Radionuclide Studies

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Abstract

Nuclear medicine scans were rather widely used in the 1980s–1990s to screen patients for renal artery disease. The most popular scans were performed after oral captopril (25–50 mg), using either ^{99m}Tc-diethylenetriamine-penta-acetic acid or ^{99m}Tc-mercaptoacetyltriglycine, which have similar, but slightly different, features. Characteristic changes on the excretory renograms were relatively straightforward to detect, especially when compared to a study that was done without captopril pre-treatment. Centers that developed experience with the test typically reported better performance characteristics than centers with smaller numbers of patients. Over the entire literature (excluding case reports and serial publications from the same investigators), captopril scintigrams had a mean weighted sensitivity of 77 % (range 9–100 %) and specificity of 78 % (range 44–100 %) over 71 reports involving 5,068 patients evaluated by angiography for renal artery stenosis. Many investigators have reported that a positive captopril-stimulated renal scintigram predicts a beneficial effect of revascularization on blood pressure (i.e., renovascular hypertension), but several large series disagree. Since the failure of randomized clinical trials to demonstrate a benefit of revascularization over intensive medical management, the role of renal nuclear medicine scans has declined. Such techniques may still be useful, especially in patients with normal renal function, when other modalities are not easily available, and blood pressure remains uncontrolled or renal function deteriorates.

Keywords

Captopril renography • Captopril scintigraphy • Excretory renograms • Renal artery stenosis • Renovascular hypertension • Sensitivity • Specificity

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Historical Overview

Radionuclide studies of renal function began in the late 1950s, with the synthesis and testing of ^{131}I-labelled 3,5-diiodo-4-pyridon-*N*-acetic acid, diethanolamine salt (diodrast), which underwent renal excretion, as well as some competing hepatic extraction. It was rather quickly replaced by ^{131}I-labeled orthoiodohippurate (hippuran), which is cleared ~80 % by tubular secretion, and 20 % by glomerular filtration. Although most often used at that time for estimating split renal function (using two scintillation counters of sodium iodide crystals, placed on the skin overlying each kidney), several early reports suggested that the time-dependent shapes of the excretory renograms were reproducibly and characteristically altered in the setting of renal artery stenosis. Because of the cumbersome nature of percutaneous radionuclide signal detection, relatively high doses of radiation, and other technical issues, rapid-sequence intravenous pyelography became the accepted standard method of screening for renal artery disease in the United States, until the mid- to late-1970s.

Gamma cameras revolutionized the practice of nuclear medicine in the early to mid-1970s, by making it possible to obtain high-quality images from deep tissues, using a variety of tracers. The renal radiopharmaceutical, ^{99m}Tc-labeled diethylenetriamine-penta-acetic acid (DTPA), is secreted nearly totally by glomerular filtration, emits 140 keV gamma rays, and has an emission half-life of ~6 h (independent of the relatively rapid renal excretion of the parent acid). These advantageous properties made it the most popular agent for nuclear medicine scans for at least two decades.

In the mid-1980s, ^{99mTc}-mercaptoacetyltriglycine (MAG3) was developed, which had about a 60 % first-pass renal extraction fraction (nearly all due to tubular secretion), compared to only 20 % for DTPA. Consequently, MAG3 has generally become the preferred radiopharmaceutical for patients with impaired renal excretory function. Some investigators have reported that it is more sensitive for bilateral renal artery stenosis than DTPA, but in general, the performance characteristics of the two agents are similar (for details, see discussion to come).

By serendipity in 1983, captopril was discovered to impressively alter the normal excretory renogram. The physiology of this effect is still debated, but the simplest explanation may be captopril's effect to acutely reduce circulating angiotensin II levels, which causes dilation of the efferent arteriole (which is more sensitive to angiotensin II than the afferent arteriole), followed by an acute reduction in glomerular filtration. This phenomenon can be observed not only with nuclear medicine scans that measure renal function, but also with ultrasound or quantitative angiographic detection. Over the next decade, many groups reported their experience with the "captopril-DTPA renal scan" as a screening test for renal artery stenosis. As with many new tests, the initial results were generally quite positive, but, over time, it was recognized that the test had many potential confounders (see next discussion for details). The time-dependent change in pooled sensitivity and specificity of the captopril DTPA test, drawn from reports with the largest numbers of included subjects (discussed next), is shown in Fig. 15.1. The variability of the test's performance characteristics, and the emergence of putatively better screening tests were highlighted in a very selective meta-analysis of screening tests for renal artery stenosis in 2001 [1]. This was followed by a "not recommended" designation by the American College of Cardiology/American Heart Association's Task Force on Peripheral Arterial Disease in 2006 [2].

There are many challenges to a proper understanding of the many causes of variability in radionuclide screening tests for renovascular hypertension. One is the distinction between diagnostic criteria for renovascular hypertension vs. renal artery stenosis. The former can classically be made only retrospectively, *after* demonstrating a lowered blood pressure, despite the same or fewer medications, 6–12 weeks after a procedure to open the stenotic artery. The latter, however, is an anatomical diagnosis, and can be made by one of a number of criteria, including (classically) a ≥75 % luminal narrowing, or a ≥50 % luminal narrowing with a post-stenotic

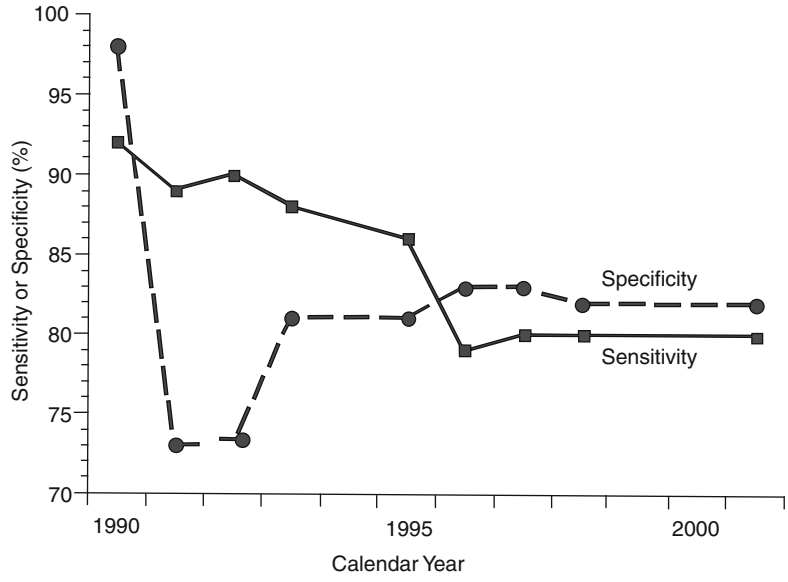

Fig. 15.1 Cumulative sensitivity and specificity of captopril-stimulated excretory renograms for renal artery stenosis in reports with large numbers of patients (i.e., ≥100 angiograms) reported from 1989 to 2001

dilatation, as demonstrated on a renal arteriogram. Today, however, many authors use a less-stringent criterion of ≥50 % stenosis, as observed on many different types of vascular imaging studies (digital subtraction intravenous angiogram, computed tomographic angiography, magnetic resonance angiography, etc.). Secondly, much of the reporting of a correlation between the results of nuclear medicine screening tests and angiography is done by radiologists, who often analyze their data using a "per-artery" approach, rather than a "per-patient" approach. This avoids problems with post-nephrectomy subjects, or those with multiple renal arteries to a single kidney, but complicates summary statistics that are based on individual patient data (which are often most useful to physicians who order these tests).

Technique

Although many "simplified" approaches to nuclear medicine screening for renal artery disease have been proposed, procedure guidelines have been written (and updated in 1998 [3]) by the Society for Nuclear Medicine. These were the first steps to standardize the protocol by which patients usually receive an oral water load (typically 7 mL/kg of body weight), followed 30–60 min later by 25–50 mg of oral captopril (often crushed to hasten absorption), and subsequently, 60 min later, an intravenous injection of radionuclide. Many variations on this common sequence have been suggested, including oral furosemide, stopping chronic angiotensin converting-enzyme (ACE) inhibitors for five serum half-lives before the test (which probably increases sensitivity just a little), pre-procedure intravenous saline (or at least a line for it, in case of hypotension), blood pressure and heart rate monitoring during and after the procedure, etc. Many centers perform the initial scan after captopril administration, and repeat it without captopril if the initial scan is abnormal. Other centers perform the initial scan without captopril, and, a few hours later, repeat the scan an hour after oral captopril, using a higher dose of radionuclide; this can be advantageous for patients who come from a distance.

Data Processing and Interpretation

Many different systems have been developed to analyze and report the results of radionuclide screening tests for renal artery disease. Most authorities recommend examining the early

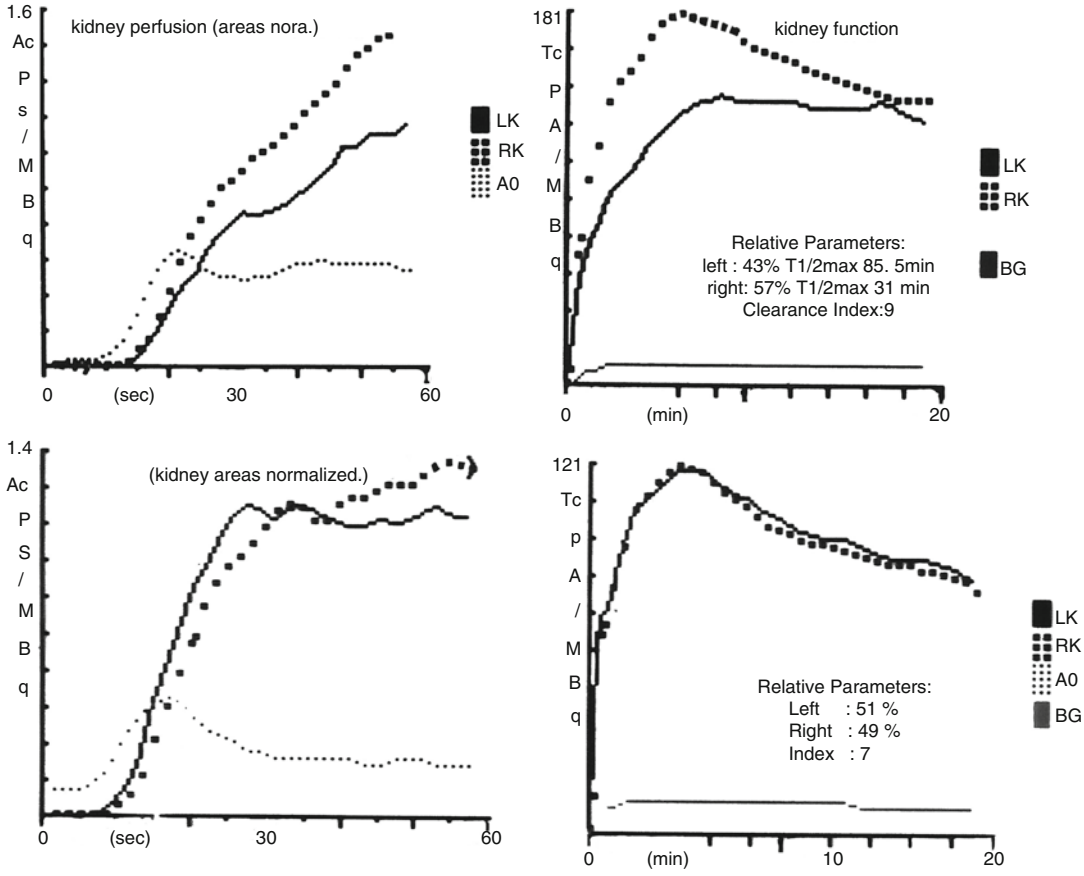

Fig. 15.2 Results of ^{99m}Tc-MAG3 excretory renograms from a 68-year old woman with resistant hypertension (initial blood pressure 192/108 mmHg despite maximum FDA-approved doses of chlorthalidone, amlodipine, atenolol, doxazosin, and lisinopril) and a serum creatinine of 1.5 mg/dL (estimated glomerular filtration rate of 37 mL/min/1.73 m^2). After discontinuing lisinopril for 5 days, the initial scan (after 25 mg oral captopril) showed decreased initial uptake (0–60 s after injection) by the left kidney (*upper left panel*), and a prolonged expiratory phase, with a 43/57 split in uptake (*left*/*right*) at 2–3 min (*upper right panel*). Three days later, the scan was repeated without captopril, which showed initial uptake that was similar bilaterally (*lower left panel*), similar excretory curves, and a 51/49 split in uptake (*left*/*right*) at 2–3 min (*lower right panel*). A week later, selective renal angiography showed a 75–80 % stenosis in the left main renal artery, with post-stenotic dilatation, which was successfully treated with balloon angioplasty and a stent. Six weeks later, her office blood pressure was 128/78 mmHg, while taking only chlorthalidone, atenolol, and lisinopril, and it remained well controlled over 6 years of follow-up, with no deterioration in renal function. *LK* left kidney, *RK* right kidney, *AO* aorta, *BG* background (Acknowledgement: The author thanks Derrick Owsley for assistance with the refinement and production of Fig. 15.2)

distribution of tracer (typically 60–90 s post-injection) for asymmetry (Fig. 15.2), comparing the uptake in background-subtracted regions of interest corresponding to each kidney during a specified interval (typically 1–3 min) after injection (Fig. 15.2), time to maximum activity for each kidney (Fig. 15.2), and a ratio of the remaining activity 20 min after injection to the maximum (particularly for MAG3, which is "normal" if <0.3) [3, 4]. Although each of these parameters may indicate an abnormality, the most specific diagnostic criterion for renovascular hypertension is the change in the renogram, with vs. without ACE-inhibitor. These changes have been most reproducibly detected across different readers [5, 6].

A family of representative curves has been promulgated as an aid to the interpretation of excretory renograms (Fig. 15.3) [3]. In general, a normal renogram after an ACE-inhibitor (Curve A in Fig. 15.3) predicts a low probability (<10 %) of renovascular hypertension. "Worsened renograms" (e.g., Curves B and C in Fig. 15.3), reduction in relative uptake by one kidney, prolongation of the renal and parenchymal transit time (or time to peak), or increase in the 20-min/peak ratio, all increase the post-test probability of renal artery disease. On the other hand, curves that show a delayed excretion without a washout phase (Curve D in Fig. 15.3), or background patterns (Curves E or F in Fig. 15.3) are best considered "intermediate probability [3]" or "non-diagnostic [7]," as either may be simply a consequence of diminished renal excretory function. A difference of 10 % in the post- vs. pre-captopril scans for tracer uptake by the kidneys, 1–3 min after injection has been proposed (but not universally accepted [7–9]) as one criterion for a "high probability" DTPA scan [3, 10], with 5–9 % considered an "intermediate response." Recent publications have demonstrated improvements in the correlation between captopril-stimulated renograms and renal angiograms after either adopting standardized criteria for the interpretation of the nuclear medicine studies [11], or use of neural networks [12].

Captopril or Other Pharmacological Options

Because of concerns about variability in the rate of absorption of oral captopril, intravenous enalaprilat (40 μg/kg) was proposed as an alternative method of obtaining ACE-inhibitor-stimulated nuclear medicine studies. In several comparative studies in animals and humans, few differences were noted. The 1998 procedure guideline recommends either agent as acceptable [3].

Like ACE-inhibitors, angiotensin receptor blockers (ARBs) can also cause an acute reduction in glomerular filtration in patients with renovascular hypertension. The effects of oral captopril on excretory renograms have been compared with those of either oral valsartan or losartan in 25 or 32 patients with renal artery stenosis, and interpreted using standard protocols. Consistent with known differences in the t_{max} of these drugs (2–4 vs. 1 h) after oral administration, valsartan was inferior to captopril [13], but losartan was not significantly different [14], in producing detectable changes in excretory renograms. Twelve of 13 patients with renal artery stenosis treated with a chronic ARB showed the expected changes in MAG3 excretory renograms after oral administration of captopril; three showed similar changes, even without captopril [15]. No false-positive results were seen in 13 patients with essential hypertension who were also treated with a chronic ARB. These limited data suggest that captopril scintigraphy may perform adequately in ARB-treated patients.

Several groups have studied aspirin (20 mg/kg, orally) [16], compared to captopril [17–19], as a possible stimulus for changes in renal scintigraphy in 12–75 patients with renal artery stenosis. When given acutely, this dose of aspirin inhibits renal prostaglandin synthesis, and reduces both renal blood flow and stimulation of the renin-angiotensin system in patients with renovascular hypertension. This method avoids some of the risk of acute hypotension seen with captopril, but appears to have performance characteristics similar to captopril scintigraphy [17–19].

Potential Confounders of the Interpretation of Radionuclide Studies

The results of excretory renograms can be affected by many different factors, as noted previously. Perhaps the most important is the presence of an elevated serum creatinine. Patients with this condition, by definition, have abnormal radionuclide studies (typically with type D or E curves in Fig. 15.3), and a high risk of ischemic nephropathy (if renal artery disease is present). Such patients risk acute kidney injury after

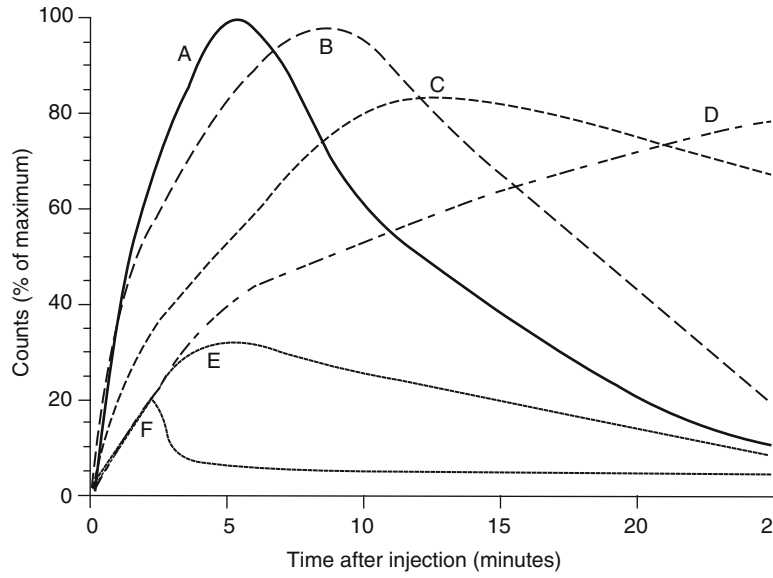

Fig. 15.3 "Typical" curves for time-dependent excretory renograms after intravenous injection of radiopharmaceutical (typically DTPA or MAG3). Curve *A* is "normal;" Curves *B–D* show various degrees of "worsening," and Curves *E* and *F* are better considered "non-diagnostic," as they are often seen in patients with impaired renal excretory function (Adapted with permission from [3])

radiocontrast injection, nephrogenic fibrosing dermopathy after gadolinium administration, so screening them for renal artery disease usually involves an initial Doppler ultrasound, rather than a radionuclide scan. Because a change in the lateralization of tracer uptake may be the most sensitive of the diagnostic criteria for radionuclide scans for renal artery disease, patients with baseline asymmetric renal function (worst-case scenario: solitary kidney) also have an increased risk of false-positive scans. Similarly, bilateral renal arterial disease is more difficult to detect with DTPA than with MAG3, but in either situation, completely symmetric uptake is uncommon. Acute hypotension after administration of captopril has been associated with poor renal perfusion and falsely-positive scan results. Two groups have reported that calcium antagonists can cause false-positive captopril scans [20, 21], which can complicate the ability to control blood pressure during the evaluation of the typical person with resistant hypertension who is suspected of renal artery disease. Rarer causes of false-positive tests include volume depletion, unilateral renal obstruction or venous thrombosis, compression of the renal hilum (e.g., from abscess or hematoma), or any condition that causes relative ischemia unilaterally. False-negative results are slightly more likely if captopril is given acutely, during chronic ACE-inhibitor therapy, with volume expansion and bilateral disease.

Results of Screening for Renal Artery Stenosis in Large Studies

Meta-Analyses and Systematic Reviews

In 2000, a review of 12 then-recent studies involving 2,291 patients, comparing the results of ACE-inhibitor scintigraphy and other testing for renal artery stenosis, concluded that the sensitivity and specificity were 93 and 92 %, although the sensitivity was artificially elevated because only 1,140 of the patients had renal angiography [4, 22]. The next year, a systematic review identified 172 reports about captopril scintigraphy, reviewed the full text of 25 studies, and selected only 14 for meta-analysis [1]. This highly-selective process was designed to include only reports that: (1) used intra-arterial angiography as the "gold standard" for renal artery stenosis; (2) tested subjects because of clinical suspicion of renovascular hypertension; (3) specified criteria and cutoff values for a "positive" test; and (4) provided absolute numbers of tests falling into each of the four diagnostic categories (true- or

false-positive, true- or false-negative). Five screening tests were compared after construction of receiver-operator curves, which showed that captopril scintigraphy had better diagnostic performance than measurement of the plasma renin activity before and after oral captopril ("the captopril test"), but was slightly worse than ultrasonography, and significant worse than magnetic resonance imaging, or computed tomographic angiography. For captopril scans, there was no significant difference between the performance of DTPA (six studies) or MAG3 (eight studies). Studies that included >50 subjects had significantly better performance than smaller studies, perhaps due to expertise that grows with experience. Although the authors cited lack of standardized criteria to define a positive test, differences across reports in case-mix, prevalence of renal artery disease (7.6–69.7 %), anatomical tests vs. functional tests, and analysis on a per-artery vs. per-patient basis, much of the heterogeneity of study results remained unexplained.

A much more inclusive systematic review of the literature was carried out in 2004 [23], and updated in 2009 [24]. All published data comparing 56 [23] (updated to 71 [24]) reports of ACE-inhibitor renography with renal angiography were included. Efforts were made to avoid data duplication, by selecting only the most recent of serial publications from a given group of investigators. The most impressive outcome of the meta-analysis was the striking statistically significant heterogeneity of the reported results ($P < 10^{-8}$ by Riley-Day test). In the 2004 data, across 4,295 subjects who had both captopril renograms and angiography, the overall sensitivity of the scan was 79 %, with a specificity of 82 % [23]. Five years later, the database included 5068 subjects, and the overall sensitivity was 77 % (range: 9–100 %), with a specificity of 78 % (range: 44–100 %) [24].

Individual Large Studies

The largest experience with renal scintigraphy and angiography was reported by Dutch investigators, who collected data from 505 subjects with suspected renovascular hypertension referred to their center from 1978 to 1992 [8]. Renal artery stenosis (≥50 %) was present in 52 % (bilateral in 19 %). Unlike many other investigators, they found only a little difference in the diagnostic performance characteristics of the renal scan, either without (n = 225) or after (n = 280) captopril. They chose a single-kidney fractional uptake of 37 % after captopril to define a positive test, which afforded a 90 % specificity, and 68 % sensitivity. They concluded that, although captopril scintigraphy was the most effective diagnostic procedure to reduce the number of normal arteriograms in patients suspected of renovascular hypertension, its usefulness as a diagnostic test is questionable, and has not been improved by the introduction of captopril or MAG3.

These results differed from those of a 16-center study in Europe, which performed DTPA scans after captopril and angiograms in 380 patients suspected of renovascular hypertension [25]. The diagnosis was made if angiography showed ≥70 % stenosis; captopril renograms were interpreted using multiple criteria, similar to those later published by the Society of Nuclear Medicine [3]. Overall, the sensitivity of the test was 83 %, with 93 % specificity, but the subgroup of patients with abnormal renal function always had lower specificity. Renal impairment, nephropathy, and prior treatment with ACE-inhibitors and diuretics were significantly more common in patients with false-positive scans; false-negative scans occurred more often in patients with lesser degrees of, and unilateral, renal artery stenosis.

A report of the experience at the Utrecht University Hospital described 158 patients who underwent both captopril scintigraphy (with MAG3) and angiography (using ≥50 % stenosis as the diagnostic criterion) [26]. In this group with a 63 % prevalence of renal artery stenosis (26 % bilateral), the sensitivity and specificity of the captopril scan were 83 and 75 %, respectively, as interpreted using the 1998 procedure guidelines [3]. Only 1 of 30 subjects with bilaterally identical renograms (21 of which were normal) had a stenosis by angiography, suggesting

that intrinsic renal disease is a more common cause of identical excretory renograms than renal artery disease.

A much less optimistic conclusion was reached in a consecutive series of 140 hypertensive patients evaluated with 25 mg of captopril before a DTPA scan, followed by renal arteriography at Duke University [9]. Only 22 % of patients had ≥50 % stenosis of a renal artery at angiography. The overall sensitivity and specificity for the captopril scan were 74 and 44 %, respectively. The investigators indicated that their population differed from others with respect to patient selection (i.e., lower prevalence of stenoses), race/ethnicity, use of calcium antagonists during testing, captopril dose, and interpretation of renograms. They could not discern which of these (if any) accounted for the difference between their experience and those of other centers.

The largest of several reports correlating the results of a captopril scan using DTPA and renal arteriography in Bologna, Italy concerns 132 patients [27]. In this population, the prevalence of ≥50 % stenosis was 52 %, although 11 % more patients had an arterial stenosis <50 %. Captopril renograms were analyzed for split renal function (90–150 s after injection), appearance of tracer into the pelvicalyceal system, and upslope of the excretory renogram. Overall, the sensitivity of the captopril renogram was 92 %, with a specificity of 97 %; none of the patients with a stenosis <50 % had a positive captopril scintigram.

A more comprehensive analysis of the results of screening of 131 patients for renal artery stenosis, using conventional and captopril renography, as well as Doppler ultrasound, was published by investigators from Aarhus, Denmark [28]. Their population had a 21 % prevalence of renal artery stenosis ≥50 %, with 14 % having stenosis ≥70 % by angiography. Excretory renograms were interpreted using the European Multicenter Study methodology [25]. As might be expected, overall sensitivity was slightly better for the higher-grade stenosis definition (89 % vs. 75 %), but specificity was slightly lower (76 % vs. 78 %). They also noted that the specificity of change in the excretory renogram after captopril (compared to a non-captopril scan) was 96 %.

The largest of the several reports regarding the Yale Vascular Center experience with captopril scintigraphy included 113 patients who subsequently underwent renal arteriography [29]. A stenosis of ≥75 % (or 50–75 % if accompanied by a post-stenotic dilatation) was seen on angiography in 51 % of the patients. Captopril scintigraphy was interpreted using a locally-derived set of criteria that served as precursors of the subsequent Society of Nuclear Medicine guidelines [3]. Overall, the captopril scan was 91 % sensitive and 87 % specific for renal artery stenosis, regardless of serum creatinine >1.5 mg/dL (46 patients) or diuretic use, although concomitant ACE-inhibitor use during testing reduced the sensitivity to 75 % (12 of 16 patients).

Screening 104 patients with suspected renovascular hypertension at the Royal Free Hospital in London, using captopril DTPA renography, followed by different types of renal angiography, resulted in 27 being diagnosed with renal artery stenosis [30]. Captopril scans were interpreted based on a local algorithm that had been developed in a pilot study. Overall, the sensitivity was 93 % and the specificity was 70 % for the scan. Sensitivity was reduced (to 75 %) in the 26 patients with renal impairment, but was not affected by bilateral stenoses. Four of six patients who showed improvements in excretory renograms after captopril had a recent presentation of "accelerated hypertension."

Of the several reports regarding captopril scintigraphy using MAG3 in Bologna, the largest included 102 hypertensive patients who underwent renal angiography within 4 weeks of renal scintigraphy [31]. Renal artery stenosis (>50 %) was found in 53 % (bilateral in 21 %), although 27 arteries had <50 % stenosis. Overall the sensitivity of the MAG3 captopril scan was 91 %, with a specificity of 84 %. The most characteristic predictors for renal artery disease were prolonged parenchymal transit time and a longer time to peak in the post-captopril study.

For ethical reasons, only 100 of the 150 patients who had positive screening by either

captopril scintigraphy or the "captopril test" in Chicago were subjected to renal angiography [10]. The prevalence of renal artery stenosis (≥75 %, or 50–74 % with post-stenotic dilatation) was 59 % (13 % bilateral) in those who underwent angiography. Captopril renograms were interpreted using a version of an algorithm that was similar to that eventually adopted by the Society of Nuclear Medicine [3]. The sensitivity of the captopril scan was 92 %, with a specificity of 80 %, for renal artery stenosis, among those who had angiography; these parameters were not significantly affected by renal impairment, bilateral disease, or previous diuretic or beta-blocker therapy. All performance characteristics of the captopril scan were significantly higher than those of the "captopril test."

Two other groups have reported the results of similarly large series of patients, using a different approach to the correlation of scintigrams and angiography, as the latter was performed first, typically for reasons unrelated to the suspicion of renovascular hypertension. In Montréal, over a 3-year period, 898 patients underwent abdominal angiography, of whom 195 were either hypertensive or were suspected of having ischemic nephropathy [32]. These patients then underwent renal scintigraphy using three different radiopharmaceuticals, including ^{99m}Tc-DTPA, but without oral captopril. Overall, 47 % of the patients had renal artery stenosis (>70 %). For the DTPA scan alone, the overall sensitivity and specificity were both 68 %; for all three scans, they were significantly higher, at 77 and 84 %, respectively. Unfortunately, their subsequent series of 41 patients who were evaluated with three different screening tests, and renal angiography showed a the captopril MAG3 scan (interpreted using standard guidelines [3]) to have a sensitivity of only 41 % and specificity of 82 %, despite a prevalence of renal artery stenosis of 76 % (≥50 % stenosis) [33].

In an attempt to interpret the results of renal angiography performed after cardiac catheterization, 131 patients in British Columbia who had "incidental" renal artery stenosis (≥50 %) discovered during this procedure were evaluated by MAG3 nuclear renography; captopril was used in 98 [34]. In only 7 of 77, or 9 % of, patients who had both baseline and post-captopril scans were the renograms positive, suggesting functionally significant renal artery stenosis. Although captopril renogram positivity was the only characteristic (of eight clinical parameters) associated with unilateral renal artery stenosis >70 %, renal angioplasty, in a cohort that overlapped with the patients in this study, was unable to demonstrate preservation of renal function [35]. These investigators therefore question whether stenoses found incidentally in the renal bed during coronary catheterization are really important.

Results for Prediction of Blood Pressure Response After Angioplasty

In 1992, [22] a systematic review of the available English-language literature concluded that the DTPA scintigram had a sensitivity of 93 % and specificity of 95 % for renovascular hypertension (defined as improvement in blood pressure after intervention, which has since been standardized [36]). This result was based on three early reports involving only 205 patients; a supplemental analysis of six studies reporting outcomes with captopril-induced changes to excretory renograms (four with iodohippurate, two with DTPA) was not nearly as optimistic. An update in 2000 summarized 12 studies, and claimed that 92 % (255 of 289) of patients with a positive ACE-inhibitor renogram experienced a blood pressure response after revascularization [4]. This selective review did not include data from some studies that had previously reported lower predictive values [10, 37]. Since 2000, however, the literature has been mixed about the ability of a captopril renogram to predict either blood pressure or renal function outcomes after an intervention for renal artery stenosis.

Intention-to-treat analyses of the randomized Dutch Renal Artery Stenosis Intervention Cooperative (DRASTIC) clinical trial were confounded by a large proportion of crossovers during the year-long follow-up (2 of 56 assigned to

angioplasty, 22 of 50 assigned to drug therapy alone) [38]. Prior to randomization, abnormal scintigrams were seen in 65 % of subjects in both groups, and significantly more remained abnormal in the drug-treated group (than the angioplastied group) at both 3 and 12 months of follow-up. Improvement of scintigrams after successful renal angioplasty has been noted by other investigators [39]. Subsequent *post-hoc* analyses of DRASTIC revealed that only patients with bilateral stenoses benefited from angioplasty [40]. An abnormal captopril renogram was not associated with improved BP or renal function after intervention, although the precise numbers of patients involved in these analyses were not provided.

Perhaps because captopril renography was not as useful as other screening techniques in identifying patients with renal artery stenosis in Uppsala, Sweden [41], the best predictor of blood pressure lowering after revascularization, which occurred in 63 % of their 152 patients was normal baseline renal function. They found no significant predictive value of renal resistance index (by Doppler ultrasound), abnormalities on the captopril renogram, or other screening modalities [42]. Ten of the 15 patients with "high-probability captopril renograms had improved blood pressures 12 months after revascularization, compared to 14 of 22 with low or intermediate-probability scans.

The largest reported experience from Montréal involved 74 patients who underwent a number of screening tests before technically successful angioplasty ± stent (in 52) [43]. Although calculated creatinine clearances did not change, blood pressures were, on average, significantly lower 3 months after angioplasty, with 31 patients "improved" and six "cured." Twenty-one of the 36 patients with a blood pressure response had positive captopril scans; 20 of 35 patients without a response had negative scans, leading to a sensitivity of 58 % and specificity of 57 %. Results of renal Doppler measurements and renal size were much better predictors of a blood pressure response than a captopril scan.

A retrospective review of diagnostic and therapeutic procedures in Helsinki found only 20 patients (a 3.8 % prevalence in their referral population) with renovascular hypertension after angiography and therapy; all had positive captopril renograms, but the specificity of the scan was only 72 % among patients who underwent angiography [44]. In an updated analysis, 24 of 35 patients had improved blood pressures after intervention, which was more common in patients with >10 % differential uptake on captopril renography (15 of 18, compared to 4 of 11 with <10 % differential uptake, $P = 0.015$) [45]. However, in multivariate analyses, younger age and unilateral disease predicted better outcomes; the captopril scan was useful only in predicting renal artery occlusion, if the ipsilateral isotopic clearance was <10 % (7 of 8 for 88 % sensitivity, and 17 of 21, for 81 % specificity).

In a report from Taiwan involving 60 patients with hypertension and diabetic nephropathy, 10 were found to have positive captopril renograms, and all had a blood pressure response after revascularization [46]. The remaining 50 had normal or intermediate probability renal scans that were unchanged after captopril, and had their blood pressures controlled over 6 months with antihypertensive drug therapy (including captopril).

In a consecutive series of 50 patients with ≥60 % renal artery stenosis seen between 2000 and 2003 in Duesseldorf, Germany, only 18 experienced a blood pressure fall after revascularization [47]. As with other German centers, the renal resistance index (by Doppler ultrasound) was the strongest predictor of outcome, followed by renal vein renin measurements. Renography at this center was performed without captopril, so no data are available from these patients about the potential usefulness of this modality in predicting outcomes.

The existing data are summarized in Table 15.1 [48–57]. Unfortunately, many reports (especially those with pessimistic conclusions) have not provided discrete patient-level data that could be incorporated into this table, so these overall predictive values are likely to be overestimates [37,

Table 15.1 Summary of numbers of patients with "positive captopril-stimulated scintigram," followed by a "positive blood pressure response" after revascularization in large series

Author	Patients with "positive blood pressure response to revascularization"	Patients with "positive" captopril renogram	Percent (%)
Oei et al. [48]	15	16	94
Erbsloh-Möller et al. [49]	15	16	94
Geyskes et al. [50]	53	59	90
Mann et al. [51]	20	27	74
Postma et al. [37]	12	22	54
Dondi et al. [52]	32	33	97
Roccatello et al. [53]	30	33	90
Elliott et al. [10]	51	54	94
Jensen et al. [54]	16	16	100
Meier et al. [55]	26	29	90
Fommei et al. [25]	41	43	95
Harward et al. [56]	39	39	100
Mittal et al. [57]	19	19	100
Eklöf et al. [42]	10	15	67
Soulez et al. [43]	21	36	58
Helin et al. [44]	15	18	83
Lin et al. [46]	10	10	100

38, 40]. In addition, because many of these reports predate guidelines for execution and interpretation of nuclear medicine scans [3], as well as reporting of outcomes after revascularization [36], there is greater heterogeneity across these reports than appears in this table. Other sources of bias may also be present: for example, some centers have been less likely to recommend revascularization if the pre-procedural captopril renogram had been normal [10].

Comparisons with Other Screening Modalities

Unfortunately, none of the available screening tests for renal artery stenosis is perfect, and each has its strengths and limitations. Even computed tomographic or magnetic resonance angiography studies that were deemed superior to older techniques in 2001 [1] were found, on reevaluation in 2004 [58], to be imperfect. In many centers, Doppler ultrasound is preferred, as it is non-invasive, inexpensive, and has been useful in predicting a blood pressure response after revascularization (using a renal resistance index of <80 mmHg). It is notoriously operator-dependent, and less useful in obese patients with overlying bowel gas, patients with branched renal arteries, and for many patients with fibromuscular disease. In the most inclusive recent summary [24], it had highly significant inhomogeneity ($P<10^{-15}$ by Riley-Day test) across reports. Nonetheless, its mean weighted sensitivity was 83 % (range 17–100 %), with a specificity of 84 % (range 55–100 %), over 67 reports involving 4,640 patients.

Computed tomographic angiography provides excellent image quality, but requires intravenous contrast injection, which increases the risk of acute kidney injury. It is more expensive and time-consuming to process and interpret than either Doppler ultrasound or captopril scintigraphy. Over 18 reports involving 1,336 patients [24], there was significant ($P<0.0001$) inhomogeneity, partly due to four studies that report nearly perfect performance characteristics [1, 24]. Overall in these reports, computed tomographic angiography had a mean weighted sensitivity of 84 % (range: 63–100 %), with specificity of 91 % (range: 56–100 %).

Magnetic resonance angiography provides excellent image quality with no radio-opaque contrast injection, but gadolinium contrast is

contraindicated for patients with Stage 3 or higher chronic kidney disease, which includes many with suspected renal artery stenosis. Although it is expensive, often does not detect distal stenoses or restenosis within a stent, and can be problematic for patients with claustrophobia, 71 reports involving 3,069 patients indicated that its mean weighted sensitivity is 90 % (range: 54–100 %), with a specificity of 86 % (range: 21–100 %) [24]. It is likely that individual patient factors, local availability and expertise in execution and interpretation, as well as cost, will likely drive the selection of a specific modality to screen for renal artery stenosis in a particular moderate-risk hypertensive patient.

The Future?

It is currently difficult to acquire pre-authorization approval for many tests for renal artery disease, including nuclear medicine scans. Part of this is due to the results of at least four recent randomized trials showing no benefit over medical management on either blood pressure control or renal function. There is also a reluctance to spend money on tests that are themselves imperfect, and frequently lead to greater utilization of healthcare resources (including very expensive angiography and angioplasty). This situation has led to a decline in the number of nuclear scans performed worldwide, as well as in the numbers of publications about recent experience with these tests.

It may be possible that newer radiopharmaceuticals can improve on the diagnostic performance of DTPA and even MAG3 in screening for renal artery stenosis. A report of 41 patients studied with the glomerularly-filtered ^{51}Cr-EDTA and tubularly-secreted ^{99m}Tc-dimercaptosuccinic acid showed reduced uptake after captopril only with the former in 21 patients who eventually were diagnosed with renal artery stenosis [59]. Perhaps because of the small number of patients, however, per-patient performance characteristics and prediction of blood pressure response to revascularization procedures were not provided.

Another distinct area in which there still appears to be ongoing use of nuclear medicine scans for renovascular hypertension is in pediatric patients. Because many children have remediable causes of their hypertension, screening tests are more often performed than in adults. Although renovascular hypertension is rare in children, as reflected in a recent survey in Turkey [60], recent reports of captopril renal scans to screen for it in children have given mixed results [61]. The largest experience was reported from Egypt, in which 81 children who had captopril renography were studied [62]. Positive scans were seen in 24 of the 51 with renal artery disease, and 8 were falsely-positive, resulting in only 48 % sensitivity and 73 % specificity. In Chile, 20 children (including two newborns) were screened using captopril renography; six of seven with renovascular hypertension, and only one of 13 without it, were positive [63]. Three non-diagnostic scans were seen in children with severely decreased renal excretory function.

Another relatively neglected, but potentially fruitful, area is cost-effectiveness of screening, diagnosis and treatment of renovascular hypertension. A 1996 cost-analysis concluded that captopril-stimulated nuclear medicine screening was the most valuable initial strategy in patients with normal kidney function if the pre-test probability of renovascular disease was >30 % [64]. Some agree [4, 7, 45], but others recommend Doppler ultrasound [42, 43, 65]. None of these analyses have accounted for the wide geographic variation in cost of testing, which has increased dramatically across all healthcare facilities during the last 15 years [66].

Conclusion

Nuclear medicine scans were moderately popular as screening tests for renal artery disease in the late 1980s and 1990s. However, even in experienced hands, captopril-stimulated excretory renograms have imperfect performance characteristics that, especially in patients with a moderate absolute risk of renal artery disease, result in too many expensive and risky renal angiograms. According to recent guidelines, less expensive and less

invasive tests (e.g., Doppler ultrasound) or tests that can more easily distinguish both anatomical and functional abnormalities (e.g., magnetic resonance imaging with blood oxygen-level dependent contrast) are more likely to be recommended. Many centers have suggested that captopril-associated changes on excretory renograms predict a beneficial effect of revascularization on blood pressure, but the largest experience (in Holland), as well as that of many other centers, strongly disagree. Because few nuclear medicine scans to screen for renal artery disease are currently being performed, it is likely that this controversy will not be resolved, even by the usual techniques of "Evidence-Based Medicine."

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