Oral hydrocortisone increases blood pressure and enhances pressor responsiveness in normal human subjects. We studied the effects of 1 week of oral hydrocortisone (200 mg/day) on blood pressure, cardiac output, total peripheral resistance, forearm vascular resistance, and norepinephrine spillover to plasma in eight healthy male volunteers. Although diastolic blood pressure remained unchanged, systolic blood pressure increased from 119 to 135 mm Hg (SED±3.4, p<0.01), associated with an increased cardiac output (5.85-7.73 l/min, SED±0.46, p<0.01). Total peripheral vascular resistance fell from 15.1 to 12.2 mm Hg/l/min (SED±1.03, p<0.05). Resting forearm vascular resistance remained unchanged, but the reflex response to the cold pressor test was accentuated, the rise in resistance increasing from 10.5 mm Hg/ml/100 ml/min (R units) before treatment to 32.6 R units after treatment (SED±6.4, p<0.025). The rise in forearm vascular resistance accompanying intra-arterial norepinephrine (25, 50, and 100 ng/min) was also significantly greater after hydrocortisone, increasing from an average of 14.9±2.4 R units before treatment to 35.1±5.5 R units after hydrocortisone (SED±6.0, p<0.05). A shift to the left in the dose–response relation and fall in threshold suggested increased sensitivity to norepinephrine after treatment. Measurement of resting norepinephrine spillover rate to plasma and norepinephrine uptake indicated that overall resting sympathetic nervous system activity was not increased. The rise in resting blood pressure with hydrocortisone is associated with an increased cardiac output (presumably due to increased blood volume). The increased responsiveness of the peripheral vasculature to reflux pressor stimuli appears to be due to changes in end-organ responsiveness since similar changes occurred with local administration of norepinephrine. (Hypertension 1989; 13:416–421)
By guest on May 4, 2017

Hydrocortisone-Induced Hypertension in Humans

Endogenous plasma norepinephrine was assayed by radioenzymatic assay. Plasma \([\text{H}]\text{NA}\) was extracted on alumina and assayed by liquid scintillation counting. Interference from dihydroxy metabolites of \([\text{H}]\text{NA}\) was less than 5%. Under steady-state conditions (plateau plasma concentration of tracer), total body and forearm norepinephrine clearance and spillover were calculated from the following relations:

\[
\text{NA clearance (whole body)} = \frac{\text{infusion rate } [\text{H}]\text{NA}}{\text{plasma } [\text{H}]\text{NA concentration}}
\]

\[
\text{NA spillover (whole body)} = \frac{\text{infusion rate } [\text{H}]\text{NA}}{\text{plasma NA specific radioactivity}}
\]

\[
\text{NA fractional extraction (e) (forearm)} = \frac{(\text{arterial } [\text{H}]\text{NA}) - (\text{venous } [\text{H}]\text{NA})}{(\text{arterial } [\text{H}]\text{NA})}
\]

\[
\text{NA spillover (forearm)} = (N_A - N_v) + N_A \cdot e \cdot PF
\]

where \(N_A\) and \(N_v\) represent venous and arterial plasma norepinephrine concentrations, \(e\) the fractional extraction of \([\text{H}]\text{NA}\) across the forearm, and \(PF\) the forearm plasma flow.

Resting forearm blood flow was measured on the side with the arterial and venous catheters, using strain-gauge plethysmography (SPG-16, Medasonic, Mountain View, California). Cold pressor stimulation was produced by application of ice to the base of the neck on the ipsilateral side for 60 seconds, and forearm blood flow was measured again. Next, norepinephrine was infused into the brachial artery in three successive doses at rates of 25, 50, and 100 ng/min each for 2 minutes. Forearm blood flow was measured at each dose. Forearm vascular resistance (FVR) was calculated from the equation:

\[
\text{FVR} = \frac{\text{mean arterial pressure (mm Hg) \ units, R)}}{\text{forearm blood flow (ml/100 ml/min)}}
\]

After the testing of pressor responses, desipramine hydrochloride was infused intravenously in a dose of 1 mg/kg body wt over a period of 30 minutes to evaluate neuronal norepinephrine uptake. Arterial and venous sampling were performed immediately after the desipramine infusion, for plasma \([\text{H}]\text{NA}\) assay, and extraction of norepinephrine across the forearm was calculated as above. Neuronal norepinephrine uptake is estimated from the fall in extraction produced by desipramine. The extraction that remains is attributable to extra-neuronal uptake.

Drug Therapy and Repeat Testing

Subjects were given hydrocortisone hemisuccinate (or placebo) 50 mg q.i.d. for 6 days. All procedures were repeated 1 week later.
**TABLE 1. Resting Hemodynamic Changes With Hydrocortisone**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Pre-F</th>
<th>Post-F</th>
<th>SED</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Body wt (kg)</td>
<td>76.0</td>
<td>77.1</td>
<td>0.22</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Resting SBP (mm Hg)</td>
<td>119</td>
<td>135</td>
<td>3.4</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Resting DBP (mm Hg)</td>
<td>70</td>
<td>71</td>
<td>4.6</td>
<td>NS</td>
</tr>
<tr>
<td>Mean amb. SBP (mm Hg)</td>
<td>124</td>
<td>136</td>
<td>2.22</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Mean amb. DBP (mm Hg)</td>
<td>69</td>
<td>75</td>
<td>3.61</td>
<td>NS</td>
</tr>
<tr>
<td>Supine CO (l/min)</td>
<td>5.85</td>
<td>7.73</td>
<td>0.46</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>TPR (mm Hg/l/min)</td>
<td>15.1</td>
<td>12.2</td>
<td>1.03</td>
<td>&lt;0.05</td>
</tr>
</tbody>
</table>

F, hydrocortisone; SBP, systolic blood pressure; DBP, diastolic blood pressure; NS, not significant; amb., ambulatory; CO, cardiac output; TPR, total peripheral resistance. SED = Standard error of the difference.

**Statistical Analysis**

Paired comparisons were made using Student’s t test for paired observations, with significance at p < 0.05. Resistance changes with the intra-arterial infusions were analyzed using analysis of variance and appropriate partitioning. Values are expressed as mean±SED, which is the standard error of the difference between two means in paired comparisons.

**Results**

**Resting Hemodynamic Measurements**

With F therapy, as shown in Table 1, body weight increased in every subject from an average of 76.0–77.1 kg (SED±0.22, p < 0.01). Resting “clinic” systolic pressure increased from 119 to 135 mm Hg (SED±3.4, p < 0.01), while clinic diastolic pressures did not alter significantly. Twenty-four-hour ambulatory blood pressure recordings showed a similar pattern. Resting supine cardiac output increased from 5.85 to 7.73 l/min (SED±0.46, p < 0.01). Total peripheral resistance fell from 15.1 to 12.2 mm Hg/l/min (SED±1.03, p < 0.05). F therapy did not alter resting forearm vascular resistance.

**Plasma and Urinary Changes**

There was a small increase in serum sodium, a small fall in serum potassium, a 4% drop in hematocrit, a rise in blood glucose, more than a doubling of serum F, and a marked fall in plasma renin activity (Table 2). Serum creatinine remained unchanged. Urine sodium and potassium concentrations fell, while urinary volume did not alter significantly. Creatinine clearance was unchanged.

**Cold Pressor Stimulation**

The average rise in mean arterial pressure with cold pressor stimulation was 6.2 mm Hg before F and 9.0 mm Hg after F therapy (SED±0.89, p < 0.025). Mean increase in heart rate to this stimulus was 11 beats/min before F and there was a similar rise after F therapy. Before F therapy, the mean rise in forearm vascular resistance with cold pressor stimulation was 10.5 mm Hg/ml/100 ml/min (R units). The rise was significantly higher after F therapy, 32.6 R units (SED±6.4, p < 0.025), Figure 1.

**Table 2. Plasma and Urinary Changes With Hydrocortisone**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Pre-F</th>
<th>Post-F</th>
<th>SED</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum Na (mmol/l)</td>
<td>141</td>
<td>143</td>
<td>0.31</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Serum K (mmol/l)</td>
<td>4.0</td>
<td>3.8</td>
<td>0.09</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Fasting glucose (mmol/l)</td>
<td>4.7</td>
<td>5.4</td>
<td>0.14</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Serum cortisol (mmol/l)</td>
<td>481</td>
<td>1013</td>
<td>159</td>
<td>&lt;0.02</td>
</tr>
<tr>
<td>PRA (ng Ang I/ml · hr)</td>
<td>1.2</td>
<td>0.4</td>
<td>0.15</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Hematocrit (%)</td>
<td>46</td>
<td>42</td>
<td>1.5</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Serum Cr. (mmol/l)</td>
<td>0.09</td>
<td>0.08</td>
<td>0.003</td>
<td>NS</td>
</tr>
<tr>
<td>Cr. clearance (ml/sec)</td>
<td>2.4</td>
<td>2.7</td>
<td>0.18</td>
<td>NS</td>
</tr>
<tr>
<td>Urine Na (mmol/24 hrs)</td>
<td>130</td>
<td>86</td>
<td>13.3</td>
<td>&lt;0.02</td>
</tr>
<tr>
<td>Urine K (mmol/24 hrs)</td>
<td>69</td>
<td>48</td>
<td>8.7</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Urine volume (ml/24 hrs)</td>
<td>1247</td>
<td>1803</td>
<td>332</td>
<td>NS</td>
</tr>
<tr>
<td>Urine Cr. (mmol/24 hrs)</td>
<td>15.0</td>
<td>13.6</td>
<td>1.5</td>
<td>NS</td>
</tr>
</tbody>
</table>

F, hydrocortisone; Na, sodium; K, potassium; PRA, plasma renin activity; Ang I, angiotensin I; Cr., creatinine; NS, not significant. SED = standard error of the difference.

**Changes in Forearm Vascular Resistance With Intra-arterial Norepinephrine**

Norepinephrine infused into the brachial artery had no effect on systemic blood pressure at the doses administered. However, there were changes in forearm vascular resistance, as shown in Figure 2. F produced a fall in threshold, a shift to the left in the dose–response relation, and a significantly greater average rise in forearm vascular resistance with norepinephrine (14.9 R units before F, 35.1 R units after F therapy, SED±6.0, p < 0.05). Plateau responses were not reached with the highest influ-
Hydrocortisone-Induced Hypertension in Humans

Sudhir et al

**Figure 2.** Line graph showing increase in forearm vascular resistance with intra-arterial norepinephrine (NA), before and after hydrocortisone (F) administration.

**Figure 3.** Line graphs showing total body (top) and forearm (bottom) spillover of norepinephrine (NA) before and after hydrocortisone (F) administration.

Our results are consistent with previous studies that have shown that F administration in humans produces systolic hypertension and increased cardiac output; mineralocorticoid effects, including hypernatremia and hypokalemia, and plasma volume expansion; and glucocorticoid effects, namely, a rise in blood glucose. The blood pressure raising or "hypertensinogenic" effect in humans has been found to occur at similar doses at which classic steroid effects are seen. We noted a 2 l/min increase in cardiac output. This may have been due to plasma volume expansion, demonstrated in previous studies of F administration, and shown in the present study by the fall in hematocrit. We also observed a 15 mm Hg rise in systolic blood pressure and a fall in total peripheral resistance. This was associated with the classic body weight, serum and urinary electrolyte, blood glucose, and plasma renin activity changes that corticosteroids are known to produce. Creatinine clearance was not altered by F therapy, in agreement with previous data. However, in that previous study, there was a rise in inulin clearance, which is a more reliable index of glomerular filtration rate in patients on steroids, as creatinine clearance may be altered by steroid-related changes in endogenous creatinine turnover.

**Discussion**

We found that the hypertensive effect of F therapy was associated with a rise in cardiac output, a fall in calculated total peripheral resistance, an increased vascular response in the forearm with cold pressor stimulation, and increased forearm vascular responsiveness to exogenous norepinephrine. There was, however, no change in overall or forearm sympathetic tone, or in norepinephrine reuptake.
In humans, mineralocorticoids are known to increase pressor responsiveness to norepinephrine and angiotensin II. However, the literature on glucocorticoid administration is less clear. Some studies have shown greater rise in blood pressure after norepinephrine and epinephrine with glucocorticoid administration. However, there are other studies of glucocorticoid excess that have not found increased pressor responsiveness. A recent study showed that oral F therapy increased pressor responsiveness to intravenous phenylephrine, and decreased the threshold for systolic and mean arterial pressure rises. In the dosage used in the present study (200 mg/day), F is acting both as a glucocorticoid and a mineralocorticoid (see Table 2), so that it is not possible to discern the relative contribution of these steroid activities.

Two problems with studying whole body blood pressure responses are that effects of the drug are 1) not uniform in different vascular beds, and 2) modified by neural reflexes. Our study was designed to examine pressor responses in the forearm vascular bed, where small intra-arterial infusions of norepinephrine allowed us to determine local vascular responsiveness, uncomplicated by systemic reflexes.

We found a significantly increased response in this vascular bed to both reflexly induced constrictor effects as well as to locally administered norepinephrine. Others, using in vitro preparations of arterial smooth muscle, have shown an increased responsiveness to both epinephrine and norepinephrine several minutes after exposure to cortisone. This would suggest postreceptor changes rather than receptor upgrading, which would be slower to occur. This could possibly be a sodium effect, since pressor reactivity to infused vasoconstrictor agents has been shown to increase with salt loading in humans. However, in experimental mineralocorticoid excess in humans, there is no clear relation between sodium retention and hypertension. Further, in a recent study in sodium-depleted subjects, it was shown that the increased pressor sensitivity to catecholamines during ACTH administration in humans is not sodium dependent. Another possible mechanism for this increased pressor response is inhibition of catechol-O-methyltransferase. Altered prostaglandin synthesis has also been suggested as a possible factor since, in dexamethasone-treated rats, the increased vascular reactivity is abolished by indomethacin administration. However, this is not seen with F administration in humans. The relation of our hemodynamic observations in this study to the sustained hypertension in Cushing's syndrome is not entirely clear. In this disease, other steroids are elevated in addition to F, and may contribute to the hypertension. Further, cardiac output is not increased in all patients with Cushing's syndrome, which suggests that peripheral mechanisms may play a role.

Studies in the rat have shown that plasma catecholamines are not altered by corticosterone treatment, although adrenal and brain medullary phenylethanolamine-N-methyltransferase (PNMT) is increased by glucocorticoid administration. Methylprednisone hypertension in the rat can partly be reversed by PNMT inhibition, which suggests some role for the sympathetic nervous system in this species. An experimental study in humans that examined fludrocortisone-induced hypertension demonstrated a fall in plasma catecholamines after 6 weeks of drug therapy. Connell et al showed no change in plasma epinephrine and a fall in plasma norepinephrine with F administration. In the present study, we found that sympathetic tone, as assessed by total norepinephrine spillover, was unaltered by F. In the forearm, there was a small fall in norepinephrine spillover in most subjects, but this did not achieve statistical significance. Changes in pressor responsiveness were thus not related to increased release of neurotransmitter by the sympathetic nervous system, at least in the resting state. F is a known inhibitor of extraneuronal uptake (uptake 2). We found that norepinephrine extraction across the forearm was unaltered by F, show-
ing no decrease in overall uptake (uptake 1 + uptake 2). Further, the decrease in extraction resulting from desipramine, a known inhibitor of neuronal uptake (uptake 1), was similar before and after F therapy. Thus, one could infer that uptake 2 also remained unchanged in the forearm at this dose of hydrocortisone. This is consistent with an earlier report of the absence of an effect of intravenously administered F on extraneuronal norepinephrine uptake in humans. 10

In conclusion, the acute hypertensive effect of F in humans, in the resting state, appears to be related to increased cardiac output, probably a result of plasma volume changes. The hemodynamic responses and rise in blood pressure with F therapy were not directly neurally mediated, since F did not increase norepinephrine release or impair neuronal reuptake of norepinephrine. The increased pressor responsiveness noted with F therapy was probably due to local postsynaptic effector mechanisms in the resistance vessels, which could be important in phasic increases in neurally mediated constrictor responses.

References


Key Words • hydrocortisone • steroid • pressor response • sympathetic nervous system
Hydrocortisone-induced hypertension in humans: pressor responsiveness and sympathetic function.
K Sudhir, G L Jennings, M D Esler, P I Korner, P A Blombery, G W Lambert, B Scoggins and J A Whitworth

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