Diagnosis of Hypertension due to Renal Arterial Stenosis

By ROBERT BIRCHALL, M.D., HUGH M. BATSON, JR., M.D., AND EUGENE G. ANDERSON, M.D.

In 1962, we published a report on the value of the comparative $U_{\text{sodium}}/U_{\text{creatinine}}$ ratio in the diagnosis of hypertension due to renal arterial stenosis. This ratio is defined as the proportional relation between the concentration of sodium and creatinine ($U_{\text{sodium}}/U_{\text{creatinine}}$) in the urine issuing simultaneously from each ureter. We also suggested that routine performance of dehydrated-hydrated intravenous pyelography on all hypertensive patients would adequately exclude renal arterial stenosis as the cause of the elevated blood pressure. In the crucible of 1 year’s time, these tenets have held. This paper extends these observations and appraises them more critically. It also describes a method whereby, without added discomfort to the patient, the difference in comparative $U_{\text{sodium}}/U_{\text{creatinine}}$ ratio, in the presence of renal arterial stenosis, is greatly exaggerated by preceding the urine collection with a provocative infusion of hypertonic saline solution.

Methods

1. Differential Renal Study for Determination of the Comparative $U_{\text{sodium}}/U_{\text{creatinine}}$ Ratio. Our technic for performing this has been previously described. Briefly, an abbreviated technic is employed whereby, after flow exceeds 2 ml./min. from at least one kidney, urine is collected from each ureteral catheter during consecutive 15-minute periods. The urine volume is measured and reported as ml./min. The urine sodium and endogenous creatinine are determined and reported as mEq./L. and mM./L., respectively. The comparative $U_{\text{sodium}}/U_{\text{creatinine}}$ ratio is calculated.

2. Differential Renal Clearance Combined with a Provocative Infusion of Hypertonic Saline Solution. At the conclusion of three clearance periods of 15 minutes each, an intravenous infusion of 2.5-per cent solution of sodium chloride, calculated to deliver at the rate of 0.25 ml. per kilogram per minute for 45 minutes, is started. Clearance periods are obtained continuously during the infusion and for three consecutive periods after infusion of hypertonic saline solution has been discontinued.

3. Comparative $U_{\text{sodium}}/U_{\text{creatinine}}$ Ratio Preceded by a Provocative Infusion of Hypertonic Saline Solution. An infusion of hypertonic saline solution, the amount being calculated as described in the preceding paragraph, is started as soon as the patient arrives for cystoscopy and is continued while number 5 or 6 ureteral catheters are being inserted. As soon as the infusion has been completed, and after the ureteral catheters have been indwelling for 15 minutes, two or three consecutive urine samples of approximately 10 ml. are collected from each ureter, without concern for leakage from the bladder. These are analyzed for sodium and creatinine concentration.

4. Dehydrated-Hydrated Intravenous Pyelography. Dehydrated intravenous pyelography is performed in the usual manner except that films are taken at 1-minute intervals for the first 5 minutes, and then at 10 minutes and 15 minutes. Rapid injection of the contrast medium is preferred.

The evening of the same day the patient is given castor oil. The next day he is given a liquid diet and is instructed to force fluids to insure adequate hydration. One hour before the dye is injected, the patient drinks 1,000 ml. of tap water within 15 or 20 minutes. This is carried out under supervision of a nurse to be certain that hydration is adequate. He then drinks 8 ounces of tap water every 15 minutes until the study is completed. (It is important that the study not be delayed, or the peak of diuresis will pass, and misleading concentration of dye may be noted on the roentgenograms.) Films are made at 5, 10, and 15-minute intervals.

5. I$^{131}$ Hippuran renograms are made according to standard technic.

Results

Aortography was performed on all patients. In order to evaluate the reliability of the

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comparative $\text{Usodium}/\text{Ucreatinine}$ ratio, the dehydrated-hydrated intravenous pyelograms, and hippuran $\text{I}^{131}$ renograms, aortography was permitted to be the final arbiter of the presence or absence of renal arterial stenosis.

For the sake of clarity and simplicity the comparative $\text{Usodium}/\text{Ucreatinine}$ ratio is expressed as a $1:X$ ratio by dividing the smaller number into the larger. In the absence of renal arterial stenosis this ratio will be close to 1:1. In the presence of renal arterial stenosis, the urine from the involved kidney will be represented by the lower number, or by 1. Bilateral renal arterial stenosis will be characterized by bilaterally low initial comparative $\text{Usodium}/\text{Ucreatinine}$ ratios because both kidneys will behave as “hypotensive” kidneys. The ratio between the two will be as close to 1:1 as the equality of the stenosis permits.

Table 1 lists the comparative $\text{Usodium}/\text{Ucreatinine}$ ratio of the six hypertensive patients whose arteriograms revealed renal arterial stenosis. Table 2 shows that in the absence of renal arterial stenosis a provocative infusion of hypertonic saline solution produces little change in the comparative $\text{Usodium}/\text{Ucreatinine}$ ratio. Table 3 illustrates the $\text{Usodium}/\text{Ucreatinine}$ ratio after provocative infusion of hypertonic saline solution in five patients with renal arterial stenosis. Table 4 illustrates the comparative $\text{Usodium}/\text{Ucreatinine}$ ratio of three patients with proved renal arterial stenosis before and after the provocative infusion of hypertonic saline solution. The sensitivity of the test was greatly increased in each instance.

### Table 1

<table>
<thead>
<tr>
<th>Patient</th>
<th>Average $\text{Usodium}/\text{Ucreatinine}$</th>
<th>Right kidney</th>
<th>Left kidney</th>
<th>Average ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 *</td>
<td>13.7</td>
<td>6.4</td>
<td>1:2.1</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>3.3</td>
<td>22.1</td>
<td>1:6.7</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>28.3</td>
<td>2.42</td>
<td>1:11.7</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>57.4</td>
<td>3.6</td>
<td>1:15.9</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>1.3</td>
<td>56.5</td>
<td>1:43.5</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>0.98</td>
<td>81.3</td>
<td>1:83.0</td>
<td></td>
</tr>
</tbody>
</table>

* Patient with proved bilateral renal arterial stenosis.

In one patient the provocative infusion of hypertonic saline solution changed the ratios from normal (1:1.28) to a strongly positive ratio of 1:50. The presence of the renal arterial obstruction was subsequently confirmed by aortography and surgically (fig. 1).

Dehydrated-Hydrated Intravenous Pyelogram. This combination was considered normal in the 21 patients whose arteriograms showed no abnormalities. In four patients, strikingly positive results (complete “washing out” of the unaffected kidney with the pyelogram of the affected kidney remaining intact, figures 1 and 2) were confirmed by arteriography.

Figures 1 and 2 illustrate the typical panels of two patients with proved renal arterial stenosis.

### Table 2

<table>
<thead>
<tr>
<th>Patient</th>
<th>$\text{Usodium}/\text{Ucreatinine}$</th>
<th>Right kidney</th>
<th>Left kidney</th>
<th>Average ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>7</td>
<td>19.2</td>
<td>19.3</td>
<td>1:1</td>
<td></td>
</tr>
<tr>
<td></td>
<td>After 124.8</td>
<td>115.9</td>
<td>1:1.1</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>Before 26.9</td>
<td>23.9</td>
<td>1:1.13</td>
<td></td>
</tr>
<tr>
<td></td>
<td>After 146.5</td>
<td>131.6</td>
<td>1:1.11</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>Before 146</td>
<td>162</td>
<td>1:1.1</td>
<td></td>
</tr>
<tr>
<td></td>
<td>After 185</td>
<td>155</td>
<td>1:1.2</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>Before 77</td>
<td>70</td>
<td>1:1</td>
<td></td>
</tr>
<tr>
<td></td>
<td>After 111</td>
<td>130</td>
<td>1:1.2</td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>Before 16.8</td>
<td>13.8</td>
<td>1:1.22</td>
<td></td>
</tr>
<tr>
<td></td>
<td>After 41.4</td>
<td>36.9</td>
<td>1:1.12</td>
<td></td>
</tr>
</tbody>
</table>

### Discussion

1. Comparative $\text{Usodium}/\text{Ucreatinine}$ ratio. In 1953, we demonstrated that after an infusion of hypertonic saline solution, hypertensive patients excrete a significantly greater percentage of filtered sodium and water than do normal subjects (fig. 3). When hypertension due to unilateral renal arterial stenosis became a recognized clinical entity, it occurred to us that this observation might have diagnostic value, since we could now compare simultaneously a hypertensive kidney.
Figure 1
The studies are arranged according to the description of figure 1. Note the hippuran $^{131}$I renogram does not localize the involved right renal artery. Patient no. 6.
with a hypotensive kidney. The alterations in the percentage of filtered sodium rejected by the tubules of each kidney (tubular reJectate fraction, or TRF) should, therefore, be moving in opposite directions. Consequently, a provocative infusion of hypertonic saline solution might be unnecessary. Our preliminary studies confirmed this. However, a differential inulin-PAH clearance test is unpleasant for the patient and technically exacting, for there must be no leakage around either ureteral catheter. Therefore, the test was simplified. It was shown that, numerically, the same comparative ratio could be obtained by comparing simultaneously the $U_{\text{sodium}}/U_{\text{creatinine}}$ in the urine issuing from each kidney. Comparison of the results obtained by each method of calculation illustrates the validity of the assumption in the final simplification.

As previously indicated, in all but three patients without renal arterial stenosis, the comparative $U_{\text{sodium}}/U_{\text{creatinine}}$ ratio was 1:1.4 or less. With the exception of one patient with proved bilateral renal arterial stenosis (1:2.1), the comparative $U_{\text{sodium}}/U_{\text{creatinine}}$ ratio in patients with renal arterial stenosis ranged from 1:6.7 to 1:83. Therefore, three patients fall within a range that might be considered suspect (1:1.5, 1:1.6, 1:1.7).

The validity of the simple comparative $U_{\text{sodium}}/U_{\text{creatinine}}$ ratio in the detection of renal arterial stenosis seems established. Others have attempted to increase its accuracy by making this simple test more complex and prolonged. In our experience, this adds greatly both to the discomfort of the patient and to the complications that are prone to follow the procedure. In order to shed more light on this grey zone of suspicious ratios (1:1.5, 1:1.6, 1:1.7) without adding materially to the discomfort of the patient, we decided to precede the test with a provocative infusion of hypertonic saline.

2. Comparative $U_{\text{sodium}}/U_{\text{creatinine}}$ Ratio Determination Preceded by a Provocative Infusion of 2.5 Per Cent Saline Solution. In the light of our initial observations (fig. 3), it seems clear physiologically that a provocative infusion of hypertonic saline solution must exaggerate the difference between the $U_{\text{sodium}}/U_{\text{creatinine}}$ ratio of a hypertensive and hypotensive kidney. Again, table 2 indicates that in the absence of renal arterial stenosis, a provocative infusion of hypertonic saline solution produces no significant change in the comparative $U_{\text{sodium}}/U_{\text{creatinine}}$ ratio. We accept 1:1.6 as the upper limit of normal. Table 3 illustrates the markedly positive results obtained in patients with proved renal

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**Figure 3**

*Hypertensive patients reject a significantly greater percentage of filtered sodium and water after a provocative infusion of hypertonic saline solution than do normal subjects. (Reproduced from Birchall et al. Circulation 7: 258, 1953.)*
HYPERTENSION DUE TO RENAL ARTERIAL STENOSIS

Table 3

Comparative $U_{\text{sodium}}/U_{\text{creatinine}}$ Ratio after Provocative Infusion of Hypertonic Saline in Patients with Renal Arterial Stenosis (Average of 3 Consecutive Periods)

<table>
<thead>
<tr>
<th>Patient</th>
<th>Right kidney</th>
<th>Left kidney</th>
<th>Average Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>12</td>
<td>26</td>
<td>179</td>
<td>1:6.9</td>
</tr>
<tr>
<td>13</td>
<td>3.9</td>
<td>71.9</td>
<td>1:18.4</td>
</tr>
<tr>
<td>3</td>
<td>91.5</td>
<td>1.29</td>
<td>1:51.1</td>
</tr>
<tr>
<td>14</td>
<td>4.55</td>
<td>228</td>
<td>1:50</td>
</tr>
</tbody>
</table>

arterial stenosis and table 4 indicates the great increase in sensitivity when the comparative $U_{\text{sodium}}/U_{\text{creatinine}}$ ratio is compared in three patients with proved renal arterial stenosis before and after the provocative infusion of hypertonic saline solution. In one patient an apparently false negative result was converted into a positive result (patient no. 14). The advantages of preceding the test with the infusion of hypertonic saline solution are:

A. The patient suffers no added discomfort, nor is use of indwelling ureteral catheters prolonged.

B. It insures a brisk flow of urine, at least from the uninvolved side, and exaggerates the difference in urinary flow from the two sides, as well as the difference in the sodium and creatinine content, and therefore in the comparative $U_{\text{sodium}}/U_{\text{creatinine}}$ ratio (table 4).

C. It should permit detection of severe, bilateral renal arterial stenosis, since both kidneys would then react as hypertensive kidneys. (Coarctation of the aorta obviously would have to be excluded.)

D. The procedure should be no more traumatic than routine retrograde pyelography and, therefore, it need be followed by a continuous infusion of a 4-per cent solution of urea only if excessive bleeding or difficulty in passing even the smaller ureteral catheter is encountered.

Obviously, hypertonic saline solution should not be administered to elderly patients or to those with potential congestive heart failure. It seems evident that a provocative infusion of the currently less available angiotensin could serve the same purpose as hypertonic saline solution. Pearl and Brown demonstrated that angiotensin produced antidiuresis in normal subjects and sodium diuresis in hypertensive patients. Biron and co-workers demonstrated that angiotensin infusions lasting 1 to 6 hours produced a drop of 51 per cent in the percentage of filtered sodium excreted in normotensive subjects, and a 323-per cent increase in the percentage of filtered sodium excreted in hypertensive patients. The difference between a hypertensive kidney and a hypertensive kidney should be even more striking. Since our goal has been simplicity, hypertonic saline solution remains the provocative infusion of choice.

We still have no experience with segmental occlusion, and we therefore do not know how accurate the comparative $U_{\text{sodium}}/U_{\text{creatinine}}$ ratio would be in detecting this lesser lesion. That it might be so detected is implicit in the observations of Madeloff and associates, who found the percentage of filtered sodium excreted to be reduced by “twenty per cent or more in the presence of segmental ischemia.” Since the “per cent E. F. sodium” is calculated by the formula $U/P_{\text{sodium}}/U/P_{\text{creatinine}}$, the ratio between the “per cent E. F. sodium of each kidney and the $U_{\text{sodium}}/U_{\text{creatinine}}$ of each kidney is mathematically identical. Recalculation of their presented data confirms this.

In the majority of patients, we now believe the provocative infusion of hypertonic saline solution to be the procedure of choice. In the occasional patient, particularly when the overall renal status is considered precarious, with

Table 4

Comparative $U_{\text{sodium}}/U_{\text{creatinine}}$ Ratio before and after a Provocative Infusion of Hypertonic Saline Solution in Patients with Proved Renal Arterial Stenosis (Average of 3 Consecutive Periods)

<table>
<thead>
<tr>
<th>Patient</th>
<th>Right kidney</th>
<th>Left kidney</th>
<th>Average Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>Before 28.3</td>
<td>2.42</td>
<td>1:11.7</td>
</tr>
<tr>
<td></td>
<td>After 91.5</td>
<td>1.29</td>
<td>1:51.1</td>
</tr>
<tr>
<td>12</td>
<td>Before 57.2</td>
<td>2.6</td>
<td>1:22</td>
</tr>
<tr>
<td></td>
<td>After 109.6</td>
<td>2.4</td>
<td>1:45.7</td>
</tr>
<tr>
<td>14</td>
<td>Before 4.69</td>
<td>6.0</td>
<td>1:128</td>
</tr>
<tr>
<td></td>
<td>After 4.55</td>
<td>228.0</td>
<td>1:50</td>
</tr>
</tbody>
</table>
nephrectomy a possibility, it is necessary to know the contribution of each kidney to the total renal function. We then prefer full inulin-PAH clearance, followed after the first three periods by a provocative infusion of hypertonic saline solution.

3. Dehydrated-Hydrated Intravenous Pyelography. In 1958, we\textsuperscript{5} demonstrated that in the presence of unilateral renal arterial stenosis, the U/P inulin determination was invariably above one and always comparatively higher than it was in the urine coming from the hypertensive kidney. This reflects the insatiable thirst of the hypertensive kidney for water, even under conditions of maximum water diuresis. We\textsuperscript{1} later, within the framework of the countercurrent theory of urinary concentration, explained why, under conditions of maximum water diuresis, the urine formed by the hypertensive kidney is, of necessity, small in volume and slightly concentrated. It then follows that comparison of a dehydrated and hydrated intravenous pyelogram should provide an extremely reliable, widely applicable, non-traumatic "screen" for excluding renal arterial stenosis in all patients with hypertension. The hydrated intravenous pyelogram is used to determine whether or not one of two kidneys which appear normal on dehydrated excretory pyelography is inherently unable to elaborate dilute urine under conditions of maximum water diuresis. In effect, the picture of the hypertensive kidney is "washed out" and that of the hypertensive kidney remains clearly visible (figs. 1 and 2).

This test has proved successful, and we have encountered neither a false positive nor a false negative result. Certain comments in interpretation are pertinent:

A. Often, faint concentration of dye will be seen on each side, and close reading might suggest that one side is slightly less faint than the other. This should be considered negative, as in each of our positive results the difference between the two sides was striking.

B. A bilateral lesion might be expected to show an adequate concentration of dye on each side. Such a conclusion is not warranted unless the hydrated intravenous pyelogram is repeated with Oxaine to preclude retention of the ingested water in the stomach as the result of pylorospasm.

C. Coarctation of the aorta is the only disease which could mimic bilateral renal arterial stenosis. We have documented this once.

D. In the presence of almost complete, unilateral, renal arterial stenosis, the hydrated intravenous pyelogram might not reveal a significant shadow on the affected side. It seems evident, however, that such a lesion would be demonstrated by the dehydrated intravenous pyelogram.

E. In the hope of detecting renal arterial stenosis by delay in appearance or disappearance of the dye on the affected side, we have routinely taken films at 1, 2, 3, 4, 5, 10 and 15-minute intervals. A delay of 1 minute was, in fact, noted in each of the three patients with proved renal arterial stenosis studied by this technic. The fact that two patients without renal arterial stenosis exhibited a similar 1-minute delay makes this facet of the examination suggestive but not diagnostic.

F. A singular advantage of the dehydrated-hydrated intravenous pyelogram as a "screen" for renal arterial stenosis is that it can be performed in any hospital, clinic, or office with roentgenologic equipment.

Renogram. We believe the hippuran-$^{131}$ renogram has not yet been fully evaluated as a "screen" for renal arterial stenosis. The expense of the equipment makes it at present impractical for widespread use. The simplicity and safety of the procedure commend it. It has been clearly abnormal in all cases of proved renal arterial stenosis studied by us, and we have encountered only one falsely negative tracing. Like others\textsuperscript{2,3} however, we have found no specific pattern characteristic of renal arterial stenosis. This lack of specificity is clearly illustrated in figure 2. The hydrated intravenous pyelogram clearly indicates the "hypotensive" kidney, whereas the renogram, although abnormal, does not indicate on which side the renal arterial stenosis is located. Also, we have several times noted "positive" renograms not associated with renal arterial disease. Since the renogram apparent-
ly cannot distinguish between renal arterial stenosis and parenchymal disease of the kidney, it can serve as a screening procedure for hypertensive patients only in the negative sense. Any hypertensive patient with abnormal renographic observations must be subjected to more accurate and definite studies before an exact diagnosis can be made.

Summary and Conclusions
The definitive diagnosis of renal arterial stenosis (full differential renal clearance and arteriography) as the cause of diastolic arterial hypertension is technically simple, but not without hazard and discomfort to the patient. Lacking has been a simple test that imposes no undue hazard or discomfort on the patient, and can be used as a "screen" on all patients with hypertension. We advocate the following.

Dehydrated-hydrated intravenous pyelography. This is the simplest, most generally applicable, and possibly most specific of the screening procedures. It is less hazardous and less uncomfortable for the patient than all but hippuran I\(^{131}\) renography. If the results are definitely negative, we believe we can dispense with further tests. If a question remains, this test can be followed by:

Comparative \(U_{\text{sodium}}/U_{\text{creatinine}}\) ratio preceded by a provocative infusion of hypertonic saline solution. The provocative infusion greatly exaggerates this ratio and so increases the sensitivity of the test.

Comparative \(U_{\text{sodium}}/U_{\text{creatinine}}\) ratio alone in those patients in whom a provocative infusion of hypertonic saline solution seems advisable.

Full inulin-PAH differential clearance combined with a provocative infusion of hypertonic saline solution if it is considered mandatory to establish separately the function of each kidney.

Hippuran I\(^{131}\) renogram. A normal result with bilaterally equal renograms will almost always exclude renal arterial stenosis. An abnormal result requires the addition of more definitive procedures, since the renogram evidently cannot distinguish between renal parenchymal and renal arterial disease. Its simplicity commends it, but the expense of the equipment and its lack of specificity make it less practical.

References
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