The Role of Laboratory Testing in the Diagnosis of Renovascular Hypertension

Thomas G. Pickering

The diagnosis of renovascular hypertension depends heavily on laboratory tests. There is no universally applicable screening test, and it should be actively sought only in patients with clinical clues suggested by the history, physical examination, and routine laboratory testing. Hyperreninemia is a characteristic finding, and acute blockade of the renin system forms the basis of diagnostic tests such as the oral captopril test and captopril renography. Other abnormal laboratory findings include hypokalemia, proteinuria, and azotemia exacerbated by angiotensin-converting enzyme inhibitors.

The diagnosis of renovascular hypertension is often difficult to make clinically, and has to be based on a high index of suspicion coupled with a judicious selection of laboratory tests. It is almost certainly underdiagnosed, but its diagnosis is important, being far the commonest curable form of hypertension and also a major cause of chronic renal failure. Although the demonstration of an anatomical renal artery stenosis is an essential part of the diagnostic procedure, this is not by itself sufficient, because the stenosis may be coincidental or, if atheromatous, may have developed secondarily to essential hypertension. To cause renovascular hypertension, the stenosis must be of sufficient magnitude to cause renal ischemia, so the complete diagnostic procedure should attempt to establish functional ischemia as well as an anatomical diagnosis.

What is needed is a screening test that is not only inexpensive and simple to perform but also accurate. An example of such a test is the measurement of serum potassium for diagnosing aldosterone-secreting tumors. Hypokalemia is present in virtually all affected patients (i.e., the sensitivity of the test is very high) and, although it is certainly not pathognomonic of an aldosteroneoma (i.e., its specificity is relatively low), other causes of hypokalemia are usually relatively easy to diagnose. Unfortunately, there is no equivalent test for renovascular hypertension. Therefore, because the available screening tests are less accurate and more costly, careful consideration must be given as to how widely they should be applied.

Association between Prevalence and the Utility of Screening Tests

As with any other clinically silent condition, the value of screening tests for the diagnosis of renovascular hypertension will depend to a large extent on its prevalence. This can be demonstrated mathematically by the application of Bayes’ theorem and has been discussed extensively in the medical literature, particularly with regard to screening for coronary artery disease (1, 2). Most screening tests require the setting of a threshold value that separates a positive from a negative test; where this threshold is set will influence the sensitivity and specificity of the test. So as not to miss diagnosing cases with the condition being screened for, it is appropriate to set the threshold at a value that will give a high sensitivity; however, this will inevitably be at the expense of a reduced specificity. The disadvantage of this decision is that it will increase the number of false positives, which, if the condition is rare, may outnumber the true positives. As shown in Table 1, which is based on a report by Vecchio (3), the predictive value of a positive test (i.e., the percentage of times that a positive test will detect an individual with renovascular hypertension) is quite low when populations with low prevalence (e.g., 2%) are screened. Even these numbers are somewhat optimistic, because they are based on the assumption that the screening test has both a sensitivity and a specificity of 95%, which is probably greater than for any currently available test.

Given these considerations, and the fact that there is no ideal screening test for detecting renovascular hypertension, the most appropriate method for making the diagnosis of this disorder would appear to involve using a series of steps, rather than applying a screening test to everyone. As described below, the clinical history and routine laboratory evaluation of hypertensive patients may provide several useful clues to the presence of hypertension, permitting an initial stratification of patients into low and high probability groups.

Prevalence of Renovascular Hypertension

The prevalence of renovascular hypertension is unknown, but almost certainly is <5% of the general hypertensive population (4); however, for patients with more severe hypertension, much higher estimates of prevalence have been reported. In a systematic evaluation of 3520 hypertensive patients who were screened with saralasin testing, Anderson et al. (5) found an

<table>
<thead>
<tr>
<th>Disease prevalence, %</th>
<th>PV positive, %</th>
<th>PV negative, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>16</td>
<td>99.9</td>
</tr>
<tr>
<td>2</td>
<td>28</td>
<td>99.9</td>
</tr>
<tr>
<td>5</td>
<td>50</td>
<td>99.7</td>
</tr>
<tr>
<td>10</td>
<td>68</td>
<td>99.4</td>
</tr>
<tr>
<td>20</td>
<td>83</td>
<td>98.7</td>
</tr>
</tbody>
</table>

Cardiovascular Center, The New York Hospital–Cornell Medical Center, 525 East 68th St., Starr–4, New York, NY 10021. Received February 22, 1991; accepted April 12, 1991.
overall prevalence of 3% for renovascular hypertension. At the other extreme, in a series of 123 patients with accelerated or malignant hypertension (grade III or IV retinopathy), Davis et al. (6) reported a prevalence of 43% in white patients and 7% in black patients. Other studies have also reported a lower prevalence in black subjects: a recent survey of 7200 black hypertensive patients detected 0.65% with renovascular hypertension, but not all of these patients were fully screened (7). The majority of such cases were due to atheroma.

These results were all based on clinical studies that, with one exception (6), did not use arteriography in all patients. The prevalence rates are therefore almost certainly an underestimate. However, the situation is complicated by the fact that the demonstration of an anatomical stenosis in the renal artery of a hypertensive patient does not imply that the lesion is causing the hypertension. In an autopsy series of 295 patients, Holley et al. (8) found renal artery stenosis (defined as a stenosis exceeding 25% of the intraluminal diameter) in 49% of normotensive subjects, and 77% of hypertensive subjects (defined by an antemortem diastolic pressure >100 mmHg). However, many of these lesions can be presumed to be hemodynamically insignificant. In another series of 500 aortograms performed for investigation of peripheral vascular disease or hypertension, renal artery stenosis was detected in 32% of normotensive and in 62% of hypertensive subjects (9).

Clinical Signs and Symptoms

Because of its relative frequency and curability, it is important not to miss the diagnosis of renovascular hypertension. Many clues to its presence may be evident in the history and clinical examination. Some of the most important features that distinguish it from essential hypertension are shown in Table 2.

In younger patients, and particularly in women, the commonest cause is fibromuscular disease, a relatively rare disease in black subjects. A family history of hypertension is less likely to be present than in cases of essential hypertension, although a familial occurrence of fibromuscular dysplasia has occasionally been described (10). Thus in a young white woman with a recent onset of hypertension and a negative family history, there should be a very high index of suspicion for fibromuscular disease. Women with fibromuscular dysplasia tend to be taller than those with essential hypertension or atheromatous renal artery stenosis (11). Conversely, the finding of hypertension in a middle-aged man with other evidence of atheromatous disease such as coronary heart disease should raise the possibility of atheromatous renovascular hypertension. In hypertensive patients undergoing coronary angiography, a surprisingly high prevalence of renovascular disease was detected (12). The importance of the patient's age and blood pressure was emphasized in the study of Anderson et al. (5). At any age, the prevalence increased with the severity of the hypertension and was highest (25%) in patients over age 60 years with diastolic blood pressures >110 mmHg.

The physical examination may also reveal clues to its presence. Abdominal bruits are present in ~40% of patients and usually signify the presence of renal artery stenosis, although they may originate from other vessels. Such bruits are, of course, most likely to be heard in thin patients.

Retinopathy may be particularly pronounced in patients with renovascular hypertension, perhaps because of its more brief and stormy course. In one series of patients with diastolic blood pressures >125 mmHg and hemorrhages or exudates in the fundi, renovascular hypertension was diagnosed in about one-third (6). In our experience, pulmonary edema in a hypertensive patient is commonly associated with bilateral renal artery stenosis (13).

A history of smoking is another potential clue to the presence of renovascular hypertension. In a series of patients with atheromatous renal artery stenosis studied by my colleagues and I (14), 88% were smokers, compared with only 42% of the patients with essential hypertension. This finding is consistent with reports of an association between smoking and atheroma in other areas, e.g., coronary heart disease and peripheral vascular disease. More surprising was our finding of a higher than expected incidence of smokers in patients with fibromuscular disease.

Laboratory Investigations

Azotemia. Evidence of impaired renal function on routine biochemical tests, e.g., above-normal results for blood urea nitrogen or creatinine, suggests either the presence of parenchymal disease or, if there is renovascular disease, the presence of bilateral renovascular damage. In the U.S. cooperative study, 15% of patients with atheromatous renal artery stenosis had an increased concentration of serum creatinine (>15 mg/L), compared with 11% of patients with essential hypertension, and only 2% of patients with fibromuscular dysplasia (10). The finding of an increase in serum creatinine is not a very specific discriminator between unilateral and bilateral disease, however. In a recent study of
elderly patients with renovascular hypertension, bilateral renal artery stenosis was only slightly more common in patients with serum creatinine >14 mg/L than in patients with normal creatinine concentration (15).

A more specific marker of renovascular hypertension may be the occurrence of a sudden increase of the serum creatinine and urea nitrogen in a patient who is started on treatment with an angiotensin-converting enzyme (ACE) inhibitor.1 This phenomenon, observed shortly after the introduction of captopril (16), was subsequently found to be particularly characteristic of patients with bilateral renal artery stenosis or with a stenosis and a solitary kidney (17). The generally accepted explanation is that when the glomerular perfusion pressure is reduced as a result of the renal artery stenosis, the glomerular filtration rate (GFR) is maintained by angiotensin-induced efferent arteriolar vasconstriction. When the angiotensin is removed by the ACE inhibitor, there is a marked decrease in GFR. This phenomenon also provides the basis of captopril renography, which is described below.

Although ACE inhibitor-induced azotemia is certainly suggestive of bilateral renovascular disease, it is not specific. Azotemia can occur with other antihypertensive agents, although less commonly, and does not always denote renovascular disease (18).

Hypokalemia. A low serum potassium is an occasional marker of renovascular disease: in the U.S. cooperative study, about 15% of patients with either atheromatous or fibromuscular disease had a potassium concentration <3.4 mmol/L. Anderson et al. (5) also found hypokalemia to be a helpful clue: the prevalence of renovascular hypertension was 1.7% when the serum potassium was 4.3-4.8 mmol/L, and 32.5% at 2.4-2.8 mmol/L. This occurs as a result of hyperreninemia, which stimulates angiotensin and aldosterone.

Urinalysis and proteinuria. Urinalysis may show a slightly increased incidence of bacteriuria. Proteinuria is not an uncommon finding in patients with renovascular hypertension (10), and may occasionally reach the values seen in the nephrotic syndrome (19). In our experience, proteinuria >500 mg/24 h usually signifies complete occlusion of a renal artery in patients with renovascular hypertension (20). This proteinuria may be reversed by surgery or angioplasty.

Table 3. Screening Tests for Renovascular Hypertension

<table>
<thead>
<tr>
<th>Test</th>
<th>Sensitivity, %</th>
<th>Specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Office tests</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Plasma renin activity</td>
<td>57</td>
<td>66</td>
</tr>
<tr>
<td>Captopril test</td>
<td>39–100</td>
<td>72–100</td>
</tr>
<tr>
<td>Tests of localization</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intravenous pyelogram</td>
<td>74–78</td>
<td>86–88</td>
</tr>
<tr>
<td>Renal scan</td>
<td>74</td>
<td></td>
</tr>
<tr>
<td>Captopril scan</td>
<td>92–94</td>
<td>95–97</td>
</tr>
<tr>
<td>Renal vein renin</td>
<td>62–80</td>
<td>60–100</td>
</tr>
<tr>
<td>Digital subtraction angiogram</td>
<td>88</td>
<td></td>
</tr>
<tr>
<td>Duplex Doppler imaging</td>
<td>84–91</td>
<td>95–97</td>
</tr>
</tbody>
</table>

Diagnostic Tests

Numerous tests have been proposed for diagnosing renovascular hypertension. The sensitivity and specificity of some of the more popular ones are given in Table 3. These tests can be classified into two categories: First are those that can be done in a physician's office, which are relatively simple to perform and inexpensive but do not indicate which kidney is involved. Measurement of peripheral plasma renin activity and the captopril test

1 Nonstandard abbreviations: ACE, angiotensin-converting enzyme; GFR, glomerular filtration rate; DSA, digital subtraction angiography, and DTPA, diethylenetriaminepentaacetic acid.

are in this category. Second are those tests that provide anatomic or functional information about each kidney, which cannot be routinely done in the office. Ideally, one or more of these tests should be done after the first-stage tests.

Peripheral plasma renin activity. Unilateral hypersecretion of renin should be the hallmark of potentially curable renovascular hypertension. We have found that peripheral plasma renin activity, when measured in the morning in a seated subject and indexed against sodium excretion, is an excellent tool for indentifying abnormally high renin secretion. This high rate of secretion is present in about 75% of patients with proven renovascular hypertension (21, 22). In our experience, a low value for plasma renin in an untreated patient virtually rules out the possibility of renovascular hypertension; however, the sensitivity and specificity of a high renin result are inadequate to be of much value as a screening test.

Captopril test. At present, the most sensitive office screening test for the diagnosis of renovascular hypertension is the captopril test. Case and Laragh (23) were the first to show that the reactive increase of renin after administration of captopril is greater in patients with renovascular hypertension than in those with essential hypertension. The criteria we have found to be the most reliable for distinguishing patients with renovascular hypertension are as follows (all three criteria must be met):

1. Stimulated plasma renin activity of 12 µg/L (ng/mL) per hour.
2. Absolute increase in plasma renin activity of ≥10 µg/L per hour.
3. Increase in plasma renin activity of 150% or more, or of 400% if baseline value is <3 µg/L per hour.

In a series of more than 200 patients we found that, with these criteria, the sensitivity and specificity of this test were better than 95% (24).

Several other groups (25–32) have reported on the use of the captopril test, with very divergent results (see Table 3). These differences may result for a number of different reasons. First, there are variations in the test. We performed our study with patients seated, whereas Postma et al. (31), who reported the lowest sensitivity (39%), had their patients supine. This is an important
difference because the renin system is more reactive in the seated position. Second, there are differences in the criteria used to define a positive test. And third, there are differences in the criteria used to define renovascular hypertension. We (33), and Fredrickson et al. (30), who also found the test to have a high sensitivity, required an angiographic stenosis of at least 75% to make the diagnosis, whereas Postma et al. (31) used 50%. This would explain why they found such a high prevalence of renovascular hypertension in their series (42%), because it is likely that many of their patients did not have a functional renal ischemia.

In a study comparing the value of several screening tests (including captopril renography and captopril-stimulated renal vein renins), Svetkey et al. (28) concluded that captopril-stimulated peripheral renin activity had the greatest sensitivity and specificity, although these values still were not very good (73% and 72%, respectively). The renin response is a much more reliable marker than the blood pressure response. Although patients with renovascular disease tended to show a greater decrease of blood pressure (average 18 mmHg in our study) than did patients with essential hypertension (average 7 mmHg), there is considerable overlap. The blood pressure response, however, may predict the blood pressure response to revascularization by surgery or angioplasty (32). The captopril test becomes less reliable in patients who are azotemic, although even here patients who show a negative test result possibly may be less likely to benefit from renal revascularization. The captopril test also does not discriminate between patients with unilateral versus bilateral disease, both of which groups usually show a positive response (24, 29).

**Differential renal vein renin determinations.** In patients with unilateral renal artery stenosis, hypersecretion of renin by the ischemic kidney is the hallmark of renovascular hypertension and can be evaluated by measuring renal vein renin. In the ideal (model) situation, the subject has not only unilateral hypersecretion but also contralateral suppression of renin secretion (21, 33, 34). This can be evaluated by comparing the renin concentration in each renal vein with that in the corresponding inferior vena cava (below the level of the renal veins), which has been shown to be the same as the concentration in the renal artery. Thus, when there is contralateral suppression of renin secretion, the renin concentration in the renal vein and the inferior vena cava will be the same. Measuring the increment of renin [as (V − A)/A, where V and A are the concentrations in the renal vein and inferior vena cava, respectively] on each side has shown to be superior to simply using the ratio between the two renal veins, because the latter cannot detect whether renin secretion is suppressed or not (21). The renin secretion by each kidney is thought to be best measured as the increment of renin between the renal artery and vein. In practice, the renin activity in plasma is the same in the renal artery as in the inferior vena cava below the level of the renal veins (21).

The test is performed by taking four blood samples. The catheter is inserted into one renal vein for one sample and then withdrawn to the inferior vena cava, where the second sample is taken. The procedure is repeated on the other side. The sensitivity of the test can be increased by repeating the measurements after acute administration of captopril, but false-negative results may still occur (35, 36).

In patients with stenoses of both renal arteries, the pattern of renin concentrations in the renal veins often shows the same degree of asymmetry as in patients with unilateral stenosis, and usually lateralizes to the kidney that shows the greatest degree of stenosis on the arteriogram (37). The most marked asymmetry is seen in patients who have complete occlusion of one renal artery, in whom (V − A)/A >2 is common. This may represent low flow through the kidney rather than hypersecretion of renin. Contralateral suppression of renin secretion may occur even in the presence of a severe stenosis of the contralateral renal artery. This asymmetry is less pronounced in the presence of azotemia. The test is thus of little value in patients with bilateral disease, except for identifying which kidney is most severely affected.

**Intravenous pyelogram.** For many years, the rapid sequence intravenous pyelogram was used as the standard screening test. Surveys of its usefulness, however, have indicated that the number of hypertensive patients whose treatment was altered as a result of previously unsuspected abnormalities is very small, being 0.9% in one series (38), and 1.3% in another (39). We no longer use it as a routine screening procedure.

**Digital subtraction angiography.** Digital subtraction angiography (DSA) represents a major advance in the evaluation of patients with suspected renovascular hypertension. Much of the information gained from conventional arteriography can now be gained from DSA, with much less expense and inconvenience to the patient. It can be performed as an outpatient investigation, and in our experience can be conveniently combined with renal vein renin measurements.

Several studies have compared the reliability of DSA with that of arteriography (41–44): in about 80% of cases, results by the two techniques agree, with DSA showing roughly 5% false positives (i.e., lesions that are not detected on the arteriogram), and 10% false negatives. For the latter, lesions of branch renal arteries are particularly likely to be missed.

Because of the relatively large volume of dye needed, the technique is not suitable for use in azotemic patients, in whom there is a risk of dye-induced nephrotoxicity.

**Renal scans.** Isotope renograms or renal scans have been available for many years, but have not attained wide acceptance as screening tests, because of their relatively low sensitivity and specificity (45, 46). The most widely used isotopes have been labeled hippuran and diethylenetriaminepentaacetic acid (DPTA); the former gives an approximate measure of renal blood flow, the latter of GFR.
Two recent developments have given these techniques a new lease on life. The first is the development of more reliable quantitative evaluation of the renogram, and the second (described below) is the use of ACE inhibitors to enhance the difference between normal and ischemic kidneys. An example of the improved quantification of DTPA scans is a recent study by Gruenewald et al. (47), who used deconvolution analysis to estimate the transit time of parenchymal tracer through the kidney. In patients with atheromatous unilateral renal artery stenosis, a prolonged parenchymal transit time was a highly specific predictor of the blood pressure response to angioplasty. These new methods of analysis require validation on a wider scale before their implications can be properly assessed.

**Captopril renography.** A potentially interesting development of the conventional renal scan is to compare the renograms obtained before and after a single dose of captopril. The rationale for this is that the glomerular filtration rate of an ischemic kidney is dependent on the effects of angiotensin on the efferent glomerular arterioles, so that inhibition of ACE produces a marked decrease in GFR. However, the changes in renal blood flow are less pronounced. Therefore, the characteristic effect of captopril in a kidney with a renal artery stenosis is to cause a decrease of DTPA uptake (a measure of GFR) with little change of hippuran uptake (a measure of renal blood flow), although the excretion phase of hippuran is delayed (48, 49).

Several recent studies report that administration of captopril (50, 51) or enalapril (52) increases both the sensitivity and specificity of renal scans. DTPA has been used most widely, although some claim that hippuran may be just as sensitive (52). Analytical techniques include estimating parenchymal tracer transit time (52) and GFR (50) when examining the effects of captopril. We identified three criteria for diagnosing renal artery stenosis (50): the percentage uptake of DTPA by the affected kidney is <40% of the total; the time to peak uptake of DTPA is >5 min longer than in the contralateral kidney; and the retention of DTPA, expressed as the fraction of peak activity 15 min after DTPA administration, is prolonged at least 20% longer than in the contralateral kidney. The sensitivity and specificity of these criteria were all greater for the post-captopril than for the pre-captopril scan, but the change induced by captopril had no additional diagnostic value (50). If this is confirmed in other studies, it suggests that the pre-captopril scan may be redundant in many instances. Captopril renography may prove particularly useful in discriminating between renovascular and parenchymal disease, although in our experience it does not work well in azotemic patients.

**Duplex Doppler imaging.** Another new technique currently being investigated is the use of Doppler ultrasound scanning to record velocity profiles from the renal arteries (53, 54).

Several criteria have been developed for diagnosing renal artery stenosis (55–57). The most reliable appears to be the ratio of peak systolic velocities in the renal artery and aorta. In patients in whom technically satisfactory readings can be obtained, a ratio >3.5 predicts renal artery stenosis of ≥60% with a sensitivity of 84–90% and a specificity of 95–97% (56, 57).

These figures are encouraging, but the technique has some limitations. First, as many as 40% of the examinations may be technically unsatisfactory because of inability to identify one or both renal arteries, owing to factors such as obesity or excessive bowel gas (58). Also, one can usually obtain an adequate examination of only the proximal end of the renal arteries, so that lesions due to fibromuscular dysplasia may be missed. Another problem is the relatively common occurrence of multiple renal arteries, which may be overlooked. Further evaluation of this test is also needed.

**Split renal-function studies.** In 1953 Howard et al. (59) introduced split renal-function studies to identify patients with surgically correctable renovascular hypertension. This remains one of the most accurate and reliable tests, but has fallen into disfavor because of its relative invasiveness—it necessitates cystoscopy and catheterization of both ureters.

**Arteriography.** The demonstration of a stenosis in a renal artery in a hypertensive patient does not necessarily imply that the stenosis is causing the hypertension, particularly when the stenosis is atheromatous. Hypertension from any cause accelerates the development of atheroma, so that in some cases a stenosis in a renal artery may occur secondary to essential hypertension. To cause renal ischemia and hypertension, a stenosis must occlude at least 75% of the arterial lumen, but the correlation between the arteriographic appearance and the degree of ischemia is poor (60, 61).

In one series, where the accuracy of arteriography in diagnosing the pathology of renal arteries was estimated by comparison with the pathological specimens removed at surgery, the sensitivity for distinguishing fibromuscular disease from atheroma was 83% (62). The absence of abdominal aortic atherosclerosis was a reliable predictor of fibromuscular disease. However, separation of the different types of fibromuscular disease could not be reliably assessed from the arteriogram.

**Sequence of Testing for Evaluating Renovascular Hypertension**

Given the low overall prevalence of the disease, and the high cost and imperfect accuracy of the available screening tests, it is inappropriate to recommend routine screening in all hypertensive patients. By using simple clinical and demographic criteria, one can identify a subgroup of patients in whom the probability of renovascular disease is quite high. In these patients an oral captopril test would be our next step, possibly combined with renography, if subsequent studies confirm its early promise. Duplex scanning of the renal arteries may also prove helpful but, whereas this test may provide anatomical information as to the presence of a stenosis, it can provide no information as to the effects of the stenosis on the kidney. An alternative
approach, which we have used extensively in the past, and which provides both fundamental and anatomical data, is a combined intravenous DSA and measurement of renal vein renin.

It is ironic that most of the available tests work quite well in patients with "simple" renovascular hypertension, where there is a discrete unilateral stenosis and normal renal function, but none of them appears adequate in patients with "complex" renovascular hypertension, with bilateral stenoses and azotemia.

References
43. Hillman BJ, Ovitt TW, Capp MD, et al. The potential impact of digital video subtractions angiography on screening for reno-