The importance of the response of the renin-angiotensin system in determining blood pressure changes with sodium restriction

G. A. MacGREGOR

Blood Pressure Unit, Department of Medicine, Charing Cross and Westminster Medical School, London W6 8RF

1 There is controversy about the efficacy of sodium restriction in the treatment of hypertension. Short-term restriction of sodium intake in normotensive subjects causes little or no fall in blood pressure. This lack of response of blood pressure to sodium restriction appears to be due, at least in part, to a reactive rise in renin and angiotensin II.

2 In patients with essential hypertension there is suppression of the renin-angiotensin system particularly as blood pressure becomes more severe. With sodium restriction there is less of a rise in renin and angiotensin II compared with normotensive subjects and patients have a greater fall in blood pressure compared with normotensive subjects but the effect is less in mild compared to severe hypertension.

3 As the formation of angiotensin II can now be blocked by the use of a converting enzyme inhibitor, the combination of moderate salt restriction in conjunction with a converting enzyme inhibitor is likely to be more effective in lowering blood pressure than either treatment on its own.

Keywords salt renin high blood pressure

Introduction

Ambard & Beaujard, in 1904, were the first to show that salt restriction lowers blood pressure in some patients with hypertension. However, most of their patients had renal disease. Their findings were confirmed by Allen & Sherrill in 1922 in patients with normal renal function, but it was not until Kempner (1948) resuscitated the idea of salt restriction that salt restriction became widely used in the treatment of hypertension. Studies at this time demonstrated that severe restriction of salt intake did lower blood pressure and that the effect was due to the restriction of salt intake rather than a reduction in protein or an increase in potassium intake (Watkin *et al.*, 1950). However, with the advent of diuretics in the late 1950s salt restriction was largely abandoned. With increasing evidence that treatment of mild hypertension may be beneficial

greater interest has been shown in the effects of more moderate restriction of salt intake, particularly in patients with mild hypertension.

Relation to severity of blood pressure

However, some recent studies have revealed what appears at first sight to be conflicting evidence, some showing a fall in blood pressure and others claiming little or no fall in blood pressure (MacGregor, 1985). In order to look at this problem further, we studied 103 normotensive and hypertensive subjects, on no treatment, on their usual diet (approximately 150 mmol of sodium/day), on the fifth day of a high sodium diet (approximately 350 mmol of sodium/day) and on the fifth day of a low sodium diet (10 mmol of sodium/day) provided by the metabolic

Correspondence: Dr G. A. MacGregor, Blood Pressure Unit, Department of Medicine, Charing Cross and Westminster Medical School, London W6 8RF

Figure 1 Mean ($\pm$ s.e. mean) blood pressure on the fifth and eighth day of sodium balance prior to captopril, 2 h after the first 25 mg dose of captopril and on the fourth and fifth day of captopril treatment and 7 days after stopping captopril (20th day) in normotensive subjects (from MacGregor *et al.*, 1983).

kitchen as outpatients. This study revealed that one of the most important predictors of the blood pressure fall, with the reduction in sodium intake, was the initial blood pressure and the plasma renin activity on the normal diet (MacGregor *et al.*, 1982a). However, relating pre-treatment blood pressure to fall in blood pressure can give statistically invalid results as the fall in blood pressure is, in part, calculated

from the pretreatment blood pressure. A statistically valid way of looking at the results is to examine the slope of the line of the pre-treatment blood pressure plotted against the post-treatment blood pressure and compare the slope of this line against the line of identity. In our study, the slope obtained was significantly less than the line of identity (MacGregor, 1985). This was so even when the results were plotted on a log

scale, confirming that salt restriction does become more effective the higher the blood pressure, slope of line obtained = 0.78; $P < 0.001$ for difference to the slope of line of identity (1.0). Furthermore, in a smaller but double-blind study of longer-term moderate salt restriction we also found the same sort of relationship, that is, the fall in blood pressure with salt restriction appeared to be related to the severity of the blood pressure before treatment (MacGregor *et al.*, 1982b).

Why should salt restriction vary in its effectiveness?

With changes in sodium and water balance, it is clear that man and other mammals have several buffering systems to protect the cardiovascular system from the induced changes in blood volume. These buffering systems include the sympathetic nervous system and the renin-angiotensin system. With the development of the competitive inhibitor of angiotensin II, saralasin, and the angiotensin converting enzyme inhibitors, it became possible to directly examine the role of the renin system in the maintenance of blood pressure and, particularly, under conditions of different sodium intakes. Twenty-nine patients with essential hypertension who had been studied on their usual diet, on the fifth day of a high and the fifth day of a low sodium diet, were infused with saralasin on the fifth day of the low sodium diet (Cappuccio *et al.*, 1985). The change in blood pressure with saralasin on the low sodium diet was inversely related to the fall in blood pressure from the high to the low sodium diet. In other words, those patients who had the least change in blood pressure with salt restriction had the greatest subsequent response to saralasin when on the low sodium diet, whereas those patients who had a big fall in blood pressure with salt restriction had little response to saralasin. These results were the first direct evidence to show that differences in the reactivity of the renin-angiotensin system to salt restriction could, at least in part, determine the blood pressure fall with salt restriction.

In a separate study in young adult normotensive subjects, we also examined the effect of the oral angiotensin converting enzyme inhibitor, captopril given for 5 days when subjects were on three fixed sodium intakes: a high (350 mmol sodium/day; $n = 7$), a normal sodium intake (120 mmol/day; $n = 8$) and a low sodium diet (10 mmol/day; $n = 5$) (MacGregor *et al.*, 1983). As found previously in normotensive subjects there was little change in blood pressure with the alteration of salt intake alone but plasma angio-

tensin II varied with salt intake showing on the high sodium diet a mean value of 17.0 ± 2.6 pmol l^{-1} (s.e. mean), on the normal diet 25.3 ± 2.3 pmol l^{-1} and on the low sodium diet 64.4 ± 9.3 pmol l^{-1} . However, with captopril treatment, particularly by the fifth day, there was an increased fall in blood pressure as salt intake was reduced (Figure 1). The pretreatment level of angiotensin II appeared to be a good predictor of the blood pressure fall (Figure 2). These results therefore supported the concept that the blood pressure fall with salt restriction can be offset by a reactive rise in renin and angiotensin II, particularly in normotensive subjects.

Moderate sodium restriction in the treatment of high blood pressure

Very low sodium diets are not practical in the long-term treatment of hypertension and there has therefore been great interest in the effect of more moderate but practical reduction in sodium intake. In a study of 19 patients with mild to moderate hypertension, we showed using a double-blind protocol employing placebo and Slow sodium tablets, that there were significant falls in mean blood pressure of approximately 6% with a reduction in sodium intake from around 160 mmol/day to 80 mmol/day (MacGregor *et al.*, 1982b) (Figure 3). Plasma renin activity and aldosterone rose significantly with moderate restriction of sodium intake suggesting that this increase in renin release might limit the fall in blood pressure that occurred (Figure 4). A subsequent study of moderate sodium

Figure 2 Pre-treatment plasma angiotensin II and the fall in mean supine blood pressure on the fifth day of captopril treatment in normotensive subjects. ● normal sodium diet (120 mmol); ▲ high sodium diet (350 mmol); ■ low sodium diet 10 mmol (from MacGregor *et al.*, 1983).

Figure 3 Blood pressure and urinary sodium excretion (mean $\pm$ s.e. mean) during normal diet in 19 patients with essential hypertension after 2 weeks of sodium restriction and at 2 weekly intervals with 1 month's treatment with Slow sodium tablets and 1 month's treatment with matching placebo tablets (from MacGregor *et al.*, 1982b).

* $P < 0.05$; ** $P < 0.01$; *** $P < 0.001$ for Slow sodium compared with placebo, ‡ $P < 0.001$ for normal diet compared with Slow sodium.

Figure 4 Plasma renin activity (○), plasma aldosterone (●), weight and urinary sodium excretion (mean $\pm$ s.e. mean) in 19 patients on their normal diet, after 2 weeks of sodium restriction during randomised crossover of 1 month's treatment with Slow sodium tablets and 1 month's treatment with matching placebo tablets (from MacGregor *et al.*, 1982b).

restriction from New Zealand which showed less of an effect of salt restriction on blood pressure (Richards *et al.*, 1984), did show a direct inverse relationship between the fall in blood pressure with salt restriction and the rise in plasma renin activity that occurred with the salt restriction, suggesting that the reactive rise in renin is an important compensatory mechanism in these patients which may limit the fall in blood pressure that occurs with salt restriction.

An epidemiological study looking at plasma renin activity in normal subjects and patients with essential hypertension showed that there was a progressive decrease in plasma renin activity with increasing age in normotensive subjects and increasing blood pressure in hypertensive subjects (Meade *et al.*, 1983). It would appear therefore that the better response of some patients with essential hypertension to moderate sodium restriction is related in part to a blunted renin-responsiveness to the salt restriction and that the degree of suppression of the renin system appears to be related to the severity of the hypertension. The fact that patients with borderline or very

mild hypertension appeared to respond less well to salt restriction than those with more severe hypertension is at first sight disappointing. However, if subjects are prepared to moderately restrict their sodium intake, the subsequent use of a drug that blocks the renin system should be much more effective in lowering blood pressure than when they are on their usual sodium intake.

To look at this more directly, we conducted a double-blind study of moderate salt restriction when patients were already on treatment with captopril. The study demonstrated an approximate 9% fall in blood pressure with moderate salt restriction when on captopril and this fall in blood pressure was significantly related to the reduction in urinary sodium excretion but not the severity of the blood pressure. Overall the study suggested that the combination of an angiotensin-enzyme inhibitor with a moderate but practical reduction in salt intake could be very effective in controlling blood pressure in many patients with essential hypertension (MacGregor *et al.*, 1987).

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