The Substitutive Role of ACTH in Supporting Aldosterone Response to Head-up Tilt During Acute Renin Suppression in Patients with Essential Hypertension

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SUMMARY The relative contribution of the renin-angiotensin system, adenocorticotrophic hormone (ACTH) and plasma electrolytes in the response of plasma aldosterone to 30 minutes of 65° head-up tilt was assessed in 10 essential hypertensive patients. Studies were carried out before and during acute blockade of renin release by propranolol, ACTH suppression by dexamethasone and combined renin and ACTH blockade.

In control studies orthostasis induced significant increases only in plasma renin activity and aldosterone. In contrast, when the renin response to tilt was acutely suppressed by propranolol administration, the aldosterone response was nonetheless maintained but now appeared to be under ACTH control, since concurrent increases in cortisol were observed. During ACTH suppression aldosterone increased during tilt and so did renin. However, during combined ACTH and renin blockade aldosterone failed to increase during tilt.

These studies suggest that the aldosterone secretory response to head-up tilt is normally mediated by the renin-angiotensin system but, when the renin response is suppressed, an ACTH response is elicited which assumes a backup role. However, when these two systems are blocked other factors appear unable to respond during tilt to support a normal aldosterone response. (Hypertension 1: 130-135, 1979)

KEY WORDS • renin-angiotensin system • adenocorticotrophic hormone • renin suppression • essential hypertension • aldosterone response • head-up tilt

ALDOSTERONE secretion has been shown to be regulated in man by angiotensin II,1,2 adenocorticotrophic hormone (ACTH),3 and potassium.4 However, the relative contribution of these mechanisms in controlling aldosterone homeostasis under various experimental and physiological conditions has not been fully defined. For instance, the increase in aldosterone that occurs during assumption of upright posture5,6 is reportedly due to concurrent increases in renin secretion5,6 and thus in circulating AII.7 However, assumption of the upright position has also been reported to reduce the metabolic clearance rate of aldosterone by as much as 50%,10 and to increase plasma potassium.11

The venous pooling associated with upright posture might be considered to be a stimulus not unlike hemorrhage, which is reported to cause greater increases in aldosterone in intact than in hypophysectomized dogs12 suggesting that ACTH may be involved in such responses. Also the observation that aldosterone increased in some anephric patients after standing, in the absence of changes in serum potassium and cortisol,13 raised the possibility that unidentified mechanisms may participate in the response. Thus, available evidence suggests that several factors may interact in controlling the aldosterone response to upright posture.

The present study was designed to dissect the contributions of these factors by studying the effect of head-up tilt during acute blockade of renin release both before and during ACTH suppression. Although head-up tilt and upright posture are not equivalent stimuli, the former has been frequently used to investigate the responses of renin and aldosterone to orthostatic stress.7,14,15,27 This maneuver offers the advantage of being standardized and it has been shown that above 60° its hydrostatic effects are the same as those of the erect position.18
Methods

Patients

Ten hospitalized patients with essential hypertension, six women and four men (six white and four black) aged 31–58 years, were included in the study, which was conducted with the approval of the committee of Human Rights in Research.

Patients with secondary causes of hypertension were excluded. All patients were free of any other associated disease or any complication related to hypertension and unless otherwise specified, ingested constant sodium (100 mEq/day) and potassium (60 mEq/day) intakes. None of them received antihypertensive treatment for at least 2 weeks before this study.

Protocol

Studies were always performed between 8 a.m. and noon. Patients were placed in the supine position in a quiet room. An ECG was continuously recorded and a slow intravenous infusion of 0.9% NaCl solution was set up. The total volume of saline infused through the studies was equal to that of collected blood.

After 60 minutes supine baseline sphygmomanometric arterial pressure (at least five readings) was recorded and baseline blood samples for renin activity, aldosterone, cortisol, sodium and potassium determinations were collected.

The patients were then tilted over the next 30 seconds, at a constant rate, to a 65° head-up position. All of them had been earlier familiarized with this maneuver.

Blood samples were again collected after 15 and 30 minutes of tilt; blood pressure was recorded every 2 minutes during tilt.

Patients were then returned to the supine position for 60 minutes after which another set of blood samples was collected. Thereafter 0.12 mg/kg of propranolol HCl were infused over 5 minutes and blood was again collected 15 minutes after the beginning of the infusion and this moment was considered the new baseline. The patients were again tilted and blood again collected after 15 and 30 minutes. After at least 5 days, the same protocol was repeated except that the patients were pretreated for 2 days with 0.5 mg of dexamethasone every 6 hours.

Laboratory Methods

Blood for renin activity and aldosterone determinations was collected in K$_2$ EDTA Vacutainers (Becton-Dickinson, Clarkson, Ontario) and processed at room temperature to avoid inadvertent activation of prorenin. Plasma renin activity was determined by radioimmunoassay of angiotensin I after incubation of plasma in presence of angiotensinase inhibitors according to Sealey and Laragh, the lower limit of sensitivity of this method is 0.15 ng/ml/hr. Plasma aldosterone was measured by radioimmunoassay according to Bühler et al. using antibodies provided by Dr. John McKenzie. Because of the high specificity of these antibodies the celite column chromatography step was not required. The lower limit of sensitivity of this method is 0.35 ng%. Blood for cortisol determination was collected in heparinized Vacutainers and plasma cortisol was measured by radioimmunoassay using a commercial kit (Diagnostic Product Corporation). This method requires no heat denaturation, organic solvent extraction or chromatography to isolate circulating blood cortisol prior to radioassay. Serum sodium and potassium determinations were performed by flame photometry.

All results are expressed as mean ± standard error of the mean. Statistical significance was tested by the Student $t$ and Spearman tests for paired data, each subject serving as his own control.

Results

Effects of Tilt Before and During $\beta$-Blockade

Six of the patients were included in these studies. Two of them were ingesting 300 mEq/day sodium, while the others were maintained on 100 mEq/day. In control studies (left panel, fig. 1) mean supine plasma renin activity was 2.2 ± 0.6 ng/ml/hr, plasma aldosterone 10.9 ± 1.8 ng%, plasma cortisol 8.7 ± 1.3 μg%. Serum sodium and potassium were 135.7 ± 1.5 and 3.7 ± 0.2 mEq/l, respectively.

During tilt mean blood pressure was unchanged. Plasma renin activity increased by 1.3 ± 0.7 (47 ± 12%) and 1.8 ± 0.9 (71 ± 13%) ng/ml/hr after 15 and 30 minutes of tilt ($p < 0.05$ for both), plasma aldosterone increased by 7.9 ± 1.8 ng% (72 ± 12%) and 18 ± 3.8 ng% (163 ± 20%), $p < 0.01$ for both, while insignificant increases in plasma cortisol of 1.1 ± 0.3 μg% (13 ± 3%) and 3.0 ± 1.7 μg% (36 ± 19%) were observed. Serum sodium and potassium did not change.

After 60 minutes in the supine position, all the parameters returned to the pretilt levels (right panel, fig. 1) and propranolol was infused. Fifteen minutes later a slight, but not significant, increase in mean blood pressure was observed. Plasma renin activity fell from 2.1 ± 0.8 to 1.7 ± 0.7 ng/ml/hr ($p < 0.05$), while plasma aldosterone, plasma cortisol and serum sodium and potassium were unchanged. During the subsequent tilt, mean blood pressure was unchanged until the last 10 minutes when a slight, but insignificant, fall was observed. The response of plasma renin activity was completely abolished. In contrast, plasma aldosterone increased by 6.1 ± 2.3 ng% (67 ± 22%) and 13 ± 3.6 ng% (174 ± 70%) at 15 and 30 minutes, respectively, $p < 0.05$ for both. This time, plasma cortisol also increased by 3.5 ± 0.7 μg% (47 ± 12%) and 10.8 ± 2.7 μg% (160 ± 53%), $p < 0.01$ for both. While the absolute and percent increases in plasma aldosterone were not different from those observed before propranolol, the increments in plasma cortisol were significantly higher ($p < 0.05$ for the 15- and 30-minute determinations). Moreover the percent
Changes in plasma aldosterone and plasma cortisol were significantly correlated ($r = 0.75$, $p < 0.01$). Again serum sodium and potassium did not change significantly.

Effects of Tilt Before and During ACTH Blockade

Six patients were included in these studies and their baseline data and the responses to tilt (left panel, fig. 2) were quite similar to those of the patients illustrated in figure 1.

During ACTH suppression supine mean blood pressure was slightly lower, plasma renin activity was unchanged ($1.8 \pm 0.4 \text{ ng/ml/hr}$) while plasma aldosterone was $54 \pm 4\%$ lower, $4.7 \pm 0.6 \text{ ng}\%$ ($p < 0.01$); plasma cortisol was reduced by $94 \pm 2.2\%$ to almost undetectable levels ($0.45 \pm 0.14 \text{ \mu g}\%$). Serum sodium and potassium were unchanged, $133.5 \pm 2.1$ and $3.7 \pm 0.2 \text{ mEq/liter}$, respectively.

During tilt (right panel, fig. 2) plasma renin activity increased by $1.4 \pm 0.6 \text{ ng/ml/hr}$ ($74 \pm 30\%$) and $2.9 \pm 1.5 \text{ ng/ml/hr}$ ($151 \pm 66\%$), $p < 0.05$ for both and plasma aldosterone by $4.3 \pm 2.4 \text{ ng}\%$ ($106 \pm 50\%$) and $16.8 \pm 5.4 \text{ ng}\%$ ($414 \pm 129\%$), $p < 0.05$ for the 30-minute determination. Although the mean percent increments in renin and aldosterone were higher than in control studies the differences were not significant. Cortisol remained suppressed and serum electrolytes did not change during tilt.

Effects of Tilt During Combined $\beta$- and ACTH Blockade

Four patients were studied during combined ACTH and renin blockade. Their control studies during ACTH suppression alone are illustrated in figure 3, left panel. After propranolol infusion, plasma renin activity decreased slightly from $1.2 \pm 0.3$ to $1.0 \pm 0.3 \text{ ng/ml/hr}$. During the subsequent tilt no increase in renin or cortisol were observed and serum sodium and potassium remained unchanged. This time there was no significant increase in aldosterone either at 15 or 30 minutes.
Discussion

These studies suggest that, under normal conditions, a renin-mediated increase in angiotensin II is the most important factor controlling the aldosterone response to head-up tilt. This conclusion is supported by the concurrent responses of renin and aldosterone, by the absence of significant changes in plasma cortisol and serum electrolytes during 30 minutes of tilt and by the lack of any response in aldosterone during combined ACTH and renin blockade.

Unlike studies of the effect of upright posture, we observed no change in serum potassium during head-up tilt. This difference may be due to more active muscle contraction during upright posture, which is reported to increase serum potassium. It is unlikely that a reduction in the metabolic clearance rate of aldosterone during tilt affected the aldosterone response, since plasma aldosterone was almost unchanged by tilt during combined renin and ACTH blockade (right panel, fig. 3).

Some controversy remains over whether the renin-angiotensin system is required to support the increased aldosterone secretion that occurs in response to upright posture since, in contrast with most reports, Mitra et al. reported posturally induced increases in aldosterone in anephric patients. Our results indicate that plasma aldosterone can increase normally during tilt even when the renin-angiotensin system is made unresponsive by acute beta-blockade; under these circumstances, orthostatic stress appears to evoke an increase in ACTH, reflected by increased cortisol levels, which appears able to replace angiotensin in stimulating aldosterone secretion.

These increases in plasma cortisol during beta-blockade are of interest. They were not merely the result of a direct effect of propranolol on cortisol secretion and/or metabolism since cortisol did not change during tilt after dexamethasone pretreatment (right panel, fig. 3); also, it seems unlikely that the

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**Figure 2.** Effects of tilt before and during ACTH blockade. The left panel shows the control studies, the right panel the studies after 2 days of treatment with dexamethasone 0.5 mg every 6 hours. The statistically significant decrease in plasma aldosterone and plasma cortisol in supine position after dexamethasone refers to the pre-dexamethasone supine values. Broken lines and asterisks as in figure 1.
lack of angiotensin II formation per se might have evoked the ACTH response, since angiotensin II has been reported to increase ACTH activity. In four of six patients there was a slight fall in blood pressure during the last 10 minutes of tilt on propranolol; however, it is unlikely that this mild hemodynamic stress or that of coping with upright posture without an active renin-angiotensin system were the only factors that caused an increase in ACTH, since in studies of converting enzyme inhibition by Sancho et al. plasma aldosterone failed to increase in response to tilt even in sodium-depleted normal subjects who fainted. One possible explanation is that propranolol might have interfered with the mechanisms that regulate the secretion of corticotrophin-releasing hormone in the central nervous system. Two observations support this hypothesis: 1) propranolol is a highly lipid-soluble drug and can rapidly achieve partition between brain and plasma; 2) acute infusion of propranolol has been shown to enhance the methylamphetamine-induced corticosteroid secretion in man. Thus, it appears that the response of the ACTH-cortisol system to orthostasis is amplified by acute β-blockade; if this phenomenon occurs even during chronic β-blockade, changes in ACTH activity might be responsible for the apparent dissociation between renin and aldosterone reported in normal subjects and in some hypertensive patients treated with oral propranolol.

Our results also indicate that the fall in supine plasma aldosterone levels after 2 days of treatment with dexamethasone were entirely dependent upon the suppression of ACTH activity since they occurred in the absence of significant modifications in plasma renin activity or serum electrolytes. Although we cannot exclude a direct inhibiting effect of dexamethasone on aldosterone biosynthesis or release, this seems unlikely since it has been shown that dexamethasone does not interfere with aldosterone synthesis in vitro. In addition, in four of the six patients, the responses of aldosterone to tilt during dexamethasone treatment were, in percent, even higher than in control studies, suggesting that after short-term ACTH suppression aldosterone responsiveness to posturally induced angiotensin stimulation was unaltered.

Our final important observation is that during combined ACTH suppression and β-blockade plasma aldosterone did not change significantly during tilt. Thus the responses of plasma aldosterone and cortisol during β-blockade alone were very likely dependent on ACTH stimulation. In addition, it appears that when the renin-angiotensin system and ACTH responses are both blocked during tilt, the aldosterone response is also blocked; accordingly, only these two factors appear able to participate in mediating the increases in aldosterone secretion during tilt.
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