriction. Also shown are additional 21 hypertensive subjects studied by the same protocol,0but who were not included in the present study. The regression line and line of identity are shown (o = normotensives, + = hypertensives, $r = 0.88$, $p < 0.001$, $n = 50$, $y = 0.93x + 4.5$).

Fig. 3: Frequency distribution of blood pressure change during low sodium diet in subjects with a positive and negative family history of hypertension. The frequency distribution is significantly different as shown by the t-test and U-test of Mann-Whitney ($p < 0.01$).

TABLE 1 : Blood pressure and biochemical data in subjects with and without a family history of hypertension (Mean + SEM)

	negative family history (n=34)		positive family history (n=28)	
	high salt diet	low salt diet	high salt diet	low salt diet
systolic blood pressure (mmHg)	117.3 ± 1.5	117.2 ± 1.3	122.5 ± 1.6	116.7 ± 2.0
		**		**
diastolic blood pressure (mmHg)	62.2 ± 1.1	61.6 ± 1.1	64.9 ± 1.3	61.6 ± 1.6
		*		***
mean blood pressure (mmHg)	81.9 ± 1.1	81.2 ± 1.0	84.8 ± 1.2	81.5 ± 1.5
		*		**
change systolic blood pressure		-1.0 ± 0.6		-5.4 ± 1.1
				**
change diastolic blood pressure		-0.6 ± 0.7		-2.5 ± 0.8
				*
change mean blood pressure		-1.0 ± 0.6		-2.9 ± 0.7
				*
average change of systolic, diastolic and mean BP		-0.93 ± 0.67		-3.53 ± 0.81
				*
24-hour urinary Na (mmol)	189.3 ± 13.7	44.8 ± 4.7	198.9 ± 13.3	35.8 ± 3.4
		***		***
24-hour urinary K (mmol)	64.1 ± 3.7	86.1 ± 6.8	74.0 ± 4.0	86.7 ± 8.1

Fig. 1.

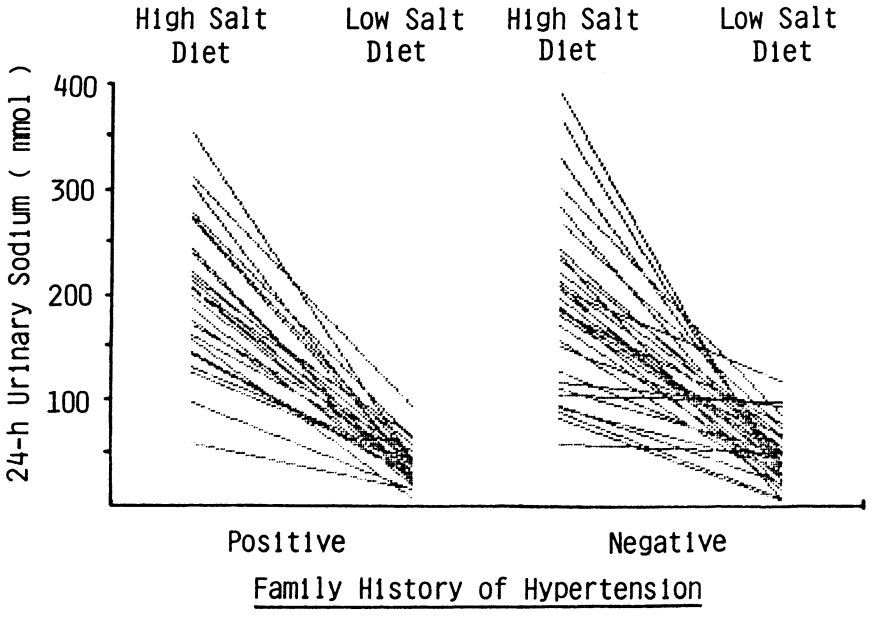
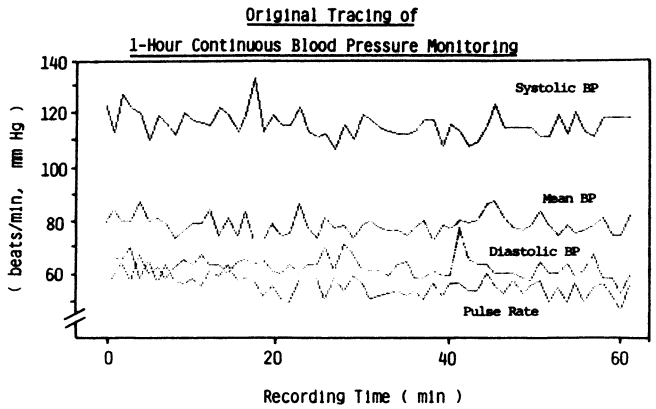

High Salt Diet
Low Salt Diet
High Salt Diet
Low Salt Diet
24-h Urinary Sodium (mmol)
400
300
200
100
Positive
Negative
Family History of Hypertension

Fig. 2.


Original Tracing of
1-Hour Continuous Blood Pressure Monitoring
(beats/min, mm Hg)
140
120
100
80
60
Systolic BP
Mean BP
Diastolic BP
Pulse Rate
0
20
40
60
Recording Time (min)

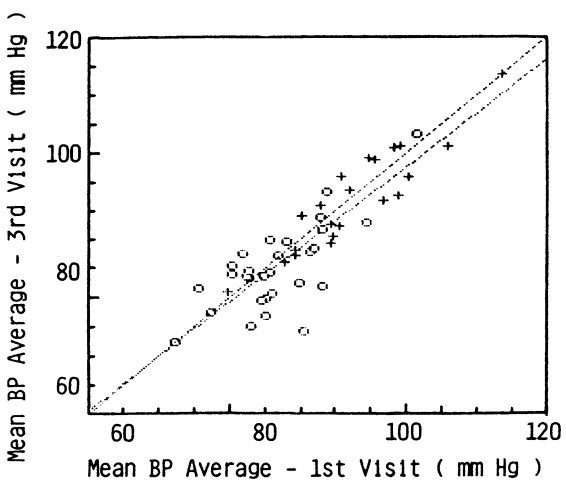
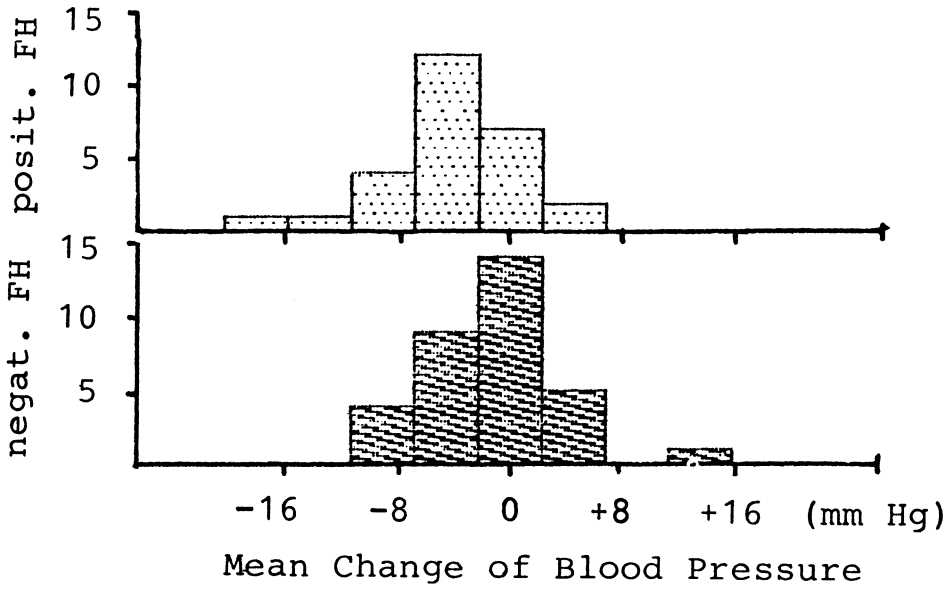

Mean BP Average - 3rd Visit (mm Hg)
120
100
80
60
60
80
100
120
Mean BP Average - 1st Visit (mm Hg)

Fig. 3.


posit. FH
15
10
5
negat. FH
15
10
5
-16
-8
0
+8
+16
(mm Hg)
Mean Change of Blood Pressure