Relationship between plasma renin and cortisol in hypertensive patients

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Summary
1. Plasma cortisol at 08.00 hours was significantly higher ($P < 0.005$) in patients with high-renin essential or renovascular hypertension ($22.6 \pm 1.6 \mu g/100 \text{ ml}$) than in patients with normal-renin ($15.4 \pm 1.2$) or low-renin ($11.9 \pm 1.2$) forms of hypertension.

2. Plasma cortisol at 12.00 or 16.00 hours did not differ significantly among the three groups; thus the diurnal swing in plasma cortisol was steepest in patients with high plasma renin.

3. Among all patients studied, there was a direct relationship between 08.00 hours plasma cortisol and ambulatory plasma renin activity ($r = 0.65, P < 0.001$).

4. In patients with high-renin values, 08.00 hours plasma cortisol fell by $39 \pm 6\%$ after 10 days treatment with the converting enzyme inhibitor captopril. No consistent decreases were observed in the normal- or low-renin groups.

5. We conclude that the renin-angiotensin system may interact with the pituitary-adrenal axis to influence circulating levels of cortisol. This effect might conceivably contribute to the pathogenesis of certain high-renin states.

Key words: adrenocorticotropic, angiotensin, cortisol, diurnal rhythm, renin.

Introduction
The renin–angiotensin system is a major regulator of aldosterone secretion [1], and its predominant role, at least in humans and dogs, has been confirmed by studies employing specific inhibitors of the system [2–4]. The steroidogenic and trophic effects of angiotensin II are generally thought to be confined to the zona glomerulosa in intact animals. However, the octapeptide hormone does have the potential to influence fasciculata–reticularis function, since it is able to stimulate cortisol production by isolated adrenal slices [5] and in hypophysectomized dogs [6]. An early study suggested that cortisol secretion might be stimulated by very high rates of angiotensin infusion in intact humans [7], but prolonged infusion at rates that produce angiotensin levels encountered in most physiological or pathological states does not appear to do so [8]. It has been hypothesized that the inability of angiotensin to sustain increased secretion of corticosteroids (other than aldosterone) in vivo may be due to glucocorticoid feedback inhibition of ACTH release [9]. Nonetheless, it has been shown that administration of an angiotensin antagonist lowers cortisol secretion in dogs with chronic thoracic caval constriction [10], a model with high plasma renin and angiotensin levels.

In the present study we demonstrate that there are differences in the diurnal pattern of plasma cortisol among patients with essential and secondary forms of hypertension, and that these differences appear to be related to the level of activity of the renin–angiotensin system.

Methods
Thirty-six hypertensive patients, off all antihypertensive drugs for 2 weeks or longer, were admitted to a metabolic balance ward and placed on an isocaloric diet containing 100 mmol of sodium and 60 mmol of potassium/day. After 4–6 days on this diet, blood was collected into EDTA at 08.00 hours in the supine position after overnight recumbency, and at 12.00 hours after ambulation for at least 90 min. An additional sample was obtained at 16.00 hours (random posture) in 25 of these subjects. Plasma was
analysed for renin activity, aldosterone and cortisol ([125]I)cortisol RIA Kit, Diagnostic Products Corp., CA, U.S.A.) by established methods [11-12]. Patients were divided into subgroups by comparing the 12.00 hours ambulatory plasma renin activity (PRA) with the concurrent daily sodium excretion [13]. By this method, 12 patients had low-renin hypertension (eight essential, four primary aldosteronism), 12 had normal-renin hypertension (all essential) and 12 had high-renin hypertension (four essential, eight renovascular).

Twenty-eight of these patients were subsequently treated with the angiotensin-converting enzyme inhibitor captopril. The initial dose was 100 mg/day (in four divided doses) and this was increased over a 3 day period to a dose that maintained diastolic blood pressure at less than 95 mmHg or until a maximum of 450 mg/day was reached (range 200-450 mg/day). Blood sampling for hormonal measurements was repeated on the fifth and tenth days of treatment.

Data were analysed by paired and unpaired Student's t-test and by the method of least squares. Non-parametric statistical tests were applied for confirmation.

**Results**

In patients with normal-renin essential hypertension, plasma cortisol at 08.00 hours averaged 15.4 ± (SE) 1.2 μg/100 ml. As a group, patients with low-renin hypertension had a significantly lower value (11.9 ± 1.2 μg/100 ml, P < 0.05). In contrast, 08.00 hours plasma cortisol was significantly greater (P < 0.005) among patients with high-renin essential (21.5 ± 1.6) or renovascular (23.2 ± 2.2) hypertension. Among all 36 patients there was a highly significant relationship (r = 0.65, P < 0.001) between 08.00 hours plasma cortisol and the log of the ambulatory PRA (Fig. 1); a correlation was also found between cortisol and the simultaneously measured supine PRA (r = 0.60, P < 0.001).

At 12.00 hours, plasma cortisol averaged 15.0 ± 1.2, 12.9 ± 1.4 and 10.4 ± 1.0 μg/100 ml in the high-, normal- and low-renin groups respectively. These were not significantly different, nor were the levels found at 16.00 hours (8.8 ± 0-8, 8.4 ± 0-8 and 8.3 ± 0.5 μg/100 ml respectively). Thus the diurnal swing in plasma cortisol was steepest in patients with high-renin levels and flattest in patients with low-renin levels.

Treatment with captopril was associated with a consistent fall in 08.00 hours plasma cortisol in 11 of 12 high-renin patients studied. In one patient with renal artery stenosis 08.00 hours cortisol fell from 27 to 13 μg/100 ml after 5 days of treatment, but by the tenth day rose to 65 μg/100 ml; the latter value was associated with relative hypotension during this period (blood pressure 100-110/60-70 mmHg) and may have represented a stress response. Among the remaining 11 high-renin patients, 08.00 hours cortisol fell from 22.6 ± 1.6 to 15.7 ± 1.5 after 5 days and to 13.8 ± 1.0 after 10 days' treatment (P < 0.005). No significant changes were observed in 12.00 or 16.00 hours plasma cortisol. A slight fall in 08.00 hours cortisol was observed in nine patients with normal-renin levels only on the fifth day (12.2 ± 1.1 vs 14.8 ± 1.6 μg/100 ml, P < 0.05) and no consistent fall in cortisol was noted in seven patients with low-renin levels.

**Discussion**

This study has described, for the first time, a relationship between endogenous levels of plasma renin and cortisol. The wide range of renin levels present in the human hypertensive population provides a useful, albeit indirect, model to examine the long-term effects of angiotensin II. We have found that patients with high-renin levels have, on average, higher plasma cortisol levels in the early morning hours and, consequently, a steeper diurnal fall in plasma cortisol, compared with patients with normal or low PRA. The direct relationship between 08.00
hours plasma cortisol and PRA, and the fall in cortisol observed during converting enzyme inhibition, provide additional evidence that these differences are related specifically to differences in circulating angiotensin II. Although administration of exogenous angiotensin to man does not consistently increase plasma cortisol [7, 8, 14], it is possible that the relationship we have observed depends on sustained, long-term differences in plasma angiotensin that cannot be mimicked by infusion studies.

The renin–angiotensin system could potentially influence plasma cortisol levels by affecting either secretion or metabolism of the steroid. The fact that renin-related differences in cortisol were observed only at 08.00 hours argues against a primary effect on metabolic clearance rate. Moreover, it is unlikely that reduced clearance alone could sustain increases in circulating cortisol if negative feedback at the hypothalamus–pituitary level were intact. Similar arguments could be made against explaining our findings by a direct steroidogenic action of angiotensin on the inner zones of the adrenal cortex. In fact, the idea that compensatory decreases in ACTH might mask such an action of angiotensin II [9] has recently received experimental confirmation in man [15, 16].

It is also possible that angiotensin II could influence the pituitary–adrenal axis at other levels. There is evidence that angiotensin increases the production of a putative corticotrophin-releasing hormone by the isolated rat hypothalamus [17], and infusion of the octapeptide into intact dogs has been reported to cause parallel increases in 11-hydroxy corticosteroids and immunoreactive ACTH [18]. Conflicting results have been reported in human studies, perhaps related to differences in study design or in the method used to estimate ACTH. Rayyis & Horton [19] reported that pressor doses of angiotensin II significantly increase immunoreactive ACTH, but this was accompanied by a fall, rather than an increase, in plasma cortisol; they postulated, in fact, that the rise in ACTH may have been secondary to angiotensin-induced inhibition of cortisol secretion [19]. In contrast, Semple and co-workers found that acute angiotensin infusion reduces plasma ACTH as measured by bioassay [16]. It is difficult to reconcile these conflicting results with the present findings, but again it is important to consider the possible differences between the effects of acute infusions and those of sustained increases in endogenously produced angiotensin. A final possibility is that angiotensin II, rather than acting directly to stimulate either ACTH release or steroidogenesis, may in some undefined manner enhance the responsiveness of the fasciculata–reticularis to the steroidogenic actions of ACTH. This might result in a preferential increase in cortisol secretion in the early morning hours, which would fit well with the present observations and which might also be compatible with the study in dogs described above [10].

Whatever the mechanisms involved, the present findings suggest that the renin–angiotensin system may interact with the hypothalamus–pituitary–adrenal axis to produce a subtle alteration in circulating cortisol levels. It is possible that the differences in plasma cortisol in the hypertensive population are of biological significance and thus may contribute to the pathogenesis of conditions associated with hypersecretion of renin, such as malignant, renovascular and some cases of essential hypertension.

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References


