Editorial Comment

Diagnostic Usefulness of Renal Scanning After Angiotensin Converting Enzyme Inhibitors

Richard Davidson and Christopher S. Wilcox

Radioisotopic renal scanning after angiotensin converting enzyme inhibition (ACEI) has proven to be an exciting area for research. The biologic activity of markers such as DTPA and hippuran, when combined with the physiological effects of ACEI, may provide noninvasive methods of diagnosing both renal artery stenosis and renovascular hypertension. Recent investigators have demonstrated that the sensitivities and specificities of these tests may vary widely; these differences are probably due to variations in study design, patient population, diagnostic criteria, and outcome measurements. We have reviewed these studies and discuss these possible sources of variation and their impact on the clinical usefulness of these diagnostic tests, especially in relation to the prevalence of disease in the population. Current results suggest that the post-ACEI DTPA scan is relatively accurate in the diagnosis of renal artery stenosis, with sensitivity generally greater than 90% and specificity around 95%. However, the best results in predicting the response to angioplasty or surgery in patients with renal artery stenosis have been with the use of post-ACEI hippuran in combination with furosemide (sensitivity, 96%; specificity, 95%). With confirmation of these findings and continued investigation, it is expected that accurate noninvasive tests will be available for widespread clinical use in the near future. (Hypertension 1991;18:299–303)

Among the hypertensive population, some 0.2–2% have radiological evidence of a narrowing of one or both renal arteries or a branch within the kidney (renal artery stenosis). Around half of these patients may be controlled or cured by relieving this obstruction (renovascular hypertension). Angiography has been the “gold standard” for the diagnosis of renal artery stenosis; however, alternative methods have been sought that are less invasive, expensive, and dangerous, and that might predict which patients will have a favorable response to angioplasty or surgery.

Renography using I-orthohippurate (hippuran) was widely evaluated during the 1960s since it is noninvasive and safe even in patients with renal insufficiency in whom radiological contrast studies are hazardous. Unfortunately, results of large trials revealed sensitivity and specificity of only approximately 75% each. Indeed, most subsequent recommendations for testing algorithms did not include renal scanning techniques.2,3

During the 1980s, reports appeared of patients with renal artery stenosis (usually bilateral or affecting a solitary or dominant kidney) whose glomerular filtration rate (GFR) deteriorated during administration of an angiotensin converting enzyme inhibitor (ACEI). McGrath et al4 first proposed that this adverse effect could be turned to advantage by using ACEI-induced changes in the GFR as a diagnostic test for renovascular disease. This suggestion has been extensively evaluated using both markers for GFR (99mTc-diethyleneetriamine pentaacetic acid [DTPA]) and renal plasma flow (RPF) (hippuran). In the current issue of Hypertension, Setaro et al5 report the experience of the Yale Vascular Center in the use of a test based on renal scanning with 99mTc-DTPA (renal scintigraphy) in 94 patients.

Animal studies of two-kidney, one clip (2K1C) models of renovascular hypertension provide a physiological background for interpreting tests based on renography or scintigraphy. In these models, administration of an ACEI during the early, angiotensin II–dependent phase reduces blood pressure sharply; the GFR of the kidney downstream from the clip falls, yet the RPF is well preserved. This fall in the
TABLE 1. Summary of Published Reports of Operating Characteristics of Angiotensin Converting Enzyme Inhibitor Scintigraphy or Renography in Renal Artery Stenosis

<table>
<thead>
<tr>
<th>Author</th>
<th>Using DTPA</th>
<th>Number (with/without RAS)</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fommei et al</td>
<td></td>
<td>12/27</td>
<td>83</td>
<td>85</td>
</tr>
<tr>
<td>Dondi et al</td>
<td></td>
<td>37/68</td>
<td>92</td>
<td>97</td>
</tr>
<tr>
<td>Mann et al</td>
<td></td>
<td>35/20</td>
<td>94</td>
<td>95</td>
</tr>
<tr>
<td>Setaro et al</td>
<td></td>
<td>44/50</td>
<td>91</td>
<td>94</td>
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</table>

<table>
<thead>
<tr>
<th>Author</th>
<th>Using 131-I-orthohippurate</th>
<th>Number (with/without RVH)</th>
<th>Criteria for diagnosis of RVH</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wenting et al</td>
<td></td>
<td>14/17</td>
<td>PTRA</td>
<td>87</td>
<td>89</td>
</tr>
<tr>
<td>Mann et al</td>
<td></td>
<td>35/20</td>
<td>PTRA or RVR</td>
<td>89</td>
<td>100</td>
</tr>
</tbody>
</table>

RAS, renal artery stenosis as diagnosed by arteriography; DTPA, 99mTc-diethylenetriamine pentaacetic acid.

filtration fraction suggests that the ACEI has reduced the glomerular capillary pressure. There is also an antidiuretic. In contrast, the GFR of the contralateral kidney is maintained, and there is an accompanying renal vasodilation and diuresis.6,7 These changes in renal hemodynamics appear quite specific for ACEIs; the subsequent differential GFR between the kidneys was the basis for early investigations into ACEI-induced changes in the DTPA scintigram as a diagnostic test of renovascular disease. DTPA is filtered at the glomerulus and not reabsorbed by the tubules. Thus, like inulin, it is an acceptable marker for the GFR. 99mTc-DTPA is readily visualized and quantitated by external counting methods; thus, the early phase accumulation of the isotope over the kidneys can estimate the relative contribution of each kidney to the total GFR by calculation of a ratio. The actual measurement of GFR is best quantitated from the rate of plasma disappearance of 99mTc-DTPA after bolus intravenous injection.8

Unlike DTPA, hippuran is secreted into proximal tubular fluid. Therefore, using the analogue of the 2K1C renovascular rat model, the ACEI should maintain the RPF, preserving renal hippuran delivery and uptake from the blood into the tubular fluid of the kidney after stenosis; additionally, the fall in fluid filtration and the enhanced rate of tubular fluid reabsorption should greatly delay transit of hippuran through the renal tubules. This is detected as a delay in the time to peak concentration of hippuran in the renal cortex or in extreme cases, as a progressive accumulation of hippuran throughout the entire course of the renogram after an ACEI.8

An analysis of publications that have used an ACEI in conjunction with renal scintigraphy or renography for the detection of renal artery stenosis or renovascular hypertension is shown in Tables 1 and 2. Most studies have used captopril as an ACEI, although intravenous enalaprilat may be equally effective.8 Because there is variability among these studies with regard to patient preparation and conduct of these tests, as well as diagnostic criteria, the values for sensitivity and specificity can only be considered as approximations, and summarization of the results could be misleading. Despite these reservations, it appears there is general agreement that the DTPA scan after ACEI is relatively accurate in

TABLE 2. Summary of Published Reports of Operating Characteristics of Angiotensin Converting Enzyme Inhibitor Scintigraphy or Renography in Renovascular Hypertension

<table>
<thead>
<tr>
<th>Author</th>
<th>Using DTPA</th>
<th>Number (with/without RVH)</th>
<th>Criteria for diagnosis of RVH</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
</tr>
</thead>
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<tr>
<td>Geyskes et al</td>
<td></td>
<td>15/19</td>
<td>PTRA</td>
<td>86</td>
<td>89</td>
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<tr>
<td>Sfakianakis et al</td>
<td></td>
<td>16/15</td>
<td>PTRA or RVR</td>
<td>48</td>
<td>100</td>
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<tr>
<td>Wilcox et al</td>
<td></td>
<td>6/6</td>
<td>RVR</td>
<td>50</td>
<td>83</td>
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<tr>
<td>Svetkey et al</td>
<td></td>
<td>11/50</td>
<td>PTRA</td>
<td>91</td>
<td>50</td>
</tr>
<tr>
<td>Mann et al</td>
<td></td>
<td>19/6</td>
<td>PTRA</td>
<td>44</td>
<td>84</td>
</tr>
<tr>
<td>Setaro et al</td>
<td></td>
<td>18/34</td>
<td>PTRA</td>
<td>83</td>
<td>81</td>
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<table>
<thead>
<tr>
<th>Author</th>
<th>Using 131-I-orthohippurate</th>
<th>Number (with/without RVH)</th>
<th>Criteria for diagnosis of RVH</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Geyskes et al</td>
<td></td>
<td>15/19 (peak time)</td>
<td>PTRA</td>
<td>87</td>
<td>89</td>
</tr>
<tr>
<td>Sfakianakis et al</td>
<td></td>
<td>15/19 (ratio)</td>
<td>PTRA</td>
<td>47</td>
<td>100</td>
</tr>
<tr>
<td>Svetkey et al</td>
<td></td>
<td>15/19 (2 of 3)*</td>
<td>PTRA</td>
<td>80</td>
<td>100</td>
</tr>
<tr>
<td>Erbsloh-Möller et al</td>
<td></td>
<td>16/15</td>
<td>PTRA or RVR</td>
<td>67</td>
<td>100</td>
</tr>
<tr>
<td>Mann et al</td>
<td></td>
<td>10/46</td>
<td>PTRA</td>
<td>80</td>
<td>42</td>
</tr>
<tr>
<td>Erbsloh-Möller et al</td>
<td></td>
<td>28/12</td>
<td>PTRA</td>
<td>96</td>
<td>95</td>
</tr>
</tbody>
</table>

RVH, renovascular hypertension; DTPA, 99mTc-diethylenetriamine pentaacetic acid; PTRA, percutaneous transluminal renal angioplasty (occasional patients had surgery instead of PTRA; diagnosis in both cases was therefore based on response to intervention); RVR, renal vein renin determinations.

*Any two of three individual criteria (two for 131-I-orthohippurate, one for DTPA). Diagnostic criteria for abnormal test results varied widely. For further details, see individual studies.
the diagnosis of renal artery stenosis (Table 1). The current study confirms this finding.

There is less agreement about the accuracy of these tests in the diagnosis of renovascular hypertension (Table 2). An inherent problem with the evaluation of diagnostic tests for renovascular hypertension is the determination of outcome. Most investigators have required response to interventional therapy as proof of the occurrence of RVH, but the efficacy of intervention varies dramatically depending on the lesion type (fibromuscular dysplasia versus atherosclerotic), location (ostial versus nonostial), severity, method of intervention (surgery versus angioplasty), and degree of expertise. The possible misclassification of patients with RVH based on failed intervention instead of lack of a functionally significant obstruction could directly affect the calculations of sensitivity and specificity, but the degree of inaccuracy cannot be determined.

It is instructive to consider three recent articles that have evaluated ACEI-induced changes in the renogram or scintigram as predictors of blood pressure response to subsequent angioplasty or surgery. Svetkey et al found that both renal scintigraphy and renography had reasonable sensitivity but very poor specificity, whereas Mann et al, in a retrospective analysis, found that DTPA scintigraphy after ACEI had a low sensitivity (44%) and marginal specificity (84%) but was more accurate than hippuran. This latter conclusion conflicts with results from other investigators. In the third paper, Erbsloh-Moller et al used the hippuran renogram after oral captopril or intravenous enalaprilat in conjunction with furosemide to diminish errors due to hippuran concentration in the collecting system. This group reports the hippuran renogram after captopril to be highly predictive of the blood pressure response to angioplasty or reconstructive surgery, with a sensitivity of 96% and a specificity of 95%. These excellent results exceed any so far published with DTPA, including those of Setaro et al. Additionally, in the majority of their patients, only one hippuran scan (after ACEI) was required. A second scan was undertaken without ACEI only in those subjects whose hippuran scan after ACEI was abnormal and who had azotemia. Renovascular hypertension was diagnosed in those whose scans changed, whereas intrinsic renal disease was characterized by a fixed defect that was unresponsive to ACEI.

Why have these studies given such widely disparate results? Major reasons include variability in design (retrospective versus prospective), patient populations (prevalence rates for renovascular hypertension varied widely), preperation of patients, performance of tests (use of furosemide and dosage of ACEI), and determinations of outcomes. The study by Setaro et al in this issue is more rigorous since criteria for diagnosis were developed retrospectively and applied to a second population prospectively. DTPA alone was used, and captopril was given in a dose of 50 mg. Criteria for renal artery stenosis required a narrowing of the main renal artery of 75% or more, or a 50–75% narrowing with dilatation after stenosis. Criteria for a positive blood pressure response to angioplasty or surgery were based on the Cooperative Study of Renovascular Hypertension. The DTPA renogram was used to diagnose both renal artery stenosis and renovascular hypertension. An important question relates to the definition of an abnormal test. The criteria used to detect renal artery stenosis were 1) a time-to-peak activity greater than or equal to 11 minutes on a before-captopril scan; 2) a time-to-peak activity greater than or equal to 11 minutes on an after-captopril scan; or 3) a GFR ratio between the two kidneys of greater than 1.5 on an after-captopril scan with or without an initial abnormal ratio. These criteria use DTPA not only to quantify GFR ratios but also to detect delayed isotope clearance from the renal cortex, which is analogous to the use of hippuran renography described above. Of 44 patients with angiographic evidence of renal artery stenosis, 40 had abnormal tests, although it is not clear which of these three test criteria were positive most frequently nor how many patients had more than one positive result. The results for the detection of renal artery stenosis, from both the retrospectively and prospectively analyzed groups, were excellent.

Setaro et al selected different criteria to predict renovascular hypertension: the development of an abnormal time-to-peak DTPA activity or an abnormal GFR ratio after captopril administration in patients with a normal initial scan. It is not clear that these criteria were established before the analysis of the data. Nevertheless, they provide a test with a sensitivity of 83% and a specificity of 81%. Were this test to be used to determine which patients with renal artery stenosis should be treated, 17% of those with hypertension that could be improved or cured would be denied treatment, and 19% of those who would not benefit would undergo an unnecessary angioplasty or surgery. Whether these operating characteristics are robust enough to be the sole determinant of intervention is a decision that must rest with the individual clinician.

A second major factor that affects the usefulness of a diagnostic test is the relation between predictive
value and disease prevalence. Setaro et al.\(^5\) used clinical criteria to select a population with a prevalence of renal artery stenosis of 47%, about half of whom had renovascular hypertension. Figure 1 is based on a sensitivity and specificity of the scintigram for the detection of renal artery stenosis of 91% and 94%, respectively, as found by Setaro et al.\(^5\) It shows the striking changes in the positive and negative predictive values at varying prevalences. The point at which the lines cross represents the “ideal” prevalence at which there is a “trade-off” between the number of false-positive and false-negative tests. This ideal prevalence is near 50%, which is similar to the prevalence of renal artery stenosis in the highly selected population studied by Setaro et al.\(^5\) However, in the general hypertensive population, the true prevalence of renal artery stenosis in one series of 482 patients with hypertension was only 5%.\(^6\) At such a prevalence, the positive predictive value would be around 40%, which implies that over half of all patients with a positive test would not have the disease (false positives). It becomes clear that none of the currently available tests proposed for screening have operating characteristics that are sufficient to apply to the general hypertensive population without generating large numbers of false-positive results. Setaro et al.\(^6\) wisely caution against the application of scintigraphy to an unselected hypertensive population; this point is worth reemphasizing. To best use screening tests in high-risk individuals, the risk/benefit ratio for the population as a whole is a function of the operating characteristics of the diagnostic test and the accuracy of the determination of the “high-risk” population.\(^7\) Clinical criteria that best select populations with a high prevalence of renovascular hypertension have been studied,\(^11\) but no clinical prediction index has been developed that has been evaluated prospectively.

Setaro et al.\(^5\) have demonstrated that in a selected group of patients at high risk for renovascular hypertension, the DTPA scan is accurate for the diagnosis of renal artery stenosis. Its accuracy in predicting the blood pressure response to surgery or angioplasty may not be sufficient to use as the sole criterion on which to base clinical decisions concerning treatment options. However, such scans will be especially useful in patients in whom the planned procedure is considered to be of high risk. Continued methodological study, with attention to protocol, patient population, and diagnostic criteria, may result in the evolution of a test from a research procedure to a routine diagnostic aid. Presently, recommendations regarding the application of these tests should be cautious. First, this and other studies\(^5\)\(^-\)\(^11\) suggest that in a selected population with a high prevalence of renovascular disease, the DTPA scan is accurate in the diagnosis of renal artery stenosis. One may choose, therefore, to terminate a renovascular hypertension workup after a negative DTPA scan, thus avoiding arteriography in some high-risk individuals, but at the risk of missing some patients (probably less than 10%) with renal artery stenosis. Second, the results of Erbslöh-Möller et al.\(^8\) show that a hippuran scan after ACEI, with furosemide washout, can accurately delineate those patients with renal artery stenosis who can be expected to respond to angioplasty or surgery with a fall in blood pressure. Confirmation of the validity of this combined diagnostic approach would represent a major clinical advance.

Acknowledgements

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