Differential Uric Acid Excretion in Essential and Renal Hypertension

By Norman M. Simon, M.D., Jon E. Smucker, M.D., Vincent J. O’Conor, Jr., M.D., and Francesco del Greco, M.D.

SUMMARY

In 59 hypertensive patients, differences between the two kidneys in the handling of uric acid were found in renal arterial stenosis and unilateral renal disease but were not found in essential hypertension and bilateral renal parenchymal disease. The differences were greatest in 11 patients with unilateral renal arterial stenosis and were derived from reduced uric acid excretion per unit of glomerular filtration rate by the ischemic kidney. Six patients with unilateral stenosis underwent surgery with subsequent cure of hypertension. Another patient, who did not have impaired ipsilateral uric acid excretion, failed to respond to nephrectomy. Successful revascularization of the ischemic kidney in two patients augmented uric acid excretion with disappearance of the differences between the kidneys. Hyperuricemia was often found in all groups of hypertensive patients. Although the mechanisms underlying the differences in renal handling of uric acid are undefined, separate determinations of the uric acid excretion by the two kidneys may possibly prove useful in the evaluation of patients with hypertension.

Additional Indexing Words:
Differential renal function Renal arterial stenosis Hyperuricemia

HYPERURICEMIA is often observed in hypertension1 and has been attributed to altered renal handling of uric acid.2-4 The mechanism of renal retention of uric acid is not clearly defined, but decreased tubular transport rather than reduced filtered load appears responsible. Lactate5,6 and angiotensin7 are known to depress tubular transport of uric acid and have been reported to be increased in the blood of some hypertensive patients.8,9

To define renal handling of uric acid further, we compared its excretion by the two kidneys in patients with essential and renal hypertension. Patients with renal arterial stenosis, in whom renal ischemia might lead to increased production of lactic acid and renin-angiotensin, were of particular interest.

Methods

Fifty-nine hypertensive patients were studied. To evaluate the cause of hypertension, intravenous pyelography, isotope renography, aortography, and divided renal function tests were carried out. In addition, assay of plasma renin activity,10 the angiotensin infusion test,11 and measurements of urinary catecholamines or of
Uric acid clearance ratios in 59 hypertensive patients. Dashed lines indicate mean values. EH = essential hypertension; URAS = unilateral renal artery stenosis; BRAS = bilateral renal artery stenosis; P-H = unilateral pyelonephritis or hydronephrosis; A = unilateral renal atrophy; RPD = bilateral renal parenchymal disease; * = value of patient unimproved after nephrectomy, not included in calculation of mean.

The response to phentolamine were performed in most patients. In some cases, renal biopsy and determination of the aldosterone excretion rate were carried out.

On the basis of these studies, essential hypertension was diagnosed in 30 patients and renal hypertension, in 29. The latter group was divided as follows: renal arterial stenosis (17 patients), unilateral pyelonephritis or hydronephrosis (five), unilateral renal atrophy of undetermined etiology (four), and bilateral renal parenchymal disease (three). The 17 patients with renal arterial stenosis included 12 with unilateral lesions and five with bilateral disease. Of the 12 patients with unilateral stenosis, six were cured or showed marked improvement in hypertension after surgery, one was unimproved after unilateral nephrectomy, and five did not undergo surgery. One patient with bilateral stenosis expired postoperatively, while four patients were not treated surgically.

Differential renal function studies were performed on all patients after salt restriction and administration of diuretics had been discontinued for at least 1 week. Following bilateral ureteral catheterization and induction of diuresis with a hypertonic urea-saline-pitressin solution, three 10-min collections of urine were made from each kidney. Blood was obtained at the midpoint of the first and third periods for calculation of renal clearances. Uric acid, sodium, and para-aminohippurate (PAH) were determined on the Technicon Autoanalyzer, and inulin was assayed by the method of Walser and associates.

Uric acid clearance values were factored by inulin clearances to allow comparison between kidneys with different glomerular filtration rates and to obviate problems arising from incomplete collection of urine due to leakage around a ureteral catheter. A uric acid clearance ratio was calculated for each patient by dividing the factored uric acid clearance of the kidney with the less urinary flow by that of the contralateral kidney. Equal handling of uric acid by the two kidneys would be indicated by a clearance ratio approximating unity regardless of differences in glomerular filtration rate.

Results

Uric acid clearance ratios for all patients are shown in figure 1 according to etiology of hypertension. The mean uric acid clearance ratios and standard deviations were 1.00 ± 0.08 in essential hypertension, 0.61 ± 0.12 in unilateral renal arterial stenosis (the value for the patient who was unimproved after surgery is not included), 0.75 ± 0.23 in bilateral renal arterial stenosis, 1.13 ± 0.12 in unilateral pyelonephritis-hydronephrosis, 0.86 ± 0.19 in unilateral renal atrophy, and 0.97 ± 0.05 in bilateral renal parenchymal disease. The mean values of all groups, except those four patients with renal parenchymal disease, differed significantly from that of patients with essential hypertension with P values listed in figure 1. The greatest differences between the kidneys in handling of uric acid were found in patients with unilateral renal arterial stenosis. The clearance ratios in this group were completely separated from those observed in patients with essential hypertension except for the result in the patient who failed to respond to nephrectomy.

Uric acid clearance values for both kidneys and clearance ratios in the patients with unilateral renal arterial stenosis are listed in table 1. Although clearance values for the two kidney overlapped, uric acid clearance ratios were consistently 0.74 or less in the 11 patients with proven or presumptive stenosis, indicating a relative retention of uric acid by the ischemic kidney. Reduced uric acid excretion was observed, with glomerular filtration rates varying from 6 to 91 ml/min in the ischemic kidney and with filtration rates equal to, or even greater than, those of the uninvolved kidney in two subjects (cases
DIFFERENTIAL URIC ACID EXCRETION

Table 1
Differential Renal Function in Unilateral Renal Artery Stenosis

<table>
<thead>
<tr>
<th>Patient</th>
<th>Involved Kidney</th>
<th>Contralateral Kidney</th>
<th>Ratio of involved/contralateral kidney</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>$C_{UA}/C_{IN}$</td>
<td>$C_{IN}$</td>
<td>$C_{UA}/C_{IN}$</td>
</tr>
<tr>
<td>Surgical cure (proven)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>M.B.</td>
<td>0.14</td>
<td>91</td>
<td>0.10</td>
</tr>
<tr>
<td>D.W.</td>
<td>0.08</td>
<td>Leakage</td>
<td>0.11</td>
</tr>
<tr>
<td>J.B.</td>
<td>0.13</td>
<td>20</td>
<td>0.19</td>
</tr>
<tr>
<td>C.S.</td>
<td>0.06</td>
<td>30</td>
<td>0.09</td>
</tr>
<tr>
<td>J.T.</td>
<td>0.14</td>
<td>6</td>
<td>0.21</td>
</tr>
<tr>
<td>L.E.</td>
<td>0.05</td>
<td>16</td>
<td>0.13</td>
</tr>
<tr>
<td>No surgery (presumptive)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N.W.</td>
<td>0.11</td>
<td>16</td>
<td>0.16</td>
</tr>
<tr>
<td>A.B.</td>
<td>0.15</td>
<td>28</td>
<td>0.23</td>
</tr>
<tr>
<td>M.G.</td>
<td>0.08</td>
<td>45</td>
<td>0.15</td>
</tr>
<tr>
<td>A.F.</td>
<td>0.07</td>
<td>46</td>
<td>0.14</td>
</tr>
<tr>
<td>G.F.</td>
<td>0.10</td>
<td>16</td>
<td>0.22</td>
</tr>
<tr>
<td>Surgical failure</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>R.J.</td>
<td>0.14</td>
<td>17</td>
<td>0.11</td>
</tr>
</tbody>
</table>

Abbreviations: $C_{UA}/C_{IN}$ = uric acid clearance/inulin clearance; $C_{IN}$ = inulin clearance, ml/min/1.73 m$^2$; $V$ = urine flow; $U_{Na}$ = urine sodium concentration; $U_{PAH}$ = urinary concentration of para-aminohippurate; $TRFR_{Na}$ = tubular rejection fraction ratio for sodium.$^{14}$

N. W. and M. B., table 1). In both patients, we suspected vascular damage of the contralateral kidney secondary to the hypertension. This was confirmed by renal biopsy in patient M. B.

Ratios of the two kidneys for urine flow, sodium and PAH concentration, and excretion fraction of filtered sodium are also recorded in table 1. Although the criteria for diagnosis of unilateral ischemia proposed by Rapaport,$^{14}$ Howard and Connor,$^{15}$ and Stamey and associates$^{12}$ were fulfilled in most instances, they were not completely satisfied in patients C. S. and N. W. Uric acid clearance ratios clearly separated these two cases from patients with essential hypertension. In patient R. J., although the Rapaport and Howard tests were positive and renal arteriography indicated unilateral stenosis, the uric acid clearance ratio was 1.27. Renin activity in venous blood from the contralateral kidney was greater than that from the ischemic

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**Figure 2**
Effect of renal arterial reconstruction on uric acid clearance ratio in patient M. B. $C_{UA}/C_{IN}$ = uric acid clearance; $C_{IN}$ = inulin clearance.

**Figure 3**
Effect of renal arterial reconstruction on uric acid clearance ratio in patient J. B. $C_{UA}/C_{IN}$ = uric acid clearance; $C_{IN}$ = inulin clearance.
kidney. Unilateral nephrectomy failed to lower blood pressure, a finding consistent with the data indicating a bilateral origin of the hypertension.

Two patients with unilateral renal arterial stenosis who were cured of hypertension by arterial reconstruction were restudied after surgery (cases M. B. and J. B.). Impaired uric acid excretion by the ischemic kidney was no longer evident as uric acid clearance ratios increased from preoperative values of 0.74 and 0.68 to 1.08 and 1.13, respectively, after surgery (figs. 2 and 3).

In three of five patients with bilateral renal arterial stenosis, uric acid clearance ratios were depressed to values of 0.75 or lower (fig. 1), thus falling within the range of those of patients with unilateral stenosis. In the patient who underwent surgery, uric acid excretion was reduced to a greater extent in the kidney with a more severely compromised blood supply as determined by measurement of pressure gradients at the time of operation.

Of the other patients with renal hypertension, only two exhibited differences in uric acid excretion outside of the range of the group with essential hypertension (fig. 1). One patient with unilateral pyelonephritis had a relative increase in uric acid excretion by the diseased kidney (uric acid clearance ratio, 1.33), while the second patient showed decreased excretion by an atrophic kidney (uric acid clearance ratio, 0.60). Surgery was not performed in either case.

Serum uric acid was often increased in the various hypertensive groups (table 2). Thirty-seven per cent of the patients with essential hypertension and 25 to 80% of the patients with renal hypertension were hyperuricemic.

Discussion

The present data demonstrate differences between the two kidneys in handling of uric acid in many patients with renal hypertension in contrast to patients with essential hypertension. Differences between the kidneys were greatest in those with unilateral renal arterial stenosis and resulted from a reduction in uric acid excretion by the ischemic kidney, which was reversible after corrective arterial surgery. Serum uric acid was often increased in all groups of hypertensive patients that were studied, a finding in accord with previous reports.

The mechanism of uric acid retention by the ischemic kidney remains undefined. Nephron hypoperfusion due to a fall in glomerular filtration rate on the ischemic side is unlikely since Berger and co-workers found no change in the ratio of uric acid clearance to inulin clearance after acute reduction of glomerular filtration rate by balloon occlusion of the aorta in dogs.

Recently, Ferris and Gorden reported a depression of uric acid clearance in normal subjects who were given infusions of angiotensin II intravenously and attributed this to a decrease in effective renal plasma flow. It is conceivable that the differences in uric acid excretion between the two kidneys in patients

Table 2

<table>
<thead>
<tr>
<th>Serum Uric Acid in Hypertension</th>
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<tbody>
<tr>
<td>Serum uric acid</td>
</tr>
<tr>
<td>----------------</td>
</tr>
<tr>
<td>Total cases</td>
</tr>
<tr>
<td>Normal</td>
</tr>
<tr>
<td>Increased*</td>
</tr>
<tr>
<td>% Increased</td>
</tr>
<tr>
<td>Mean C_IN †</td>
</tr>
</tbody>
</table>

* Serum uric acid > 6.0 mg/100 ml in women; > 7.0 mg/100 ml in men. † Mean C_IN = mean inulin clearance of both kidneys, ml/min/1.73 m².
with renal arterial stenosis may be due to a local action of angiotensin generated from release of renin by the ischemic kidney. If this is so, the effect of angiotensin on tubular transport of uric acid is not mediated simply through a reduction in renal plasma flow, as uric acid clearance is depressed disproportionately more than para-aminohippurate clearance (mean \( C_{UA}/C_{PAH} \) is 0.028 in the ischemic kidney as compared to 0.044 in the contralateral kidney).

Similarly, release of lactic acid by ischemic renal tissue might selectively depress excretion of uric acid. Aviram and associates\(^\text{17}\) demonstrated an increase in urinary lactate-to-pyruvate ratios on the ischemic side in experimental renal arterial stenosis. However, in preliminary studies of several patients with unilateral stenosis, we have been unable to find a difference in renal venous blood lactate content for the two kidneys.\(^\text{18}\)

Whatever the mechanisms responsible for dissimilar handling of uric acid by the two kidneys, determination of divided uric acid excretion appears to be useful in the evaluation of patients with hypertension, supplementing urine flow, sodium, and para-aminohippurate data. The findings of a difference in uric acid excretion between the kidneys in a patient with renal arterial stenosis confirms the functional significance of the arterial lesion and suggests a favorable response to surgery.

References
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