Mechanisms in Human Renovascular Hypertension
ANDREW H. MASLOWSKI, M.D., M. GARY NICHOLLS, M.D., ERIC A. ESPINER, M.D.,
HAMID IKRAM, M.D., AND PHIL J. BONES, PH.D.

SUMMARY To clarify the pathophysiology of renovascular hypertension, we monitored intraarterial pressure continuously and measured hourly hormone levels for 24 hours under carefully controlled conditions in two hypertensive patients with unilateral renal artery occlusion. Comparison of the results with those obtained when the patients were normotensive 3 months after uninephrectomy indicated that, while the renin-angiotensin system played a central role in maintaining the hypertension, the sympathetic nervous system also contributed and, in addition, modulated short-term arterial pressure fluctuations. In the untreated state, the sympathetic regulation of renin secretion was heightened, and angiotensin II/aldosterone dose-responsiveness was augmented. It is suggested that these adaptive changes might serve to offset the tendency to severe sodium depletion and thence exacerbation of the hypertension. (Hypertension 5: 597–602, 1983)

KEY WORDS • renal hypertension • renin • angiotensin • aldosterone • catecholamines

THE mechanisms underlying renal hypertension are unclear despite intensive study. For the more common form in humans — unilateral renal artery stenosis with the contralateral kidney intact (the equivalent of two-kidney, one clip hypertension in experimental animals1), the renin-angiotensin system is thought to play a central role both in the development and maintenance of hypertension.2 More contentious and less researched is involvement of the sympathetic nervous system in regulating arterial pressure and controlling renin release from the ischemic kidney. Much of our knowledge linking pressure and hormone changes is based on animal experiments, but prominent species differences3 4 hamper application of these findings to humans. Previous studies in humans have tended to focus on a single pathophysiological variable — usually renin — and an integrated assessment of hormone–blood pressure relationships has not yet been undertaken. To clarify these interrelationships we monitored arterial pressure continuously, and measured pressor hormone levels at hourly intervals for 24 hours in two patients with renovascular hypertension. The studies were repeated 3 months after removal of the ischemic kidney when blood pressure was normal.

Methods
The patients were studied before uninephrectomy and again under identical conditions of dietary electrolyte intake and body posture 3 months after surgery. Antihypertensive medications before the initial study were labetolol and cycloplotiazide (stopped 5 weeks prior to hospitalization) and prazosin (withdrawn 5 days before starting the constant electrolyte diet) in the case of Patient MC. For Patient HE, α-methyladopa and prazosin were withdrawn 2 weeks and 3 days respectively prior to initiation of the study diet. No medications were taken by either patient before the second (postnephrectomy) study. On the fourth day of a diet that was caffeine-free and of constant sodium (44 mmol/day in Patient HE, 153 mmol/day in MC) and potassium (59 mmol/day in HE, and 64 mmol/day for MC) content, the left brachial artery was catheterized percutaneously for continuous blood pressure measurement, and an arm vein was cannulated for hourly blood sampling. From 1000 to 2100 hours on the experimental day, the patients were standing or walking except for the first 15 minutes of each hour when they were supine in bed. During the remainder of the 24 hours (2100 to 0900) they remained in bed while direct

From the Departments of Endocrinology and Cardiology, The Princess Margaret Hospital, Christchurch, New Zealand.
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Address for reprints: Dr. M. Gary Nicholls, Endocrinology Department, The Princess Margaret Hospital, Christchurch, New Zealand.
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arterial pressure recordings and hourly blood sampling continued. Venous samples, 10 ml each, were drawn on the hour, after 45 minutes upright between 1000 and 2100, and while supine for the subsequent 12 hours. Meals were taken at 1000, 1300, and 1800, with a snack at 2100. Patient MC slept intermittently during the night of both studies, whereas HE slept soundly.

The arterial pressure signal was recorded continuously with a transducer unit, along with the EKG signal from chest leads, on a Medilog Mark I miniaturized tape recorder (Oxford Medical Systems Oxford, England). The method and its validation have been described elsewhere.

Venous samples for hormone analyses were taken into chilled containers, centrifuged at +4°C, and the plasma stored at −20°C. Established methods were used to measure plasma renin activity (PRA), angiotensin II, aldosterone, cortisol (radioimmunooassay with kits from Diagnostic Products Inc., Los Angeles), norepinephrine, and epinephrine. Samples from the two studies in each patient were analyzed in separate assays. Interassay variation from at least 10 consecutive assays was lowest for cortisol (coefficient of variation less than 6%) and highest for PRA (17.8%).

For statistical purposes, arterial pressure integrated over 5 minutes prior to each blood sampling was correlated with hormone levels. The BMDP (University of California) package of programs was used for determination of correlation coefficients and the significance of difference between means (paired t test). 11 For comparison of slopes of regression lines, use was made of the relationship between blood pressure and hormone levels was more obvious for diastolic and mean, than for systolic blood pressure readings.

Patients

Patient MC was noted to be hypertensive in 1978 at the age of 35 years. She was referred to us in 1981 because of hypertension (200/120 mm Hg) resistant to medication. Renal arteriography revealed total atheromatous occlusion of the left renal artery and a small left kidney. Renal vein sampling showed a high left/right PRA ratio (29.1/15.7 nmol/liter/hr) when the concomitant peripheral PRA value was 14.5 nmol/liter/hr. Left nephrectomy was performed in October, 1981, and the blood pressure subsequently fell to 120/60–140/80 mm Hg without medication.

Patient HE, a 68-year-old woman, was hospitalized with headache and fluctuating neurological signs in September, 1980. Because of hypertension (200/100 mm Hg), orthostatic hypotension, hyponatremia, and hypokalemia, renal arteriography was done, which showed a small left kidney and total occlusion of the left renal artery. Peripheral and right vein PRA values were similar (33.2 and 36.2 nmol/liter/hr respectively), and the left/right renal vein PRA ratio was high (103/36.2 nmol/liter/hr). The ischemic kidney was removed in November, 1980. Subsequent outpatient blood pressure levels ranged from 100/65 to 155/80 mm Hg off all treatment.

Results

From the four studies in two patients, three blood samples (one each for PRA, norepinephrine, and aldosterone) were lost, and one blood pressure was not recorded due to a technical problem.

While absolute levels for blood pressure and hormones were different for the two patients (table 1), the patterns and their response to surgery (shown for Patient HE in fig. 1) were similar. Exceptions were plasma cortisol (Patient HE) and epinephrine (Patient MC) which were lower in the postsurgery study (table 1).

Arterial Pressure and Hormones

The relationship between blood pressure and hormone levels was more obvious for diastolic and mean, than for systolic blood pressure readings.

<table>
<thead>
<tr>
<th>TABLE 1. Blood Pressure, Hormone, and Electrolyte Levels (mean ± SEM)</th>
<th>Patient MC</th>
<th>Patient HE</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Systolic arterial pressure (mm Hg)</strong></td>
<td>203 ± 4</td>
<td>185 ± 3</td>
</tr>
<tr>
<td><strong>Diastolic arterial pressure (mm Hg)</strong></td>
<td>126 ± 3</td>
<td>96 ± 3</td>
</tr>
<tr>
<td><strong>Plasma renin activity (nmol/liter/hr)</strong></td>
<td>5.6 ± 0.7</td>
<td>23.2 ± 1.3</td>
</tr>
<tr>
<td><strong>Plasma angiotensin II (pmol/liter)</strong></td>
<td>165 ± 16</td>
<td>508 ± 32</td>
</tr>
<tr>
<td><strong>Plasma aldosterone (pmol/liter)</strong></td>
<td>1007 ± 131</td>
<td>4058 ± 254</td>
</tr>
<tr>
<td><strong>Plasma cortisol (nmol/liter)</strong></td>
<td>461 ± 39</td>
<td>389 ± 38</td>
</tr>
<tr>
<td><strong>Plasma norepinephrine (pg/ml)</strong></td>
<td>538 ± 45</td>
<td>511 ± 63</td>
</tr>
<tr>
<td><strong>Plasma epinephrine (pg/ml)</strong></td>
<td>104 ± 8</td>
<td>69 ± 10</td>
</tr>
<tr>
<td><strong>Plasma sodium (mmol/liter)</strong></td>
<td>139</td>
<td>133</td>
</tr>
<tr>
<td><strong>Plasma potassium (mmol/liter)</strong></td>
<td>3.1</td>
<td>3.3</td>
</tr>
</tbody>
</table>

Conversion to SI Units: plasma norepinephrine = 1 nmol/liter = 160 pg/ml; plasma epinephrine = 1 nmol/liter = 180 pg/ml.

* Differences between pre- and postsurgery values were not statistically significant (paired t test); all other comparisons were significant (p < 0.05).
Renin-Angiotensin System

Uninephrectomy reduced arterial pressure, PRA, and angiotensin II levels (table 1). In the preoperative study, diastolic pressure showed a positive correlation with PRA ($r = 0.57$ in Patient MC, $r = 0.50$ in Patient HE; $p < 0.01$) and with angiotensin II ($r = 0.67$ and 0.35 respectively, $p < 0.001$ and < 0.1). Three months after surgery, these correlations were lost in Patient MC but remained for Patient HE ($r = 0.81$ for PRA and $r = 0.62$ for angiotensin II, $p < 0.001$), presumably because her sodium intake was restricted. For any given level of PRA or angiotensin II, arterial pressure was considerably higher before than after surgery. Pressor responsiveness to endogenous angiotensin II, assessed by comparing slopes of the regression lines (log angiotensin II vs diastolic pressure), appeared diminished preoperatively compared to the second study. However, a formal comparison was hindered by minimal overlap, for both indices, of pre- and postoperative results (table 1, fig. 1).

Sympathetic Nervous System

Whereas arterial pressure declined after removal of the ischemic kidney, norepinephrine levels were unchanged (table 1). Diastolic pressure correlated closely ($p < 0.001$) with concurrent plasma norepinephrine levels in the initial study of both patients and again 3 months after uninephrectomy (fig. 2). The regression line relating these two indices exhibited a parallel downward shift (fig. 2), suggesting that pressor responsiveness to endogenous sympathetic stimulation was similar before and after surgery.

Sympathetic System and the Renin-Angiotensin System

Plasma norepinephrine showed a positive correlation with PRA before surgery in both patients ($r = 0.44$ and 0.62, $p < 0.05$ and < 0.001) but the relationship was less obvious after operation in Patient MC (fig. 3). Compared with the norepinephrine/PRA regression line after uninephrectomy, that before surgery was significantly steepened as well as elevated (fig. 3). In the initial study, therefore, PRA values were higher for any given level of norepinephrine, and an increase in norepinephrine was associated with greater PRA increments (fig. 3).

Plasma Aldosterone

Correlations between plasma aldosterone and angiotensin II were close before and after surgery ($p < 0.01$ to $p < 0.001$) in both patients (fig. 4). Aldosterone responsiveness to endogenous angiotensin II, assessed by comparing the slopes of regression lines on semilogarithmic plots, was heightened before surgery compared with after (fig. 4). Substituting PRA for angiotensin II gave similar results. The correlation of plasma cortisol (which reflects biological ACTH activity) with aldosterone was relatively weak ($r = 0.33$ to 0.35, $p < 0.1$) except in the second study of Patient MC ($r = 0.79$, $p < 0.001$).
**Figure 2.** Plasma norepinephrine (log scale) and diastolic blood pressure before (Δ) and 3 months after (●) uninephrectomy in Patients MC (top panel) and HE (lower panel).

**Figure 3.** Plasma norepinephrine (log scale) and plasma renin activity before (Δ) and 3 months after (●) removal of the ischemic kidney. Slopes of the regression lines were significantly different whether analyzed by χ² (as shown) or by t test.
FIGURE 4. Concurrent plasma angiotensin II (log scale) and aldosterone levels before (Δ) and 3 months after uninephrectomy (●). Slopes of the regression lines were significantly different for both patients whether analyzed by $\chi^2$ (as shown) or by $t$ test.

**Discussion**

Previous studies in human renovascular hypertension have relied on only a few measurements of hormone activity, insufficient to categorize any possible dose-response relationships. The present study has used an objective and continuous arterial pressure monitoring technique, together with hourly hormone sampling in two patients before and after uninephrectomy to clarify the mechanisms of hormone-blood pressure control.

Several important observations were made. First, the positive correlations of angiotensin II (and PRA) with blood pressure before surgery, together with the fact that uninephrectomy lowered both arterial pressure and angiotensin II levels, support the contention that the renin-angiotensin system plays a central role in the maintenance phase of renovascular hypertension. However, acute pressor responsiveness to endogenous angiotensin II (as assessed by comparing slopes of log angiotensin II/arterial pressure regression lines) did not appear enhanced, and may even have been diminished — a phenomenon previously observed in experiments employing angiotensin II infusion in patients with renal ischemia.

Second, though activity of the sympathetic nervous system, contrary to some previous reports, was not increased before surgery, there was a close positive correlation of plasma norepinephrine with arterial pressure fluctuations. This relationship was similar pre- and postnephrectomy. These results suggest that the sympathetic nervous system modulates short-term pressure fluctuations, and further contributes to maintenance of the hypertension by retaining "normal" levels of activity rather than opposing it by resetting to a lower level of activity. This conclusion confirms and extends early experimental results from animals.

Third, sympathetic modulation of renin release is heightened in established renovascular hypertension. Whereas the dose-response relationship of sympathetic activity (plasma norepinephrine) to PRA was steep before uninephrectomy, it was markedly flattened after surgery in one patient and obliterated in the other. These findings in humans are consistent with data from dogs showing potentiation of renin release in response to sympathetic stimulation (using either isoproterenol infusion or renal nerve stimulation) in the presence of renal artery constriction. The phenomenon explains, at least in part, the exaggerated renin response to upright posture — a feature that has been used to screen patients for renal hypertension.

Finally, our results clarify angiotensin–aldosterone relationships in human renovascular hypertension.
fore surgery, extremely high aldosterone levels were maintained by angiotensin II despite the inhibitory effects of mild hypokalemia (3.3 mmol/liter in Patient HE, 3.1 mmol/liter in Patient MC). While there is still controversy concerning the effect of sustained increases in angiotensin II on aldosterone,22-23 the present findings support those of the Glasgow group25 who showed similar angiotensin/aldosterone relationships in a mixed group of patients with malignant hypertension, renin-secreting tumor, and renal artery stenosis.

We conclude, first, that long-standing elevations in angiotensin II secondary to renal ischemia can sustain high circulating levels of aldosterone; and, second, that aldosterone responsiveness to endogenous angiotensin II stimulation is increased in established renovascular hypertension. Although the present study does not clarify the mechanism(s) underlying the augmented aldosterone responsiveness, high angiotensin II levels, which are claimed to have a trophic action on the adrenal glomerulosa,24 may have played a central role, while it is possible that body sodium content was depleted before uninephrectomy,26 and further contributed.23

Taken together, our results show that, with sustained high levels of plasma angiotensin II due to unilateral renal ischemia, vascular sensitivity to acute fluctuations in angiotensin II was not increased and may be diminished, but the pressor responsiveness to endogenous sympathetic stimulation remained unpaired and contributed significantly to blood pressure fluctuations. In contrast to the vascular response, aldosterone sensitivity to angiotensin II was enhanced. Such differences in vascular and adrenal sensitivity have also been described in salt-depleted humans.27,28 In renovascular hypertension, it might be surmised that these adaptive changes work to counteract the tendency for sodium loss and thence the onset of severe or accelerated hypertension.26,29,30

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