RESPONSE OF THE RENIN-ANGIOTENSIN-ALDOSTERONE SYSTEM TO UPRIGHT TILTING AND TO INTRAVENOUS FRUSEMIDE: EFFECT OF PRIOR METOPROLOL AND PROPRANOLOL

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- 1 Upright tilting in normal volunteers caused increases in plasma active and total renin, angiotensin II and aldosterone; a slight but significant fall in inactive renin accompanied these changes.
- 2 The alterations in the renin-angiotensin-aldosterone system on tilting took up to 1 h upright to become fully established.
- 3 Large intravenous doses of propranolol or metoprolol attenuated, without abolishing, the rises in active renin, angiotensin II, and aldosterone; the attenuation was most evident soon after tilting and was largely overcome by 1 h upright. Inactive renin did not fall significantly after β -adrenoceptor blockade.
- 4 Intravenous frusemide caused immediate rises in plasma active, total and inactive renin, angiotensin II, and aldosterone, which then declined over 2 h despite increasing cumulative sodium losses.
- 5 Intravenous propranolol or metoprolol attenuated, without abolishing, these early increases in the components of the renin-angiotensin-aldosterone system after frusemide.
- 6 Prior oral metoprolol or propranolol, while significantly slowing the heart, did not limit the early rise in plasma angiotensin II following intravenous frusemide.
- 7 Thus in contrast to previous workers, we did not find that propranolol eliminated the response of the renin-angiotensin system to upright tilting; in part this difference appeared to be due to the longer tilt we employed.
- 8 Also in contrast to earlier work, we found attenuation by both intravenous propranolol and metoprolol of the immediate rise in renin after intravenous frusemide.

Introduction

Two powerful stimuli causing an increase in circulating concentrations of renin, angiotensin II and aldosterone are upright tilting (Brown *et al.*, 1966; Zanchetti *et al.*, 1976; Padfield & Morton, 1977) and the administration of frusemide (Fraser *et al.*, 1965; Meyer *et al.*, 1968; Davis, 1973; Konrads *et al.*, 1981). β -adrenergic receptor mechanisms are probably involved in both of these responses (Love *et al.*, 1971; Stella & Zanchetti, 1977). However, several aspects of the phenomena remain obscure.

It is controversial whether the initial increase in active renin, and hence in angiotensin II, on tilting or ambulation is accompanied by a fall in plasma inactive renin (Derkx *et al.*, 1976; Millar *et al.*, 1978; Rumpf *et al.*, 1978; Konrads *et al.*, 1981); and it is not

known if the increase in plasma aldosterone is solely or predominantly a consequence of the elevation of plasma angiotensin II, or whether other factors, such as a rise in plasma corticotrophin (Davies *et al.*, 1978; Morganti *et al.*, 1979) or plasma potassium (Sonkodi *et al.*, 1981) contribute. Not all workers have studied changes on return to the horizontal, and the time-course of several events at that stage remains to be clarified. Some authors have reported that propranolol completely abolishes the increase in plasma renin on tilting (Davies & Slater, 1976; Davies *et al.*, 1978; Morganti *et al.*, 1979), an observation which would imply dominance of the adrenergic control of renin secretion in these circumstances. However, others have not found this total suppression of the renin response (Viol *et al.*, 1976; Sonkodi *et al.*, 1978).

The initial rise in plasma renin following frusemide administration is known to be independent of ex-

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ternal sodium loss (Meyer *et al.*, 1968; Imbs *et al.*, 1977). Nevertheless, the magnitude of the early and late increases in renin, angiotensin II and aldosterone when frusemide is given remain incompletely defined, as do any changes which may occur in the proportions of circulating active and inactive renin (Weinberger *et al.*, 1977; Millar *et al.*, 1978; Rumpf *et al.*, 1978; Konrads *et al.*, 1981). Plasma renin-substrate does not change in the first 2 h after intravenous frusemide (Millar *et al.*, 1978). There is evidence that in man, β -adrenergic receptor blocking drugs can, at least partially, suppress the renin response to frusemide (Attman *et al.*, 1975). However, in the dog, Imbs *et al.* (1977) found that the immediate, in contrast to the late, rise in plasma renin activity was unaffected by propranolol administration. Thus more detailed information, especially on the early time-course of the effect of frusemide, and of the response of the different components of the system, is needed.

Considerable dispute continues concerning the extent to which the renin-suppressing property of β -adrenergic receptor blocking drugs contributes to their antihypertensive action (Bühler *et al.*, 1972, 1973; Robertson *et al.*, 1975; Leonetti *et al.*, 1975; Hollifield *et al.*, 1976; Birkenhäger *et al.*, 1977; Weber & Drayer, 1980). The potency of different β -adrenoceptor blockers in reducing plasma renin and hence angiotensin II in the face of stimuli such as tilting or frusemide is clearly relevant to these arguments.

In the present paper we have examined in detail the response of the renin-angiotensin-aldosterone system in normal subjects to upright tilting and to intravenous frusemide. We have also studied the modification of these responses induced by the non-selective β -adrenoceptor-blocker propranolol and by the predominantly cardioselective β -adrenoceptor blocker metoprolol.

Some parts of this work have been reported previously (Millar *et al.*, 1978; Sonkodi *et al.*, 1978, 1981).

Methods

Experiments were performed on normal volunteers, none of whom was receiving any medication. All were fully informed of the various procedures, which had been approved by the Ethical Supervisory Committee of the Western Infirmary, Glasgow.

Each experiment was supervised constantly; pulse rate was checked throughout and blood pressure was measured with a clinical sphygmomanometer, diastolic being recorded at the point of disappearance of arterial sounds. The volunteers were not permitted to sleep or smoke during any of the experiments.

Plasma samples were analysed for active (normal range 10–50 μ U/ml) and total (60–200 μ U/ml) renin concentrations using an antibody trapping technique

(Millar *et al.*, 1978, 1980); inactive renin concentration was derived by subtracting active from total. Plasma concentrations of angiotensin II (normal range 5–35 pg/ml) (Düsterdieck & McElwee, 1971; Morton *et al.*, 1976) and aldosterone (up to 18 ng/100 ml) (Fraser *et al.*, 1973) were measured by radio-immunoassay. Plasma cortisol was estimated by the method of Mason & Fraser (1975); plasma and urinary sodium, potassium and creatinine were estimated using automated techniques. Haematocrit was recorded in the second tilt experiment. Care was taken at blood sampling to avoid haemolysis or forearm muscular exercise, since these can both cause a spurious rise in plasma potassium concentration (Brown *et al.*, 1970).

Statistical comparisons were made by paired *t*-test after logarithmic transformation of the data and also by non-parametric methods. Significance values were similar with each of these techniques and those quoted are for the paired *t*-test. Only the paired *t*-test was performed in the second series of tilt experiments.

Experiments on tilting

First study Eight normal male volunteers, aged 20 to 37 years, and weighing 56–78 kg, participated (two other subjects who fainted on tilting were excluded from further consideration). Each experiment was conducted in an isolated room and started between 13.00 and 14.00 h, 1 h after the subject had eaten a light lunch.

The experimental protocol followed closely that of previous studies (Brown *et al.*, 1966; Love *et al.*, 1971; Morton *et al.*, 1976; Padfield & Morton, 1977). For the initial hour the subject lay horizontal on a mechanically-operated tilting table; this was then tilted head-up to 85° for 2 h, and finally returned to the horizontal for 1 h. Blood samples (maximum volume of each 35 ml) were taken from an arm vein 15 and 5 min before upright tilting; after 1 and 2 h of tilting; and 1 h after return to the horizontal. Pre-tilt values were obtained from the means of estimations on both basal samples.

Every subject participated in three experiments with at least 5 days between each, receiving in sequence an intravenous injection of propranolol (Imperial Chemical Industries Pharmaceutical Division) or metoprolol (Astra Chemicals), or an equal volume of 5% dextrose solution (control) immediately before tilting. The first four volunteers received 10 mg propranolol and 10 mg metoprolol, while the four others were given 20 mg of each drug. The dose was increased after little or no suppression of the rise in plasma angiotensin II had been seen in the first four studies; the increased dose was no more effective and data from all eight volunteers have therefore been analysed together (Table 1). The

various injections were randomly allocated for each subject, who was unaware which he was receiving on each occasion.

Second study This was performed so as to clarify the effects of β -adrenergic receptor blockade on the response of the renin-angiotensin-aldosterone-system in the initial hour of tilting, because the first study had shown little or no suppression at 1 and 2 h upright (Table 1). Five normal volunteers, aged 19–32 years, weighing 52–74 kg, and including two females, participated. Five other volunteers fainted and are excluded from consideration. Experiments on females were conducted in the first half of the menstrual cycle. The five volunteers received in random sequence 10 mg propranolol, 10 mg metoprolol or an equal volume of 5% dextrose intravenously. They were tilted upright for 1 h before being returned to the horizontal for 1 h. Blood samples during the tilt were drawn after 5, 15, 30 and 60 min upright, and 30 and 60 min after return to the horizontal (Figure 1). In all other respects the procedure was identical with that followed in the first tilt study.

Intravenous frusemide with and without prior intravenous β -adrenoceptor blockade

Seven normal male volunteers aged 20–21 years and weighing 60–84 kg, took part in this experiment. Each was studied on three occasions at intervals of no less than 1 week receiving in random sequence an intravenous injection of 10 mg propranolol, 10 mg metoprolol or an equivalent volume of 5% dextrose.

Experiments began between 08.00 h and 09.00 h when the fasted subject lay recumbent after emptying his bladder. At 40 and 45 min of recumbency, blood samples were drawn from a peripheral vein. Basal values are the means of estimates of these two samples. At 55 min the intravenous injection of β -adrenoceptor blocker or placebo was given as above, the subject being unaware of which drug was administered on each occasion. At 60 min the subject emptied his bladder again and was given water to drink equal to the volume of urine passed. Frusemide (Hoechst) 50 mg was then administered by intravenous bolus. Further urine samples were obtained 30, 60 and 120 min after frusemide administration, with an equivalent volume of water being replaced orally. Blood samples were taken 15, 30, 60 and 120 min after frusemide.

Urine flow rate, sodium and potassium excretion, and endogenous creatinine clearances, were determined for each of the periods in which urine was collected.

Intravenous frusemide with and without prior oral β -adrenoceptor blockade

Six normal male volunteers aged 22–34 years and

weighing 64–76 kg, participated. The experimental design was as for frusemide with intravenous β -adrenoceptor blockade as above, except that oral placebo, 100 mg metoprolol or 80 mg propranolol was given in random sequence 2 h before the injection of frusemide. Blood and urine samples were collected as before, but only angiotensin II, cortisol, electrolytes and creatinine were estimated in plasma.

Results

Tilt experiments

First study (Table 1)

(i) *Control tilt* Upright tilting after dextrose injection was accompanied by a significant rise in pulse rate and diastolic pressure and a slight but insignificant fall in systolic pressure. Plasma angiotensin II and aldosterone concentrations rose significantly. Plasma sodium concentration fell and plasma potassium concentration increased; these aspects are addressed in more detail elsewhere (Sonkodi *et al.*, 1981). When the subjects were restored to the horizontal position, all of these variables returned to values not significantly different from those before tilting.

(ii) *Tilt following propranolol or metoprolol* Only minor differences were observed between the effect of the two drugs, which are therefore considered together.

β -adrenoceptor blockade inhibited the normal rise in pulse rate on upright tilting. After return to the horizontal, heart rate was significantly slowed.

Systolic pressure fell on tilting with β -adrenoceptor blockade and, after return to recumbency, remained significantly lower than before the tilt.

The normal rise in diastolic pressure on tilting was not affected by either propranolol or metoprolol however, and the post-tilt diastolic pressures were similar to those before tilting and drug administration.

Neither propranolol nor metoprolol prevented the rise in plasma angiotensin II and aldosterone on tilting, and the levels achieved were not significantly lower than in the control tilt. Post-tilt values fell to pre-tilt levels with the exception of plasma aldosterone concentration following metoprolol, which remained significantly elevated.

Following β -adrenoceptor blockade, changes in plasma sodium and potassium levels occurred which were similar to those of control tilting, although the fall of plasma sodium did not achieve statistical significance after either drug and the rise in plasma potassium was significant only after propranolol.

Second study (Figure 1)

Changes in pulse rate, arterial pressure and plasma electrolytes on tilting with or without β -adrenergic

Figure 1 Second tilt study. Changes in plasma concentrations of active and inactive renin, angiotensin II and aldosterone on upright tilting for 1 h, followed by return to horizontal for 1 h. O = control; Δ = with propranolol; □ = with metoprolol. Means ± s.e. mean plotted. Significance in comparison with before tilt: * $P < 0.05$, ** $P < 0.02$, *** $P < 0.01$. Significance in comparison with control run: + $P < 0.05$, ++ $P < 0.02$, +++ $P < 0.01$.

receptor blockade were similar to those in the first study and are not therefore reported in detail. Haematocrit (%) rose from a basal mean ± s.e. mean of 44.0 ± 3.4 to 47.5 ± 3.4 at 30 min upright ($P < 0.05$) and to 47.0 ± 3.6 at 60 min ($P < 0.05$), falling again to 43.6 ± 3.4 1 h after return to recumbency.

In the control tilt, there were progressive parallel increases in plasma concentrations of active renin, angiotensin II and aldosterone. Total renin is not shown separately in Figure 1, but was significantly raised ($P < 0.05$) at 1 h upright. By contrast, the

plasma concentration of inactive renin fell in the control tilt, and this fall achieved conventional levels of statistical significance ($P < 0.05$) at 15 min. After return to the horizontal, active renin, angiotensin II and aldosterone fell towards pre-tilt values, although remaining slightly elevated up to 1 h later.

On tilting after β -adrenoceptor blockade, the increases in plasma active renin, angiotensin II and aldosterone, although distinct, were less marked than in the control run; however all achieved statistical significance by 1 h upright apart from that of active renin with prior propranolol. Total renin was also raised at 1 h ($P < 0.01$) after metoprolol. Inactive renin did not fall on tilting after either propranolol or metoprolol.

Studies with intravenous frusemide

Control experiments Intravenous frusemide caused the expected sharp increase in urine flow, creatinine clearance rate and in sodium and potassium excretion (Figure 2). These changes were most marked in the 30 min immediately after frusemide, subsiding thereafter. Plasma potassium was unchanged throughout, but plasma sodium fell significantly by 60 and 120 min after frusemide (139.9 ± 0.5 (s.e. mean) mmol/l basal; 138.7 ± 0.4 at 60 min and 137.8 ± 0.5 at 120 min; $P < 0.01$ for each). Heart rate and arterial pressure did not alter significantly up to 2 h after the frusemide injection.

Plasma concentrations of active renin, total renin, and angiotensin II increased promptly after frusemide. The greatest changes were at 15 min and 30 min following the injection, and values subsided towards the baseline thereafter, despite the increasing cumulative sodium and potassium deficits. Mean plasma inactive renin also increased, with the highest value at 30 min ($P < 0.05$). The increase in plasma aldosterone was significant by 15 min after frusemide administration, reaching a peak at 30 min. Plasma cortisol concentrations were unchanged throughout.

With intravenous β -adrenoceptor blockade When frusemide was given after the injection of propranolol or metoprolol, the increases in urine flow, creatinine clearance and in sodium and potassium excretion, were as in the control experiment (Figure 2). In contrast to frusemide given alone, when frusemide was given after β -adrenoceptor blockade, systolic blood pressure fell 1 and 2 h after the injection (with propranolol mean ± s.e. mean 119.9 ± 1.6 mmHg basal; 112.8 ± 2.4 at 60 min and 112.0 ± 3.0 at 120 min; with metoprolol, 120.4 ± 0.9 basal; 115.3 ± 2.5 at 60 min and 114.7 ± 2.8 at 120 min ($P < 0.01$ for all). Diastolic was not altered. Prior β -adrenoceptor blockade significantly reduced heart rate in comparison with the control experiments (means ± s.e. mean post-frusemide 64.2 ± 1.3 beats/min in the control study,

Figure 2 Intravenous frusemide without (○) and with intravenous propranolol (Δ) or metoprolol (□). Significant differences from pre-frusemide baselines indicated thus: * $P < 0.05$; ** $P < 0.01$; *** $P < 0.001$. β -adrenoceptor blockade did not affect frusemide diuresis but attenuated variously the increases of active, total and inactive renin, angiotensin II and aldosterone. Increases in aldosterone were not significant after propranolol or metoprolol. Not plotted is inactive renin, which was raised ($P < 0.05$) 30 min after frusemide in the control experiment, but was unchanged after β -adrenoceptor blockade. Means $\pm$ s.e. mean shown.

55.0 ± 1.3 after propranolol and 55.3 ± 1.1 after metoprolol; $P < 0.001$ for each).

The post-frusemide increases in active and total renin and in angiotensin II, showed a similar pattern to those seen in the placebo control study, but were diminished in magnitude. All the increases nevertheless achieved conventional levels of statistical significance apart from that of total renin after propranolol, of angiotensin II after metoprolol, and of inactive renin concentration after each of the β -adrenoceptor blockers.

The increases in mean plasma aldosterone after frusemide were not significant with prior propranolol or metoprolol. As in the control study, potassium and cortisol were unaltered throughout. Also, as in the control study, plasma sodium fell after frusemide (for propranolol mean $\pm$ 139.7 $\pm$ 0.7 s.e. mean mmol/l basal; 137.5 $\pm$ 0.5 at 2 h, $P < 0.02$; for metoprolol 141.3 $\pm$ 0.8 basal; 139.3 $\pm$ 0.5 at 1 h, $P < 0.02$ and 138.4 $\pm$ 0.6 at 2 h, $P < 0.01$).

With oral β -adrenoceptor blockade The pattern and magnitude of the increase in urine flow, creatinine clearance, and sodium and potassium excretion, both with and without prior oral β -adrenoceptor blockade, were virtually identical to those seen in the earlier studies of intravenous β -adrenoceptor blockade, and are therefore not reported in detail here. Plasma

potassium and cortisol also remained unchanged throughout in all studies, while plasma sodium fell slightly but significantly as before.

Arterial pressure was unaffected by either oral propranolol or oral metoprolol, but both drugs significantly reduced heart rate in comparison with placebo (Figure 3, $P < 0.001$).

Angiotensin II rose significantly in the control study with, as before, peak values 30 min after frusemide, falling towards the baseline by 2 h afterwards (Figure 3). The plasma angiotensin II increase was altered very little when frusemide was given following oral metoprolol or propranolol (Figure 3).

Discussion

In considering stimuli to renin release and their modification by adrenergic neurone blocking agents, it must be remembered that the renin-containing juxtaglomerular cells are basically highly specialised smooth muscle, innervated by autonomic nerves. As such these cells, and hence renin secretion, are likely to be governed by both pre- and post-synaptic α - and β -adrenoceptors (Brown *et al.*, 1979).

The present experiments on controlled upright tilting in normal subjects have shown that the early increase in active renin is accompanied by a slight but

Figure 3 Intravenous frusemide without (○) and with prior oral propranolol (Δ) and metoprolol (□). Heart rate, significantly reduced ($P < 0.001$) by both β -adrenoceptor blockers. In all three studies plasma angiotensin II was significantly elevated ($P < 0.05$ – $P < 0.001$) 15 and 30 min after frusemide. Means $\pm$ s.e. mean plotted.

significant fall in inactive renin. This contrasts with our earlier findings (Millar *et al.*, 1978), and with some other reports (Rumpf *et al.*, 1978; Konrads *et al.*, 1981), but is consistent with the paper by Derkx *et al.* (1976), which we have criticised (Millar *et al.*, 1978) because of the unorthodox statistical treatment of the results. The present method of measurement of inactive renin, which is a derived value, involves the combined errors of measurement of both active and total renin. The low order of significance ($P < 0.05$) of our present findings emphasises the desirability of further confirmation of this fall in inactive renin on tilting. The issue is important, because the evidence indicates activation of inactive renin as at least part of the acute response to the stimulus of orthostasis. Moreover, the abolition of a fall in inactive renin by β -adrenoceptor blockade would implicate β -adrenergic nerves in renin activation.

The slower response of plasma aldosterone than of renin and angiotensin II to tilting is to be expected if the rise in aldosterone is angiotensin II-dependent. The sustained elevation of aldosterone after return to the horizontal is consistent with a contribution to the stimulation of aldosterone secretion by increases in corticotrophin (Morganti *et al.*, 1979) and plasma potassium (Sonkodi *et al.*, 1981). Little is known of the time-course of any increases in corticotrophin, but plasma potassium falls more slowly than does renin after assuming recumbency (Sonkodi *et al.*, 1981). Moreover, hepatic and renal blood flow are reduced by tilting, and these changes (especially the former) diminish the metabolic clearance rate of aldosterone (see Balikian *et al.*, 1968).

Our present findings confirm earlier work suggesting that propranolol and metoprolol have similar suppressive effects on the renin response to tilting (Viol *et al.*, 1976). Any minor differences between the two drugs observed here probably relate to differences in the effective dose than to more fundamental variations in their mode of action, although Attman *et al.* (1975) considered they were equipotent, weight for weight, in blocking β_1 -adrenoceptors. The β_1 -adrenoceptor thus seems important in mediating the adrenergic component of the rise in active renin on tilting.

In contrast to the findings of Davies & Slater (1976), Davies *et al.* (1978) and of Morganti *et al.* (1979), we did not find that propranolol completely abolished the increase in renin on tilting, despite the greater doses of propranolol we employed. Nevertheless, our findings do not conflict with theirs in all respects; in particular we employed a more prolonged upright tilt, and it is apparent from the present work that the changes in the renin-angiotensin-aldosterone system take up to 1 h to become fully developed. However, some reinterpretation of their conclusions is needed. It is interesting that we found with β -adrenoceptor-blockade that the aldosterone response to orthostasis was delayed, in parallel with the delayed rise in angiotensin II, strongly suggesting a causative relationship. While we agree with Morganti *et al.* (1979) that a rise in corticotrophin may be important in reinforcing the elevation in plasma aldosterone on tilting following propranolol, the increase in angiotensin II still must contribute during prolonged orthostasis, as must also the rise in plasma potassium, and falls in hepatic and renal clearances.

The importance of an immediate and very marked, stimulant effect on the renin-angiotensin system when administering intravenous frusemide (Meyer *et al.*, 1968; Imbs *et al.*, 1977; Konrads *et al.*, 1981) was confirmed in the present studies. At 1 and 2 h after frusemide injection, the increased plasma concentrations of active and total renin, angiotensin II and aldosterone were already declining, despite increasing cumulative deficits of sodium and potassium, both

of which would tend to enhance renin secretion (Brown *et al.*, 1963; Brunner *et al.*, 1970). The immediate response is clearly independent of such electrolyte losses (Meyer *et al.*, 1968; Imbs *et al.*, 1977). The initial increase consists mainly of a rise in the concentration of active renin; mean plasma inactive renin concentration rose only slightly after frusemide.

We found that both propranolol and metoprolol attenuated, without abolishing, the early response of the renin-angiotensin system to frusemide. This finding agrees with earlier work in man (Attman *et al.*, 1975) indicating that the β_1 -adrenoceptor is important for the rise in renin when frusemide is given. However, Attman *et al.* (1975) took their first blood sample for renin assay 1 h after frusemide, at a time when renin would already be declining. In the anaesthetised dog, Imbs *et al.* (1977) did examine the immediate renin peak after frusemide but, rather differently from the present results, they saw no attenuation following propranolol.

Plasma aldosterone did not, in the present study, rise significantly after β -adrenergic receptor blockade, emphasising that the immediate rise of aldosterone with intravenous frusemide is dependent upon angiotensin II.

Thus β -adrenergic receptor blockade diminishes, but by no means abolishes, the rise in plasma renin and angiotensin II on upright tilting or frusemide injection. Our results are in accord with the proposal by Davis (1973) that the renal nerves probably modulate renin release but are not essential for hypersecretion of renin to occur. These aspects need to be considered in any arguments on the role of renin suppression in the antihypertensive effect of β -adrenergic receptor blockade.

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