Hydrocortisone-Induced Hypertension in Humans: Pressor Responsiveness and Sympathetic Function

Krishnankutty Sudhir, Garry L. Jennings, Murray D. Esler, Paul I. Korner, Peter A. Blombery, Gavin W. Lambert, Bruce Scoggins, and Judith A. Whitworth

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 reflex 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)

Hypertension is common in clinical conditions of corticosteroid excess.1 In experimental studies in humans, both corticotropin and hydrocortisone (F) have been shown to increase blood pressure.2,3 Oral F therapy was found to increase pressor responsiveness to intravenous phenylephrine, decreasing the threshold for, and increasing the magnitude of systolic and mean arterial pressure responses.4 We wished to investigate in greater detail the hemodynamic mechanisms of experimental steroid hypertension in humans and to examine the role of the sympathetic nervous system in the enhanced pressor responsiveness. To this end, we studied the effect of oral F therapy on central hemodynamic variables and on regional vascular responses in the forearm. We also examined total body and forearm sympathetic nervous system function, with a view to assessing the contribution of altered norepinephrine release or uptake to increased pressor responsiveness.

Subjects and Methods

Hemodynamic changes and sympathetic nervous system function were studied in normal human subjects, before and after a week of F therapy. Ten healthy male volunteers (mean age 20, range 18–22 years) were recruited by advertisement. Two were randomly allocated to receive placebo therapy. Care was taken to exclude subjects with a history of hypertension, chronic drug ingestion, acid peptic disease, asthma, atopy, or psoriasis. The study was approved by the Medical Research Ethics Commit-
Before the study, all subjects maintained their dietary sodium intake close to 140 mmol/day for a 1-week period. Subjects were studied on two separate occasions, 1 week apart, with F or placebo administered in between. Subjects reported at 8:00 AM on each study day. Body weight was measured, and supine systolic and diastolic blood pressure were determined using a random zero sphygmomanometer, after the subject had been resting for 20 minutes. A forearm vein was cannulated, and blood was drawn for measurement of plasma sodium, potassium, hematocrit, fasting blood glucose, serum F, serum creatinine, and plasma renin activity. A 24-hour urine collection, completed at 7:00 AM on the morning of the study, was analyzed for sodium, potassium, and creatinine content, and creatinine clearance was calculated. Cardiac output was measured noninvasively using the indirect Fick technique. Ambulatory blood pressure recordings (Spacelabs, Hillsboro, Oregon) were obtained before and after F therapy (i.e., in the 24-hour period after each hemodynamic study). Half-hourly readings were recorded, and mean systolic and diastolic pressures were calculated.

High specific activity tritiated 7-norepinephrine ([\(^{3}H\)NA]A) was infused at a constant rate (0.35 \( \mu \)Ci/min) through the forearm venous cannula. By means of a pressure monitoring set (3.0F, 20-gauge, 5-cm catheter, William Cook Australia, Pty. Ltd., Melbourne, Australia), the brachial artery was cannulated on the side opposite to the [\(^{3}H\)NA] infusion. Arterial pressure was monitored from this line throughout the experiment with an AE 840 physiological pressure transducer (Aksjeselskapet Mikro-Elektronikk, Horten, Norway). On the same side as the arterial cannula, the axillary vein was catheterized using an Intramedicut catheter kit (16 gauge, 70 cm, Sherwood Medical, St. Louis, Missouri); this catheter was inserted percutaneously under local anesthesia into an antecubital vein. This line was used for sampling forearm venous drainage, the catheter in the axillary vein ensuring that the sample was representative of total forearm venous drainage (i.e., both skin and muscle). (With antecubital venous sampling, the relative mix of skin and muscle drainage at a particular sampling site is uncertain.) Patency of the lines was maintained by intermittent flushing with heparin in normal saline, 5 units/ml.

After 80 minutes of infusion, 15 ml blood was collected from the brachial artery and from the axillary vein. Of this, 10 ml was added to lithium heparin tubes for plasma [\(^{3}H\)NA] assay and 5 ml in plain tubes that contained a reduced glutathione-EGTA mix for endogenous norepinephrine assay. After centrifugation at 2,000 rpm for 20 minutes, plasma was separated. Sodium metabisulphite (1 mg/ml) was added to plasma for [\(^{3}H\)NA] assay, and all plasma samples were stored at -20°C until subsequent assay.

Endogenous plasma norepinephrine was assayed by radioenzymatic assay. Plasma [\(^{3}H\)NA] was extracted on alumina and assayed by liquid scintillation counting. Interference from dihydroxy metabolites of [\(^{3}H\)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 [\(^{3}H\)NA]}}{\text{plasma [\(^{3}H\)NA] concentration}}
\]

\[
\text{NA spillover (whole body)} = \frac{\text{infusion rate [\(^{3}H\)NA]}}{\text{plasma NA specific radioactivity}}
\]

\[
\text{NA fractional extraction (e) (forearm)} = \frac{(\text{arterial [\(^{3}H\)NA]} - \text{venous [\(^{3}H\)NA])}}{\text{(arterial [\(^{3}H\)NA])}}
\]

where \( N_A \) and \( N_A' \) represent venous and arterial plasma norepinephrine concentrations, \( e \) the fractional extraction of [\(^{3}H\)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, Medasonics, 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:

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

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 [\(^{3}H\)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 extraneuronal 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.

**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 infusion.
Hydrocortisone-Induced Hypertension in Humans

Sudhir et al

**Sympathetic Nervous System Function**

Total body spillover of norepinephrine was unchanged by administration of F. Forearm spillover of norepinephrine fell in six subjects, but rose in two, so that there was no significant overall change (Figure 3). Baseline extraction of norepinephrine across the forearm remained unaltered. There was a significant fall in extraction with desipramine before F $p<0.05$, and a similar decrease after F therapy $p<0.05$. The relative contributions of uptake 1 and uptake 2 processes to forearm extraction were similar before and after F therapy (Figure 4).

**Effect of Placebo**

Changes in forearm vascular resistance with cold pressor stimulation and intra-arterial norepinephrine infusion were similar on the two study days in the subjects on placebo, and closely resembled the changes before F therapy in the eight subjects. Likewise, total body and forearm spillover and reuptake showed a reproducible pattern in the subjects on placebo, similar to the data before F therapy.

**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.

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.
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 rise. 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 constritor 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.

In another study, the increased vascular reactivity is abolished by indomethacin administration. Altered prostaglandin synthesis has also been suggested as a possible factor since, in dexamethasone-treated rats, the increased vascular reactivity is 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-
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 helping in neurally mediated constrictor responses.

References

24 Nicholls MG, Ramsay LE, Boddy K, Fraser R, Morton JJ, Robertson JS: Mineralocorticoid-induced blood pressure, electrolyte, and hormone changes and reversal with spironolactone in healthy men. Metabolism 1979; 28:584-593

Key Words: hydrocortisone • steroid • pressor response • sympathetic nervous system

Sudhir et al

Hydrocortisone-Induced Hypertension in Humans 421

Downloaded from http://hyper.ahajournals.org/ by guest on April 6, 2017
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

doi: 10.1161/01.HYP.13.5.416

Hypertension is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1989 American Heart Association, Inc. All rights reserved.
Print ISSN: 0194-911X. Online ISSN: 1524-4563

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://hyper.ahajournals.org/content/13/5/416

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Hypertension can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Hypertension is online at:
http://hyper.ahajournals.org//subscriptions/