7. Britton KE. Radionuclide studies. In: Whitfield HN, Hendry WF, eds. *Textbook of genitourinary surgery.* Edinburgh, Scotland: Churchill Livingstone; 1985:67–103.
8. Britton KE, Nawaz MK, Whitfield HN, et al. Obstructive nephropathy: comparison between parenchymal transit time index and frusemide diuresis. *Br J Urol* 1987;59: 121–132.
9. Cosgriff PS, Berry JM. A comparative assessment of deconvolution and diuresis renography in equivocal upper urinary tract obstruction. *Nucl Med Commun 1982;3: 377–384.*
10. Taylor AJ, Nally JV. Clinical applications of renal scintigraphy. *Am J Roentgenol* 1995;164:31–41.
11. Homsey YL, Mehta PJ, Huot D. et al. Intermittent hydronephrosis. A diagnostic chalenge. *J Urol* 1988;140:1222–1226.
12. The "well tempered" diuretic renogram: a standard method to examine the asymptomatic neonate with hydronephrosis or hydroureteronephrosis. *J Nucl Med* 1992;33: 2047–2051.
13. Kletter K, Nurnberger N. Diagnostic potential of diuresis renography: limitations by the severity of hydronephrosis and by impairment of renal function. *Nucl Med Commun* 1989;10:51–61.
14. Brown SCW, Upsdell SM, O'Reilly PH. The importance of renal function in the interpretation of diuresis renography. *Br J Urol* 1992;69:121–125.
15. Chaiwatanarat T, Padhy AK, Bomanji JB, et al. Validation of renal output efficiency as an objective quantitative parameter in the evaluation of upper urinary tract obstruction. *J Nucl Med* 1993;34:845–848.
16. Lupton EW, Lawson RS, Shields RA, Testa HJ. Diuresis renography and parenchymal transit time studies in the assessment of renal pelvic dilatation. *Nucl Med Commun* 1984;5:451–459.
17. Gonzales R, Chiou RK. Diagnosis of upper urinary tract obstruction in children. Comparison of diagnosis and perfusion pressure flow studies. *J Urol* 1985;133:646–649.

Consensus Report on ACE Inhibitor Renography for Detecting Renovascular Hypertension

Andrew Taylor, Joseph Nally, Mattias Aurell, Donald Blaufox, Maurizio Dondi, Eva Dubovsky, Eugene Fine, Enza Fommei, Gijsbert Geyskes, Goran Granerus, Daniel Kahn, Kathryn Morton, Hong-Yoe Oei, Charles Russell, George Sfakianakis and James Fletcher

Division of Nuclear Medicine, Department of Radiology, Emory University Medical Center, Atlanta, Georgia; Department of Nephrology and Hypertension, Cleveland Clinic, Cleveland, Ohio; Department of Nephrology, Shalgrenska Hospital, Goteborg, Sweden; Department of Nuclear Medicine, Albert Einstein College of Medicine and Montefiore Medical Center, Bronx, New York; Servizio de Medicina Nucleare, Ospedale per gli Infermi, Faenza, Italy; Division of Nuclear Medicine, University of Alabama Hospital, Birmingham, Alabama; Institute of Clinical Physiology, University of Pisa, Pisa, Italy; Hospital New Nickerie, Suriname; Department of Clinical Physiology, University Hospital, Linkoping, Sweden; Nuclear Medicine Service, VA Medical Center, University of Iowa College of Medicine, Iowa City, Iowa; Division of Nuclear Medicine, VA Medical Center, Portland, Oregon; Department of Nuclear Medicine, University Hospital Dijkzigt, Rotterdam, The Netherlands; Division of Nuclear Medicine, University of Miami School of Medicine, Miami, Florida; Division of Nuclear Medicine, St. Louis University Medical Center, St. Louis, Missouri

Key Words: ACE inhibitor; renography; renovascular hypertension

J Nucl Med 1996; 37:1876–1882

The primary purpose of this consensus report is to assist nuclear medicine physicians in performing and interpreting angiotensin converting enzyme inhibitor (ACEI) renography for the evaluation of patients with suspected renovascular hypertension. The secondary purpose is to provide guidelines for future publications and to suggest directions for future research.

CONSENSUS PROCESS

There is considerable variation in the performance and interpretation of ACEI renography between different centers. This variation often makes it difficult to compare results and can lead to confusion regarding what procedures should be followed and what interpretative criteria should be applied. To address these problems, the Scientific Committee of the Ninth International Symposium on Radionuclides in Nephrourology established a Consensus Group on ACEI renography. Members of the Consensus Group consisted of those nominated by the Scientific Committee or selected by the chair.

The Delphi process was used as a guide to developing consensus (*1*). A preliminary list of statements regarding ACEI renography was submitted to the panel members, of whom each was asked to rate each statement from 1 to 10 on the basis of importance. Panel members were also invited to comment on the adequacy of the statements. A number of specific questions were raised as well as the methodological question of evaluating statements based on importance compared with agreement. In response to these questions, two detailed lists were prepared each containing approximately 150 statements. These lists were sent to the panelists and each panelist was asked to score the statements on one list on the basis of importance and score the second list on the basis of agreement. The scores were tabulated and a mean and s.d. were calculated for each statement. The anonymous individual scores, means and s.d.s of all the previous statements as well as a draft document based on the first round of scoring were sent to all panelists. The panelists were then asked to score the original statements again as well as to score a set of additional statements added to clarify ambiguities; panelists were also asked to comment on the draft. Based on the second round of scores and comments on the initial draft, the consensus report was redrafted and submitted to all the panelists as well as to all attendees at the Ninth International Symposium on Radionuclides in Nephrourology, which was held in Santa Fe, New Mexico, May 1–3, 1995. There was a 30-min presentation of the consensus report at the Symposium followed by one hour of open discussion. Subsequently, several

Received Feb. 2, 1996; revision accepted Feb. 28, 1996.
For correspondence or reprints contact: Andrew Taylor, Jr, MD, Division of Nuclear Medicine, Department of Radiology, Emory University School of Medicine, Clifton Rd., NE, Atlanta, GA 30322.

attendees submitted written comments to the chair. Based on comments at the meeting and written suggestions, a third draft was prepared and resubmitted to the panelists along with a new list of 40 statements designed to address issues not fully covered by the previous set of statements. After receiving the scores and comments on the third draft, a fourth draft was prepared and submitted to the panelists for their review. Comments were incorporated into a fifth draft and the changes were resubmitted to the panelists for their final approval.

BACKGROUND AND PATHOPHYSIOLOGY

Background

Renovascular hypertension is estimated to affect 0.5%–3% of the unselected hypertension population and up to 15%–45% of patients referred to a subspecialty center because of refractory hypertension (*2–4*). Advances in percutaneous renal angioplasty and surgical techniques have renewed interest in developing better screening tests for determining which patients have potentially correctable hypertension due to renovascular disease. However, it is important to distinguish between renovascular hypertension and stenosis of the renal artery. Stenosis of the renal artery is common in nonhypertensive elderly persons and may be an associated but nonetiologic finding in a number of hypertensive patients (*5*). A large body of literature supports the use of ACE inhibitors in conjunction with radionuclide renography to enhance the sensitivity and specificity for detection of renovascular hypertension (*4,6,7*). The goals of ACE inhibitor renography are two-fold: to detect those patients with hypertension who have renal artery stenosis as the cause of their hypertension and would benefit from revascularization, and to determine which hypertensive patients do not have renovascular hypertension and obviate the necessity of angiography or revascularization.

Renovascular Hypertension

Renovascular hypertension is defined as an elevation in blood pressure caused by a stenosis of the renal artery or one of its major branches. The hypertension can be cured or ameliorated by a revascularization procedure.

Radiopharmaceuticals

The most common renal radiopharmaceuticals used to detect renovascular hypertension are:

1. Technetium-99m-MAG3 (mercaptoacetyltriglycine). The clearance of ^{99m}Tc-MAG3 is approximately 60% that of OIH. Technetium-99m-MAG3 is more highly protein-bound than OIH and its clearance is almost completely due to tubular secretion. The rates that OIH and MAG3 are excreted into the urine are almost identical.
2. Technetium-99m-DTPA (diethylenetriaminepentaacetic acid). Technetium-99m-DTPA is cleared by glomerular filtration.
3. Iodine-131- or ^{123}I-OIH (orthoiodohippurate). The clearance of OIH is approximately 83% of the clearance of para-aminohippuric acid and provides a measure of effective renal plasma flow (*8*). It is secreted by the renal tubules and, to a much lesser extent, filtered.

Pathophysiology

Renovascular hypertension depends on secretion of renin from the juxta-glomerular apparatus of the stenotic kidney due to a reduced perfusion pressure distal to the stenosis. Renin converts angiotensinogen to angiotensin I, which is then converted to angiotensin II by angiotensin converting enzyme (ACE). Locally produced angiotensin II within the kidney (juxtaglomerular cells) plays an important role in the autoregulation of the GFR; a reduction in the perfusion pressure distal to the renal artery stenosis leads to the production of angiotensin II, which preferentially constricts the efferent arteriole. This action raises the pressure gradient across the glomerular capillary membrane and tends to maintain GFR in spite of reduced perfusion pressure. ACE inhibitors block the production of angiotensin II. Consequently, ACE inhibitors reduce the angiotensin II dependent constriction of the postglomerular arteriole and this process lowers the transcapillary forces that maintain glomerular filtration. The resulting decrease in individual kidney glomerular filtration can be assessed noninvasively using conventional scintigraphic studies (*6,9*).

The uptake of a purely glomerular agent, such as ^{99m}Tc DTPA, in the affected kidney tends to decrease after ACE inhibition, whereas it tends to remain unchanged in the unaffected contralateral kidney or kidneys of patients with essential hypertension (*10–12*). This is often manifested as a change in absolute or relative renal uptake compared to the baseline study. Unless the stenosis is severe, the uptake of the tubular secreted radiopharmaceuticals such as ^{131}I or ^{123}I-OIH and ^{99m}Tc-MAG3 during ACE inhibition often remains unchanged (*4,13–15*). With tubular agents, however, renovascular hypertension can usually be detected by cortical retention after ACE inhibition. Cortical retention occurs secondary to the decrease in glomerular filtration induced by ACE inhibition. The reduction in GFR leads to decreased urine flow in the renal tubules and delayed washout of OIH and MAG3. Reduced tubular flow can also result in cortical retention of DTPA (*16*). Radionuclide renography combined with ACE inhibition improves the detection of renovascular hypertension compared with radionuclide renography alone. This report focuses on studies in adult patients with native kidneys. Preliminary results using captopril renography to detect renovascular hypertension in patients with a solitary kidney or a renal transplant, however, have generally been encouraging (*17–20*), and captopril renography may also be useful in children (*21,22*).

INDICATIONS

To be cost-effective, the test should primarily be used in patients with a moderate-to-high risk of renovascular hypertension (*23*). Clinical features associated with a moderate-to-high risk of renovascular hypertension include abrupt or severe hypertension (diastolic blood pressure > 120 mmHg), hypertension resistant to medical therapy, abdominal or flank bruits, unexplained azotemia, worsening renal function during therapy with ACE inhibitors, end organ damage such as left ventricular hypertrophy or Grade 3 or 4 hypertensive retinopathy, occlusive disease in other vascular beds and onset of hypertension under age 30 or over the age of 55.

PATIENT PREPARATION

Patients should be instructed to drink only water or eat a light breakfast, depending on the ACE inhibitor used (see section below on Which ACE Inhibitor and What Dose?). Patients should be instructed to arrive well-hydrated before testing. A suggested hydration protocol is 7 ml of water per kilogram of body weight 30 to 60 min prior to the study. If two studies are performed on the same day, hydration should continue between studies.

Placement of an intravenous line for normal saline infusion is recommended for high-risk patients and those receiving intravenous enalaprilat (see section below on Hypotension). In other patients, placement of a heparin lock at the time of injection is an appropriate precaution to allow quick venous access in case of hypotension.

Chronic administration of ACE inhibitors may reduce the sensitivity of the test and should ideally be withheld for 3–5 days before the study depending on their half life (*24,25*). Setaro et al. used a one-day protocol and ^{99m}Tc-DTPA and reported that captopril renography had a sensitivity of 75% (12/16) in detecting renal artery stenosis in patients taking ACE inhibitors compared to a sensitivity of 98% (39/40) in patients not taking these drugs (*25*). In spite of recommendations to patients and physicians, some patients will present on therapeutic ACE inhibitors. In these patients it is reasonable to give the ACE inhibitor and perform captopril or enalaprilat renography, although the referring physician should understand that there may be a slight loss in sensitivity (*24,25*).

Chronic administration of diuretics may alter sensitivity of ACEI renography (*25,26*). In one study, captopril renography had a sensitivity of 87% (33/38) for detecting renal artery stenosis in patients taking diuretics compared to a sensitivity of 98% (39/40) in patients not taking diuretics (*25*). Alternatively, patients taking diuretics may arrive relatively dehydrated. Dehydration can increase the risk of acute hypotension and inhibit diuresis which may compromise the interpretation of the test by making it difficult to distinguish ACEI-induced parenchymal retention from calyceal activity due to dehydration. Hypotension may also result in bilateral parenchymal retention. In well-hydrated patients, chronic diuretics probably will not significantly affect the test results but, for the above reasons, some centers request that diuretics be stopped several days before the study (*27,28*).

Many referring physicians find it unacceptable to discontinue all antihypertensive medications before ACEI renography. Other antihypertensive medications are not known to interfere with ACEI renography in humans, but this is an area for further investigation (*27*).

CHOICE OF RADIONUCLIDE

A number of clinical studies are still in progress, and the optimal radiopharmaceutical remains to be determined. Technetium-99m-MAG3, ^{123}I or ^{131}I-OIH and ^{99m}Tc-DTPA are all acceptable agents (*29*). Because of the image quality and favorable dosimetry, ^{99m}Tc-MAG3 is preferred over ^{131}I-OIH. Because of the higher extraction efficiencies, ^{99m}Tc-MAG3 or ^{123}I-OIH are preferred over ^{99m}Tc-DTPA in patients with elevated creatinine levels (*6,7,30–35*).

WHICH ACE INHIBITOR, AND WHAT DOSE?

Captopril and enalaprilat are both acceptable for ACEI renography. Captopril (25–50 mg crushed and administered orally with 150–250 ml of water) provides an acceptable dose. A 25-mg tablet is sufficient unless the patient has delayed gastric emptying or poor absorption from the gastrointestinal tract. Since the presence of food in the gastrointestinal tract reduces the absorption of captopril by 30%–40% (*36*), patients should not eat a solid meal within 4 hr of captopril scintigraphy.

Peak blood levels of captopril occur approximately 60 min after ingestion; for this reason, radiopharmaceutical administration should be delayed 60–90 min after captopril administration.

Enalaprilat (Vasotec, 40 μg/kg intravenously over 3–5 min) is an acceptable alternative. However, the total dose of enalaprilat should not exceed 2.5 mg (*37*). Clinical results suggest that renovascular hypertension can be reliably detected when there is a 10-min delay between enalaprilat and administration of the radiopharmaceutical (*4,38*). However, the panel recommends that the radiopharmaceutical not be administered until at least 15 min have elapsed after intravenous enalaprilat administration. The hypotensive effect of the enalaprilat usually occurs within 15 min, with the maximal effect occurring at 1–4 hr (*39,40*). However, it is important to note that animal studies have shown that ACE inhibition may produce renogram abnormalities in the clipped kidney without affecting systolic blood pressure (*41*). Animal data further suggest that the drug effectively inhibits ACE activity within 3 min after injection (*42*) and results in abnormal renograms in the clipped kidney within 5–10 min of injection (*43*). The use of enalaprilat reduces the time of the procedure and avoids the potential problems of delayed gastric emptying or poor absorption; it may increase the risk of hypotension and an intravenous line is recommended.

FUROSEMIDE

A few centers advocate furosemide-augmented captopril or enalaprilat renography for the detection of renovascular hypertension (*4,38*). With the tubular agents MAG_3 and OIH, the diagnosis of renovascular hypertension is based primarily on cortical retention of the radiopharmaceutical. Physiologic retention of these radioactive agents in the renal pelvis or calyces can distort both the visual and quantitative analysis (time to maximal activity and the 20-min to maximum count ratio). Furosemide is a loop diuretic and acts distal to the proximal tubules where MAG_3 and OIH are secreted. Consequently, furosemide can wash out the radiopharmaceutical from the calyces and pelvis, but it does not affect cortical retention in the proximal tubules (*38*). A disadvantage of furosemide is volume depletion and a greater risk of severe hypotension. If furosemide is used, an intravenous line should be considered for supplemental hydration and management of a possible hypotensive response. Alternatively, a heparin lock can be placed for venous access. Administration of furosemide is an option for individual centers, but it is not considered to be an essential component of ACEI renography.

HYPOTENSION

Blood pressure should be measured before administration of the ACE inhibitor and monitored every 10–20 min until stable. ACE inhibitors can result in a major hypotensive episode, although the prevalence appears to be low in a well-hydrated, nonsalt-depleted patient. Some centers also monitor the blood pressure at 5–10 min intervals during the study since asymptomatic hypotension may result in bilateral, symmetrical renal retention of the radiopharmaceutical (Taylor A, *personal communication*, 1994).

Hypotension can usually be reversed by placing the patient in the supine position, raising the patient's legs and, if this does not suffice, infusing normal saline. Some centers routinely establish an intravenous line before ACEI scintigraphy; this precaution is recommended for high-risk patients and patients receiving intravenous enalaprilat. High-risk patients who may benefit from intravenous fluid include those with a history of carotid disease, stroke, transient ischemic attacks, angina and recent myocardial infarction.

The patient should not be allowed to leave the department unless the standing blood pressure is at least 70% of baseline and the patient is asymptomatic. Some centers observe the patient for an additional 30 min.

COMPARISON OF ONE- AND TWO-DAY PROTOCOLS

In a two-day protocol, some centers begin with captopril or enalaprilat renography because normal findings on ACE inhibitor renography indicate a low probability of RVH and obviate a baseline study. Normal findings include normal images, a Grade 0 renogram curve with normal times to Tmax, normal

20/max ratios for OIH/MAG3 and normal OIH/MAG3 clearances or a normal GFR. If the results are abnormal or equivocal, the specificity can be improved by obtaining a baseline renogram; however, the patient will have to return for the baseline study several days later.

The study can be completed in 1 day by using 1 mCi ^{99m}Tc-DTPA or ^{99m}Tc-MAG_3 for the baseline study, administering the ACE inhibitor and then obtaining a second renographic study with 5–10 mCi. If 3–5 mCi are used for the baseline study, results may be improved by subtracting a residual activity image from the second portion of the study. Since this protocol requires two studies on the same day, the patient is required to spend a longer time in the department but the complete study is finished in a single day.

One- and two-day protocols are acceptable and the choice is largely dependent on the patient population and local factors. The second day of the two-day protocol can be omitted when the ACE inhibition study is performed on the first day and is normal. The two-day protocol is less costly if the time required for the patient to return on a second day for a baseline test is not factored into the calculation. Some centers use a one-day protocol in patients with a relatively high likelihood of disease and a two-day protocol in patients with a relatively low likelihood of disease where ACEI renography is likely to be normal.

ACQUISITION

In patients with native kidneys, the study should be acquired with the patient suppine and a large field-of-view camera positioned posteriorly. For ^{99m}Tc agents and ^{123}I-OIH, a low-energy, all-purpose collimator is recommended. A high-energy collimator is preferred for ^{131}I-OIH. Patients should void before each acquisition and a post-void image is suggested.

The field of view should include the heart, kidneys and bladder. If only two organs can be imaged, the field of view should include the kidneys and bladder, unless cardiac data are required for transit time calculations. The study should be acquired in a 128 × 128 matrix to better define the ROIs, although a 64 × 64 matrix is acceptable.

If a flow study is obtained, the time per frame should be 1–3 sec for the first minute and 10–30 sec per frame thereafter. Some deconvolutional protocols require data collection at 10 sec per frame.

QUALITY CONTROL

The images should be reviewed in a dynamic format to check for motion. An image over the injection site is suggested to check for infiltration. A small degree of infiltration should not affect the renogram interpretation, but it may cause inaccuracies in plasma-based clearance measurements. Infiltration of a large percentage of the dose can affect the shape of the renogram curves.

CLEARANCE MEASUREMENTS

Clearance measurements provide a useful assessment of global renal function at the time of renal scintigraphy. Glomerular filtration is usually reduced in the stenotic kidney of patients with RVH and calculation of individual kidney GFR is suggested when DTPA is administered. Clearance measurements may also be useful when OIH or MAG3 are administered.

ACE inhibitors usually do not cause a significant reduction in renal blood flow compared to the baseline study. Consequently, in patients with mild to moderate stenosis, there are usually no major changes in the clearances of OIH and MAG3. A single-clearance measurement using tubular radiopharmaceuticals rarely provides diagnostic information in patients with suspected renovascular hypertension although a decrease in clearance in the suspected kidney accompanied by an increase in the clearance of the contralateral kidney is a useful diagnostic sign. Serial clearance measurements, however, are useful for monitoring changes in single kidney function resulting from renovascular disease. Since preservation of renal function is a recognized goal in managing renovascular disease, a quantitative measurement of baseline function at the first visit to the nuclear medicine clinic is advocated whenever possible. This can be obtained at the time of the imaging study.

DATA PROCESSING

The relative uptake of MAG3 and OIH should be measured from 1–2 min or 1–2.5 min postinjection. These time intervals are preferred over 2–3 min because tracer may already be leaving the kidney by 3 min and this could lead to erroneous estimates of relative function. There was no consensus regarding the most appropriate interval for measuring the relative uptake of DTPA. Some panelist preferred making the measurement at 1–2 min or 1–2.5 min for the reasons listed above. Others preferred the 2–3 min postinjection period to avoid the error associated with a relatively high background activity at earlier time periods and one panelist suggested a slope calculation. Background subtraction is recommended using a ring, elliptical or perirenal ROI.

Renogram curves should be generated. Some centers prefer cortical renograms using parenchymal ROIs that exclude any activity in the calyces or pelvis. Cortical renograms are especially important if there is pelvic or calyceal retention (*12*,44,45). Other centers use whole kidney renograms and some centers generate both. The time-to-maximum activity should be determined.

For OIH and MAG3, the 20-min/peak activity ratio should be calculated (if the study is extended beyond 20 min, a 25- or 30-min/peak activity ratio would be appropriate). A measurement of parenchymal transit time using a parenchymal ROI is recommended if the algorithm is readily available. Sequential images should be displayed at 1-, 2- or 3-min intervals.

INTERPRETATION

Published results using ACEI renography to detect RVH must be interpreted with caution because the protocols are often complex and the diagnostic criteria are not well standardized. The most specific diagnostic criterion for renovascular hypertension is a captopril-induced change in the renogram. Table 1 is a synopsis of the captopril renographic studies in hypertensive patients with suspected renovascular disease, most of which include a subset of patients in whom the gold standard was a revascularization procedure. The table summarizes the number of patients with and without renovascular disease, radiopharmaceutical used, sensitivity and specificity for detecting renal artery stenosis, and positive predictive response to revascularization. The criteria for a positive test varied among institutions. Different diagnostic criteria as well as different populations of patients may account for the variations in results. The overall accuracy of ACE inhibitor renography in showing which patients have renal artery stenosis appears to be quite acceptable, with reported sensitivities and specificities approaching 90%. More importantly, the data suggest that renographic findings indicative of renovascular hypertension indicate a high probability that blood pressure will be reduced after revascularization.

Test results should be interpreted as indicating high, low or

TABLE 1
Sensitivity and Specificity of ACEI Renography for Detecting Renal Artery Stenosis and Predicting Response to Revascularization

Reference	No. of patients	No. of patients with renal artery stenosis	Radiopharmaceutical*	Prevalence of renal artery stenosis	Sensitivity	Specificity	Positive predictor of blood pressure response†
Oei et al. (*28*)	35	16	DTPA/^{131}I OIH	46%	94%	100%	94% (15/16)
Erbsloh-Möller et al. (*38*)	50	28	^{131}I OIH	56%	96%	95%	94% (15/16)
Geyskes et al. (*46*)	94	58	^{131}I OIH (47)	62%	91%	62%	90% (53/59)
			MAG3 (47)				
Setaro et al. (*47*)	94	44	DTPA	47%	91%	94%	83% (15/18)
Mann et al. (*48*)	55	35	DTPA	64%	94%	95%	69% (11/16)
			^{131}I OIH		83%	85%	82% (9/11)
Dondi et al. (*31*)	51	32	DTPA (38)	63%	87%	93%	97% (32/33)
			MAG3 (13)				
			DTPA (202)				
Roccatello et al. (*33*)	667	36	^{131}I OIH (99)	5%	90%	94%	NA
Elliott et al. (*27*)	150	59	DTPA	39%	92%	91%	NA
Jensen et al. (*49*)	20	20	DTPA	100%	65%	—	100% (16/16)
Meier et al. (*50*)	50	27	DTPA	54%	96%	87%	90% (26/29)
Fommei et al. (*34*)	454	157	DTPA (380)	35%	83%	91%	93% (40/43)
			MAG3 (74)		83%	100%	

*Number in parenthesis indicate the number of studies with each radiopharmaceutical.
†These values represent the percent of patients with an abnormal test whose blood pressure improved or returned to normal following revascularization.
OIH = orthoiodohippurate; MAG3 = ^{99m}Tc-mercaptoacetyltryglycine; DTPA = ^{99m}Tc-diethylenetriaminepenta-acetic acid; NA = not available. The patient population and criteria for findings indicative of disease varied among investigators.

intermediate probability of disease (*51*). Normal findings on ACE inhibition renography indicate a low probability (less than 10%) for renovascular hypertension. Abnormal baseline findings (Grade 1 or, occasionally, Grade 2 renograms) that improve after ACE inhibition also indicate low probability for renovascular hypertension. The probability of renovascular hypertension due to a kidney with greater than 30% relative uptake and a Grade 1 renogram curve (Fig. 1) that does not change after ACE inhibition is less than 20%. A majority of panelists considered this pattern to be low probability (less than 10%).

Patients with an intermediate probability of disease have abnormal baseline findings indicative of reduced renal function but the renogram is unchanged after ACE inhibition. This group includes some azotemic patients and hypertensive patients who have a small, poorly functioning kidney. The sensitivity of such abnormal baseline findings that are unchanged after ACE inhibition is quite high (greater than 90%), but the specificity is poor, probably in the range of 50%–75%. Published results in this population vary (*3,4,6,*47,52) and further studies, coupled with standardized protocols, will probably better characterize subgroups.

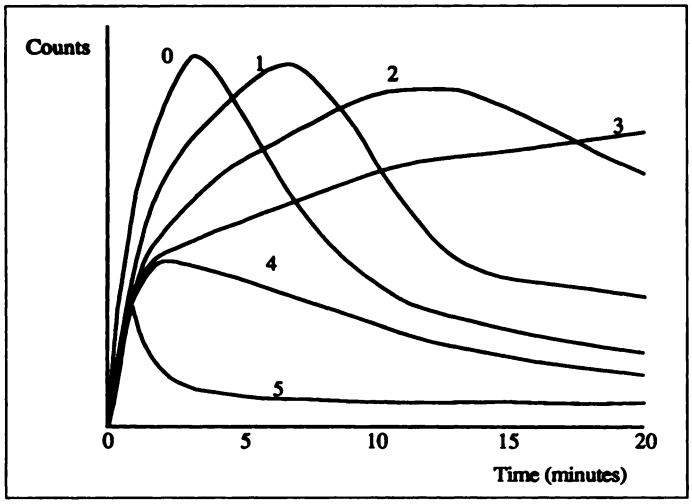

FIGURE 1. Patterns of renographic curves from normal to an accumulation type curve [adapted from Fommei (*3*)], where: 0 = normal; 1 = minor abnormalities, but with Tmax > 5 min and, for OIH and MAG3, background subtracted 20 min per maximum parenchymal ratios > 0.3; 2 = markedly delayed excretion rate with a preserved washout phase; 3 = delayed excretion rate without a washout phase (accumulation curve); 4 = renal failure pattern with measurable kidney uptake; and 5 = renal failure pattern without measurable kidney uptake (blood background type curve).

Bilateral symmetrical changes in the renogram curve after ACE inhibition have been associated with salt depletion, hypotension during the study, insufficient hydration and a distended bladder (*33,*53). If these conditions are excluded, preliminary data suggest that this pattern represents an intermediate probability of renovascular hypertension (*54*).

The probability is considered high (greater than 90%) when, compared to baseline findings, marked deterioration of the renogram curve occurs after ACE inhibition. Due to the different clearance mechanisms of glomerular and tubular agents, ACEI induced changes in DTPA renogram curves often differ from those obtained with OIH or MAG3. For DTPA, this change can best be quantitated by measuring the change in relative function or absolute individual kidney function. In contrast to DTPA, an abnormal response to ACE inhibition using OIH or MAG3 is best quantitated by a change in the 20-min to maximum count ratio or a prolongation of the Tmax. In patients with normal renal function and in the absence of pelvic or calyceal retention, a normal 20-min to maximum ratio (using background subtracted renogram curves) for OIH (*38*) or MAG3 (Taylor A, *personal communication*, 1994) is less than 0.3; a 0.15 change (i.e., 0.3–0.45) after ACE inhibition is considered to be significant. A 0.1 to 0.15 change is borderline. The level of confidence is increased if there is no tracer retention in the renal calyces or pelvis. Parenchymal ROIs that avoid the renal pelvis or activity in the calyces are preferred to whole kidney ROIs (*12,44,45*).

A small, poorly functioning kidney (<30% uptake with a Tmax ≤ 2 min) that shows no change after ACEI renography is intermediate probability for renovascular hypertension (*3*).

Criteria associated with renovascular hypertension include a change in the renogram curve (Fig. 1), reduction in relative uptake, prolongation of the renal or parenchymal transit time, an increase in the 20-min to maximum ratio and prolongation of the time to maximum activity.

Measurements of the time to maximum activity, parenchymal transit time and 20-min to maximum ratio using parenchymal ROIs are more specific than the whole kidney measurements because the effect of any tracer retention in the renal pelvis or calyces is minimized (*12,44,45*).

Interpretive Criteria for MAG3 and OIH

In comparison to the baseline study, unilateral parenchymal retention after ACEI is high probability (>90%) for renovascular hypertension and is the most important criterion for MAG3 and OIH. Unilateral parenchymal retention after ACE inhibition is a sensitive indicator for RVH even without a baseline study, but specificity can be improved by the baseline examination.

Unilateral parenchymal retention may be measured by a change in the renogram grade (Fig. 1). A change ≥ 2, i.e., 0 to 2 or 1 to 3, is considered to be high probability for RVH. The majority of panelists also considered a change ≥ 1 for a cortical renogram curve to be high probability for RVH. Parenchymal retention can also be evaluated by a change in the 20-min to maximum ratio of the cortical renogram curve of 0.15 or greater or a significantly prolonged parenchymal transit time after ACEI (normal limits for parenchymal transit time vary depending on the particular software; for this reason, normal limits and the degree of change required to be considered significant need to be established for each center). Unilateral parenchymal retention may also be detected by a delay in excretion of the tracer into the renal pelvis ≥ 2 min after ACEI (*55*) or an increase in the Tmax of at least 2 min or 40%. A change in Tmax from 5 to 7 min is much more significant than an increase in the Tmax from 18 to 20 min. A change in relative uptake of OIH or MAG_3 ≥10% (i.e., 50/50 to 60/40) after ACEI is uncommon in patients with RVH; however, when it is present, it indicates a high probability study.

Interpretive Criteria for DTPA

With ^{99m}Tc-DTPA, the most important criteria are changes in relative renal function or absolute individual kidney function compared to the baseline study. A reduction in relative uptake greater than 10% (i.e., 50/50 to 60/40) indicates high probability of RVH (*56*). Similarly, a 10% decrease in calculated GFR of the ipsilateral kidney after ACE inhibition also indicates a high probability of RVH.

Asymmetrical uptake (60/40 or greater) after ACE inhibition is a sensitive indicator for RVH even without a baseline study, but the specificity can be improved by a baseline examination.

Compared to the baseline study, an ACEI-induced change in the relative uptake of 5%–9% is considered an intermediate response and should be correlated with the various indicators of parenchymal retention. A change in the renogram grade ≥ 2 also represents a high-probability study. Compared to a Grade 1, 2 or 3 baseline study, the renal failure patterns (Grades 4 and 5) are uncommonly observed with tubular tracers after ACEI. However, when DTPA is used, these patterns may occur after ACEI and when they do occur, the change is a very specific finding for renovascular hypertension. Some centers find that the time to maximum activity or 20-min to maximum count ratio can also be useful, but others have reported that the 20- and 30-min to maximum count ratios for DTPA do not improve the accuracy of the test (*57,58*).

Marked unilateral parenchymal retention after ACEI compared to the baseline study is uncommon using DTPA but, when present, it indicates a high probability (>90%) for RVH. Even without a baseline study, unilateral parenchymal retention is also a sensitive indicator of RVH, but specificity can be improved by a baseline examination. Parenchymal retention may be measured, as described above, except that there is less confidence that an increase in the renogram of one grade represented a high-probability study even using parenchymal ROIs. For this reason, a change in renogram of one grade should not be considered high probability unless the abnormality is corroborated by other measures. It is important to note that DTPA is not extracted as efficiently as MAG3 and OIH. Consequently, the renogram curve is flatter and modest ACEI induced changes in the DTPA renogram curve should be interpreted with caution (*57*). For example, even using parenchymal ROIs, captopril was observed to increase the 20-min and 30-min to maximum count ratios by 0.15 and 0.16, respectively, in patients without renal artery stenosis (*57*).

RECOMMENDATIONS

Because of the relatively high prevalence of renal artery stenosis in the elderly population and because the goal of the test is to determine which patients will respond to revascularization, the endpoint or reference standard in future studies should be the outcome and the response to revascularization, not angiographic evidence of renal artery stenosis. Results may vary depending on the subgroup studied. For this reason, studies need to clearly define subgroups such as: results in patients with fibromuscular dysplasia compared with ateriosclerosis; results in azotemic patients compared with nonazotemic patients; results in patients with normal baseline studies compared with results in patients with abnormal baseline studies; results in patients taking diuretics, beta blockers or ACE inhibitors compared with patients not taking these drugs. Specific beta blockers should be listed.

Certain minimal standardized measurements should be made: time to maximum activity and the 20-min to maximum (preferably using parenchymal ROIs), and relative uptake. Data from the studies suggested above should be listed in tabular form in future publications to facilitate pooling of data from different institutions.

Additional data are needed in well-defined subgroups. The utility of 1 to 3-sec dynamic images in the detection of RVH is uncertain (*11,29,59–61*). Analysis of the perfusion phase of the renogram could serve a complementary role and enhance the sensitivity or specificity of the study in selected cases and might represent an area for future research when ^{99m}Tc agents are administered.

Further data are needed correlating bilateral symmetrical changes in the renogram curve with angiography and with revascularization if renal artery stenosis is present. The degree of symmetry should be defined with standardized parameters (Tmax, 20-min to maximum ratios, and relative uptake).

Additional studies are needed in patients with solitary kidneys or renal transplants. Additional data are also needed regarding the impact of chronic administration of diuretics, beta blockers and ACE inhibitors on the sensitivity and specificity of the test.

An abnormal baseline renogram that does not change after ACEI is considered to have intermediate probability. Better characterization of the baseline abnormality may allow the identification of subgroups with better defined probabilities.

The effects of salt loading and the state of hydration may affect the results and should be further studied.

Additional data are needed regarding the interpretation of sequential images. Preliminary data suggest that a series of 1-min images may needed to appreciate the delay in the excretion of the tracer into the renal pelvis (*55*).

ACKNOWLEDGMENTS

We appreciate the assistance of Wendy Smith in tabulating the data and of the physicians not on the panel who participated in the consensus process. This paper was presented at the Ninth International Symposium on Radionuclides in Nephrourology in Santa Fe, NM, May 1995.

REFERENCES

1. Fletcher JW, Woolf SH Royal HD. Consensus development for producing diagnostic procedure guidlines: SPECT brain perfusion imaging with exametazime. *J Nucl Med* 1994;35:2003–2010.
2. Hillman BJ. Imaging advances in the diagnosis of renovascular hypertension. *Am J Roentgenol* 1989;153:5–14.
3. Fommei E, Ghione S, Hilson AJW, et al. Captopril radionuclide test in renovascular hypertension: a European multicenter study. *Eur J Nucl Med* 1993;20:625–644.
4. Sfakianakis GN, Bourgoignie JJ, Georgiou M, et al. Diagnosis of renovascular hypertension with ACE inhibition scintigraphy. *Radiology Clin North Am* 1993;31:831–848.
5. Holley KE, Hunt JC, Brown AL Jr, et al. Renal artery stenosis: a clinical-pathologic study in normotensive and hypertensive patients. *Am J Med* 1964;37:14–22.
6. Prigent A. The diagnosis of renovascular hypertension: the role of captopril renal scintigraphy and related issues. *Eur J Nucl Med* 1993;20:625–644.
7. Oei HY. Dynamic and static renal imaging. In: Murray IPC, Ell PJ, eds. *Nuclear medicine in clinical diagnosis and treatment*, vol. 1, Churchill Livingstone, London, England:1994;213–227.
8. Bubeck B, Brandau W, Weber E, et al. Pharmacokinetics of technetium-99m MAG3 in humans. *J Nucl Med* 1990;31:1285–1293.
9. Wilcox CS. Use of angiotensin-converting-enzyme inhibitors for diagnosing renovascular hypertension. *Kidney International* 1993;44:1379–1390.
10. Miyamori I, Yashuhara S, Takeda Y, et al. Effects of converting enzyme inhibition on split renal function in renovascular hypertension. *Hypertension* 1986;8:415–421.
11. Nally JV, Clarke HS, Windham JP, et al. Technetium-99m-DTPA renal flow studies in Goldblatt hypertension. *J Nucl Med* 1985;26:917–924.
12. Fine EJ, Blaufox MD The Einstein/Cornell collaborative protocol to assess efficacy and methodology in captopril scintingraphy. Early results in patients with essential hypertension. *AJH* 1991;4:716S–720S.
13. Nally JV, Clarke HS, Gupta BK, et al. Captopril renography in two kidney and one kidney Goldblatt hypertension in dogs. *J Nucl Med* 1987;28:1171–1179.
14. Wenting GJ, Derkx FHM, Lies HT, et al. Risk of angiotensin converting enzyme inhibition in renal artery stenosis. *Kidney Int* 1987;31:180–183.
15. Taylor A, Eshima D. Renal artery stenosis and ischemia: effect on renal blood flow and extraction fraction. *Hypertension* 1994;23:96–103.
16. Jonker GJ, Visscher CA, de Zeeuw D, et al. Changes in renal function induced by ACE-inhibition in the conscious two-kidney, one-clip Goldblatt hypertensive dog. *Nephron* 1992;60:226–231.
17. Dubovsky EV, Russell CD. Diagnosis of renovascular hypertension after renal transplantation. *Am J Hypertens* 1991;4:724S–730S.
18. Erley CM, Duda SH, Wakat J-P, et al. Noninvasive procedures for diagnosis of renovascular hypertension in renal transplant recipients: a prospective analysis. *Transplantation* 1992;54:863–867.
19. Fanti S, Dondi M, Corbelli C, et al. Evaluation of hypertensive patients with a solitary kidney using captopril renal scintigraphy with Tc-99m-MAG3. *Nucl Med Commun* 1993;1:969–975.
20. Shamlou KK, Drane WE, Hawkins IF, Fennell RS. Captopril renography and the hypertensive renal transplantation patient: a predictive test of therapeutic outcome. *Radiology* 1994;190:153–159.
21. Majd M, Potter BM, Guzzetta PC, et al. Effect of captopril on efficacy of renal scintigraphy in detection of renal artery stenosis [Abstract]. *J Nucl Med* 1983;24:P23.
22. Sfakianakis GN, Chandar J, Georgiou MF, et al. Diagnosis of renovascular hypertension from renal ischemia in children with the use of converting enzyme inhibition scintigraphy. In: Taylor A, Nally J, Thomsen H, eds. *Radionuclides in nephrourology*. Reston, VA: Society of Nuclear Medicine; in press.
23. Blaufox MD, Middleton ML, Bongiovanni J, Davis BR. A cost analysis of the detection of renovascular hypertension. *J Nucl Med* 1996;37:171–177.
24. Visscher CA, de Zeeuw D, Huisman RM. Effect of chronic ACE inhibition on the diagnostic value of renography for renovascular hypertension: a preliminary report. *Nephrol Dial Transplant* 1995;10:263–265.
25. Setaro JF, Chen CC, Hoffer PB, Black HR. Captopril renography in the diagnosis of renal artery stenosis and prediction of improvement with revascularization. *Am J Hypertens* 1991;4:S698–S705.
26. Kopecky RT, Deaver TF, McAfee JG. Furosemide augments the effects of captopril on nuclear studies in renovascular stenosis. *Hypertension* 1987;10:181–188.
27. Elliot WJ, Martin WB, Murphy MB. Comparison of two noninvasive screening tests for renovascular hypertension. *Arch Intern Med* 1993;153:755–764.
28. Oei HY, Geyskes GG, Dorhout Mees EJ, Puylaert CBAJ. The significance of caaptopril renography in renovascular hypertension. *Contr Nephrol* 1987;56:95–103.
29. Blaufox MD, Dubovsky EV, Hilson AJW, et al. Report of the working party group on determining the radionuclide of choice. *Am J Hypertens* 1991;4:747S–748S.
30. Sfakianakis GN, Bourgoignie JJ, Jaffe D, et al. Single-dose captopril scintigraphy in the diagnosis of renovascular hypertension. *J Nucl Med* 1987;28:1383–1392.
31. Dondi M, Fanti S, De Fabritiis A, et al. Prognostic value of captopril renal scintigraphy in renovascular hypertension. *J Nucl Med* 1992;33:2040–2044.
32. Dondi M, Monetti N, Fanti S, et al. Use of ^{99m}Tc-MAG$_3$ for renal scintigraphy after angiotensin-converting enzyme inhibition. *J Nucl Med* 1991;32:424–428.
33. Roccatello D, Picciotto G, Rabbia C, et al. Prospective study on captopril renography in hypertensive patients. *Am J Nephrol* 1992;12:406–411.
34. Fommei E, Ghione S, Hilson AJW, et al. Captopril radionuclide test in renovascular hypertension: European multicenter study. In: O'Reilly PH, Taylor A, Nally JV, eds. *Radionuclides in nephrourology*, vol. 1. Blue Bell, PA: Field and Wood Medical Periodicals, Inc.; 1994:33–37.
35. Kahn D, Meis DM, Kirchner P. Captopril enhanced ^{99m}Tc-MAG3 renal scintigraphy in subjects with suspected renovascular hypertension. *Nucl Med Commun* 1994;15: 515–528.
36. *Physicians' desk reference*, 49th ed. Montvale, NJ: Medical Economics Data Production Co.; 1995:711.
37. Black HR, Bourgoignie JJ, Pickering T, et al. Report of the working party group for patient selection and preparation. *Am J Hypertens* 1991;4:745S–456S.
38. Erbsloh-Möller B, Dumas A, Roth D, et al. Furosemide I-131 hipppuran renography after angiotensin-converting enzyme inhibition for the diagnosis of renovascular hypertension. *Am J Med* 1991;90:23–29.
39. *Physicians' desk reference*, 49th ed. Montvale, NJ: Medical Economics Data Production Co.; 1995:1648.
40. Evans RR, Henzler MA, Weber EM, DiPette DJ. The effect of intravenous enalaprilat (MK-422) administration in patients with mild to moderate essential hypertension. *J Clin Pharmacol* 1987;27:415–418.
41. Kopecky RT, Thomas FD, McAfee JG. Furosemide augments the effects of captopril on nuclear studies in renovascular stenosis. *Hypertension* 1987;10:181–188.
42. Cohen ML, Kurz KD, Schenck KW. Tissue angiotensin converting enzyme inhibition as an idex of the diposition of enalapril (MK-421 and metabolite MK-422). *J Pharmacol Exp Ther* 1983;226:192–196.
43. Kopecky RT, McAfee JG, Thomas FD, et al. Enalaprilat-enhanced renography in a rat model of renovascular hypertension. *J Nucl Med* 1990;31:501–507.
44. Taylor A, Nally JV. Clinical applications of renal scintigraphy. *Am J Roentgenol* 1995;164:31–41.
45. Klingensmith WC III, Briggs DE, Smith WI. Technetium-99m-MAG3 renal studies: normal range and reproducibility of physiologic parameters as a function of age and sex. *J Nucl Med* 1994;35:1612–1617.
46. Geyskes GG, deBruyn AJG. Captopril renography and the effect of percutaneous transluminal angioplasty on blood pressure in 94 patients with renal artery stenosis. *Am J Hypertens* 1991;4:685S–689S.
47. Setaro JF, Saddler MC, Chen CC, et al. Simplified captopril renography in diagnosis and treatment of renal artery stenosis. *Hypertension* 1991;18:289–298.
48. Mann SJ, Pickering TG, Sos TA, et al. Captopril renography in the diagnosis of renal artery stenosis: Accuracy and limitations. *Am J Med* 1991;90:30–40.
49. Jensen G, Moonen M, Aurell M, et al. Reliability of ACE inhibitor-enhanced ^{99m}Tc-DTPA gamma camera renography in the detection of renovascular hypertension. *Nucl Med Commun* 1993;14:169–175.
50. Meier GH, Sumpio B, Setaro JF. Captopril renal scintigraphy: a new standard for predicting outcome after renal revascularization. *J Vasc Surg* 1993;17:280–287.
51. Nally JW Jr, Chen C, Fine E, et al. Diagnostic criteria of renovascular hypertension with captopril renography. *Am J Hypertens* 1991;4:749S–752S.
52. Blaufox MD Should the role of captopril renography extend to the evaluation of chronic renal disease? [Editorial] *J Nucl Med* 1994;35:254–256.
53. Patrois F, Hignette C, Froissart M, Prigent A. Interpretation de la scintigraphie rénale avec prise de captopril: à propos d'un faux positif bilatéral. *Medécine Nucléaire* 1995;13:309–313.
54. Dubovsky EV, Russell CD, Japanwalla M, Mangipudy M. Bilateral response to captopril is nonspecific [Abstract]. *Eur J Nucl Med* 1991;18:575.
55. Oei HY, Kooy PPM, Pieterman H, et al. Sensitivity and specificity of captopril renography in detecting renal artery stenosis based on visual evaluation of sequential images performed with ^{99m}Tc-MAG3. *Radionuclides in nephrourology*. Blue Bell, PA: Field and Wood Medical Periodicals, Inc.; 1994:43–50.
56. Chen CC, Hoffer PB, Vahjen G, et al. Patients at high risk for renal artery stenosis: a simple method of renal scintigraphic analysis with ^{99m}Tc-DTPA and captopril. *Radiology* 1990;176:365–370.
57. Dey HM, Hoffer PB, Lerner E, et al. Quantitative analysis of the ^{99m}Tc-DTPA captopril renogram: contribution of washout parameters to the diagnosis of renal artery stenosis. *J Nucl Med* 1993;34:1416–1419.
58. Subramanian K, Sarkar S, Mann S, et al. Single-dose captopril renography with ^{99m}Tc-DTPA and ^{131}I Hippuran in renovascular hypertension (RVH) [Abstract]. *J Nucl Med* 1987;28(suppl):735.
59. Chandler ST, Gibson CJ, Elliott L. Models of renal blood flow and their use in the detection of renal artery stenosis. *Nucl Med Comm* 1990;11:427–436.
60. Peters AM, Brown J, Crossman D, et al. Noninvasive measurement of renal blood flow with ^{99m}Tc-DTPA in the evaluation of patients with suspected renovascular hypertension. *J Nucl Med* 1990;31:1980–1985.
61. Gorten RJ. The actual clinical value of captopril renal function imaging. *Eur J Nucl Med* 1994;21:S39