

# Society of Nuclear Medicine Procedure Guideline for Diagnosis of Renovascular Hypertension

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## I. Purpose

The purpose of this guideline is to assist nuclear medicine practitioners in recommending, performing, interpreting, and reporting the results of renal procedures for diagnosis of renovascular hypertension.

## II. Background Information and Definitions

Renovascular disease includes renal artery stenosis, renovascular hypertension, and azotemic renovascular disease (ischemic nephropathy). It is important to distinguish between renovascular hypertension and renal artery stenosis. Stenosis of the renal artery is common in nonhypertensive elderly persons and is an associated but noncausative finding in a number of hypertensive patients. Renovascular hypertension is defined as an elevated blood pressure caused by renal hypoperfusion, usually resulting from anatomic stenosis of the renal artery and activation of the renin-angiotensin system. Azotemic renovascular disease refers to renal functional impairment associated with renal atrophy, intrarenal vascular lesions, and interstitial nephritis and fibrosis in the presence of severe atherosclerotic renal artery stenosis. Causes of renovascular hypertension in neonates and infants include renal artery thrombosis after umbilical artery catheterization and coarctation of the aorta. The goal of a screening test for renovascular hypertension in adults is to detect those patients who have renal artery stenosis as the cause of hypertension and to predict curability or amelioration of hypertension after intervention.

Renovascular hypertension is estimated to affect fewer than 1%–3% of the unselected hypertensive population and up to 15%–30% of patients referred

to a subspecialty center because of refractory hypertension. Clinical features should indicate which patients have moderate or high risk of renovascular hypertension. Clues include abrupt or severe hypertension, hypertension resistant to 3-drug therapy, bruits in the abdomen or flank, unexplained azotemia or recurrent pulmonary edema in an elderly hypertensive patient, or worsening renal function during therapy with angiotensin-converting enzyme inhibitors (ACEIs). ACEI renography is designed to be a test for renovascular hypertension, not for renal artery stenosis. The optimal reference test or “gold standard” in future studies should be the outcome—the response to successful revascularization—not angiographic evidence of renal artery stenosis.

## III. Common Indications

The test is most cost effective if used primarily in patients who have a moderate-to-high risk of renovascular hypertension. Clinical features associated with a moderate-to-high risk of renovascular hypertension have been published and include:

- Abrupt onset or severe hypertension;
- Hypertension resistant to 3-drug therapy in a compliant patient;
- Abdominal or flank bruits;
- Unexplained azotemia in an elderly hypertensive patient;
- Worsening renal function during antihypertensive therapy, especially with ACEIs or angiotensin II receptor blockers;
- Grade 3 or 4 hypertensive retinopathy;
- Occlusive disease in other vascular beds;

- Onset of hypertension under age 30 y or over age 55 y;
- Recurrent pulmonary edema in an elderly hypertensive patient;
- Hypertension in infants with an umbilical artery catheter; and/or
- Hypertension in children.

#### IV. Procedure

##### A. Patient Preparation

Patients need to be well hydrated before testing. If an oral ACEI is used, patients should drink only water and should not eat a solid meal within 4 h of the study. A moderate hydration protocol will likely lead to greater accuracy in the interpretation of the images and quantitative data. Dehydration and overhydration should be avoided. One suggested protocol is 7 mL water/kg body weight ingested at a minimum of 30 and preferably 60 min before the study. Hydration should continue between studies when 2 studies are performed on the same day. An intravenous line should be placed in high-risk patients and in those receiving intravenous enalaprilat so that normal saline can be promptly infused if the patients become hypotensive (see IV.C. Precautions).

The sensitivity of ACEI renography may be reduced in patients receiving ACEIs. For this reason, short-acting ACEIs, such as captopril, should be withheld for 3 d before the study. Longer acting ACEIs should be withheld for 5–7

d, depending on the ACEI. Although no available data evaluates the effect of angiotensin II receptor blockers on the sensitivity of ACEI renography, angiotensin II receptor blockers such as losartan may have an effect comparable to ACE inhibitors, and these drugs also should be discontinued before ACEI renography.

Some patients will present for the test without discontinuing therapeutic ACEIs or angiotensin II receptor blocking agents. In these circumstances, it is acceptable to proceed with the procedure with the understanding that there may be a slight loss in sensitivity. When proceeding with the study without discontinuing chronic ACEIs, most practitioners give the test ACEI (captopril or enalaprilat) to make sure the patient is adequately inhibited, in case the patient has not taken his or her prescribed medication. The chances of a hypotensive response are low, because the patient has shown that he or she tolerates an ACEI without symptomatic hypotension.

Chronic administration of diuretics may lead to volume depletion resulting in a decrease in specificity. Furthermore, the volume depletion associated with chronic diuretic administration may potentiate the effects of ACE inhibition, leading to an increased risk of symptomatic hypotension. If possible, chronic diuretic administration should be stopped several days before the study. The effect of other antihypertensive medications upon ACEI renography is not completely understood but appears small, although

#### Radiation Dosimetry for Adults (Normal Renal Function)

Radiopharmaceutical	Activity MBq (mCi)	Organ Receiving the Largest Radiation Dose* mSv/MBq (rem/mCi)	Effective Dose Equivalent mSv/MBq (rem/mCi)
<sup>99m</sup> Tc-DTPA	37–370 (1–10)	Bladder wall 0.051 (0.19)	0.0054 (0.020)
<sup>99m</sup> Tc-MAG3	37–370 (1–10)	Bladder wall 0.046 (0.17)	0.0041 (0.016)

\*Dosimetry calculations assume the patient voids at 30 min postinjection and every 4 h thereafter (Stabin M, Taylor A. Jr., Eshima D, Wooten W. Radiation dosimetry for technetium-99m-MAG3, technetium-99m-DTPA, and iodine-131-OIH based on human biodistribution studies. *J Nucl Med.* 1992;33:33–40.) DTPA = diethylenetriaminepentaacetic acid; MAG3 = mercaptoacetyl triglycine.

## Radiation Dosimetry in Children (5 Years Old; Normal Renal Function)

Radiopharmaceutical	Administered Activity MBq (mCi/kg)	Organ Receiving the Largest Radiation Dose* mSv/MBq (rem/mCi)	Effective dose Equivalent mSv /MBq (rem /mCi)
<sup>99m</sup> Tc-DTPA	3.7 (0.1)	Bladder wall 0.086 (0.32)	0.012 (0.044)
<sup>99m</sup> Tc-MAG3	3.7 (0.1)	Bladder wall 0.18 (0.67)	0.015 (0.056)

\*Treves ST, ed. *Pediatric Nuclear Medicine*. 2nd ed. New York, NY: Springer-Verlag; 1995:567–569. DTPA = diethylenetriaminepentaacetic acid; MAG3 = mercaptoacetyl triglycine.

bilateral symmetrical abnormalities have been reported in patients taking calcium channel blockers. For this reason, it is reasonable to discontinue calcium channel blockers when there is no contraindication. If hypertension is severe, it is not necessary to discontinue all antihypertensive medications before the procedure. If the patient's blood pressure returns to very high pre-treatment levels, the renin-angiotensin system may not be activated and there may be a loss in test sensitivity.

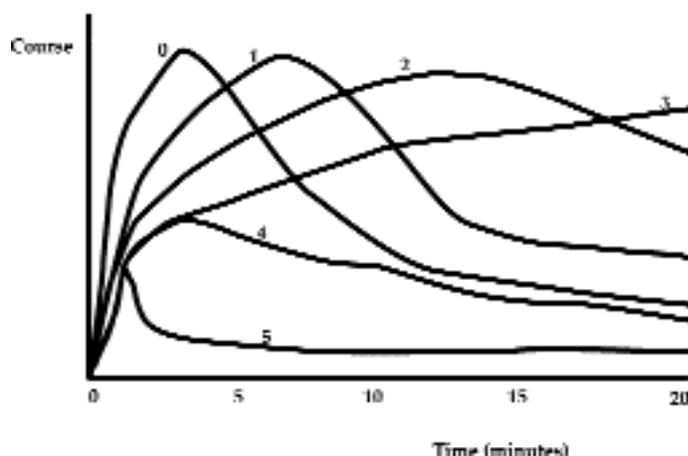
### B. Information Pertinent to Performing the Procedure

A relevant history should be obtained and should include any history of cardiovascular or cerebrovascular disease, medications, when diuretics or ACEIs were stopped, serum creatinine, and the efficacy of blood pressure control. A sitting and standing blood pressure and heart rate

should be measured before the exam, at the conclusion of the test, and before patient discharge. For patients receiving enalaprilat, blood pressure also should be measured every 5 min during the exam.

### C. Precautions

ACEIs can cause significant hypotension. Therefore, blood pressure and pulse should be monitored and recorded before ACEI and radiopharmaceutical administration, every 5–15 min thereafter, and at the end of the study. An intravenous line should be established in high-risk patients (history of carotid disease, stroke, transient ischemic attack, angina, recent myocardial infarction, and severe salt depletion after diuretics) and in patients who receive intravenous enalaprilat or who are taking diuretics. A patient should not be sent home unless the standing mean blood pressure is at least 70% of baseline



**Figure 1.** Patterns of renographic curves from normal to blood background type curve. 0 = normal; 1 = minor abnormalities, but with  $T_{max} > 5$  min and a 20-min/max cortical ratio  $> 0.3$ ; 2 = a marked delay in excretion rate with preserved washout phase; 3 = delayed excretion rate without washout phase (accumulation curve); 4 = renal failure pattern with measurable kidney uptake; 5 = renal failure pattern without measurable kidney uptake (blood background type curve). (Adapted from Fommei E, Ghione S, Hilson AJW, et al. Captopril radionuclide test in renovascular hypertension: a European multicentre study. *Eur J Nucl Med*. 1993;20:625–644.)

and the patient is asymptomatic when standing.

#### D. Radiopharmaceuticals

The optimal radiopharmaceutical in individuals with normal renal function remains to be determined. However,  $^{99m}\text{Tc}$ -mercaptoacetyltriglycine (MAG-3) and  $^{99m}\text{Tc}$ -diethylenetriaminepentaacetic acid (DTPA) are most commonly used. Because of its higher extraction,  $^{99m}\text{Tc}$ -MAG3 is preferred over  $^{99m}\text{Tc}$ -DTPA in patients with elevated creatinine.  $^{123}\text{I}$ -hippuran is an acceptable alternative in countries where it is available.

#### E. Image Acquisition

##### 1. Study protocol

Both 1- and 2-d protocols are acceptable. If the 2-d protocol is to be performed, ACEI renography should be performed on the first day and the requesting physician and the patient must be aware that the patient may need to return on a second day for the baseline study to maximize the specificity of the test. If the ACEI renogram is normal (grade 0 renogram curve; see Fig. 1), the chance that the patient has renovascular hypertension is low, and there is no need to have the patient return on the second day for a baseline study. For this reason, some centers begin with the 2-d protocol if there is a relatively low likelihood of renovascular disease, because the ACEI renogram is likely to be normal.

The 1-d protocol requires that the patient remain in the department for a longer period of time, but the entire study is completed in 1 d. With the 1-d protocol, baseline renography should be performed first with approximately 40 MBq (~1 mCi) of  $^{99m}\text{Tc}$ -DTPA or  $^{99m}\text{Tc}$ -MAG3. The administered activity for the ACEI renogram should be 200–400 MBq (~5–10 mCi) to overwhelm any residual counts from the baseline study. Sufficient time should elapse between the 2 studies to avoid problems in interpretation of the ACEI study that might result from residual activity from the baseline study. The time required will depend on the radiopharmaceutical, the administered dose for the baseline and ACEI studies, and method of data processing. When 40 MBq (~1 mCi) are administered for the baseline study, the ACEI study can begin as soon as the baseline study is concluded.

##### 2. Instrumentation, positioning, and timing of images

The study should be acquired with the gamma camera facing the lower back of the supine patient. A large-field-of-view camera is preferred, so that the heart, kidneys, and bladder can all be included in the field of

view. If only 2 organs can be imaged, the kidney and bladder should be visualized, unless a time–activity curve over the heart is required for data processing. For  $^{99m}\text{Tc}$  agents and  $^{123}\text{I}$ -orthoiodohippurate (OIH), a low-energy, high-resolution, all-purpose collimator should be used. Matrix resolution is preferably  $128 \times 128$ , although  $64 \times 64$  is acceptable. When a dynamic flow study is desired, higher activities should be injected. The time per frame should be 1–3 s for the first 60 s and 10–30 s/frame for the remainder of the study. The total acquisition time should be 20–30 min. Images should be displayed at 1-, 2-, or 3-min intervals. Patients should void before beginning the study, and a postvoid image is recommended.

##### F. Interventions

Although captopril has been the most widely used ACEI, captopril and enalaprilat are both acceptable for ACEI renography. The recommended dose of captopril is 25–50 mg by mouth. Crushing the tablets and dissolving them in 150–250 mL water may enhance absorption. Unless the patient has delayed gastric emptying or poor absorption from the gastrointestinal tract, 25 mg are sufficient. Patients should not eat a solid meal within 4 h of the study, because food in the gastrointestinal tract decreases absorption of captopril. The radiopharmaceutical should be administered 60 min after captopril administration, because peak blood levels occur approximately 60 min after oral ingestion and then begin to decline. Enalaprilat can also be used. The recommended dose is 40  $\mu\text{g}/\text{kg}$  administered intravenously over 3–5 min with a maximum administered dose of 2.5 mg. Radiopharmaceutical administration should be delayed at least 15 min after enalaprilat administration. The procedure time is slightly shorter than that with captopril, and potential problems with gastrointestinal absorption are avoided. An intravenous line is recommended, because enalaprilat may be associated with hypotension (see next paragraph).

**Option:** Administration of furosemide with captopril or enalaprilat is not considered to be an essential component of ACEI renography. Because furosemide is a loop diuretic, it can wash the radiopharmaceutical out of the distal nephron, calyces, and pelvis and thereby improve detection of cortical retention of radiotracers, especially tubular agents, such as  $^{99m}\text{Tc}$ -MAG3 and  $^{123}\text{I}$ -OIH, and potentially increase the sensitivity and specificity of the test. One approach is to administer 20 mg furosemide at the beginning of the baseline study simultaneously

with  $^{99m}\text{Tc}$ -MAG3 administration and a second dose of 20 mg furosemide with  $^{99m}\text{Tc}$ -MAG3 at the beginning of the ACE inhibition study. Furosemide can cause volume depletion and increase the risk of hypotension. If furosemide is used, an intravenous line and normal saline administration are recommended. Many experienced nuclear medicine physicians believe that good hydration and attention to parenchymal retention are sufficient.

#### G. Processing

Background subtraction is recommended using either a ring, elliptical, or perirenal region of interest (ROI). The 1998 Radionuclides in Nephrourology consensus committee suggested that the renal uptake of  $^{99m}\text{Tc}$ -MAG3,  $^{123}\text{I}$ -OIH, and  $^{99m}\text{Tc}$ -DTPA be measured at 1–2- or 1–2.5-min intervals after injection of the radiopharmaceutical, using whole-kidney ROIs. In an extremely well-hydrated patient, some of the tracer may leave the renal ROI after 2.5 min in 1 or both kidneys and could conceivably lead to an incorrect estimate of relative function if relative function is measured at 2–3 min. In addition to whole-kidney renogram curves, it is often helpful to generate renogram curves from ROIs that are selectively assigned to the renal parenchyma (cortical ROI). Exclusion of the pelvis and calyces is important if there is retention of activity in these structures. The time to maximum counts ( $T_{\text{max}}$ ) should be determined. A 20-min/peak min (20 min/maximum) count ratio should be calculated for  $^{99m}\text{Tc}$ -MAG3 and  $^{123}\text{I}$ -OIH. A 30-min/peak count ratio is equally acceptable. Similar ratios for  $^{99m}\text{Tc}$ -DTPA may also be helpful.

**Option:** Some centers measure the renal parenchymal transit time using a parenchymal ROI if the software algorithm is available and use an ACEI-induced prolongation of the transit time to detect renovascular hypertension. This approach has not been standardized.

#### H. Interpretation Criteria

The most specific diagnostic criterion for renovascular hypertension is an ACEI-induced change in the renogram. In patients with normal or minimally reduced renal function (creatinine < 1.7 mg/dL), ACEI renography has a sensitivity and specificity of about 90% for diagnosis of renovascular hypertension. In azotemic patients, the sensitivity and specificity are reduced. Most important, ACEI-induced renographic findings of renovascular hypertension indicate a high probability that the hypertension will be cured or improved after revascularization.

A normal ACEI renogram indicates a low probability (<10%) of renovascular hyperten-

sion. Bilateral symmetrical changes after ACE inhibition usually do not represent renovascular hypertension and may be associated with hypotension, salt depletion, the use of calcium channel blockers, and/or a low urine flow rate. Criteria associated with renovascular hypertension include worsening of the renogram curve, reduction in relative uptake, prolongation of the renal and parenchymal transit time, an increase in the 20- or 30-min/peak ratio, and prolongation of the time to maximum activity. A small, poorly functioning kidney (<30% uptake, abnormal renogram) that shows no change after ACEI renography represents an intermediate probability for renovascular hypertension.

**Specific interpretive criteria for  $^{99m}\text{Tc}$ -MAG3 and  $^{123}\text{I}$ -OIH.** Unilateral parenchymal retention after ACEI is the most important criterion for  $^{99m}\text{Tc}$ -MAG3 and  $^{123}\text{I}$ -OIH. In patients with normal renal function and in the absence of a unilateral small kidney, this finding represents a high probability (>90%) for renovascular hypertension. This can be measured by a change in the renogram grade (see Fig. 1), prolongation of the transit time, and/or, for parenchymal ROIs, an increase in the 20- or 30-min/peak ratio of 0.15 or greater from the baseline study. It can also be detected as a delay in the excretion of the tracer into the renal pelvis by 2 min after ACEI or an increase in the  $T_{\text{max}}$  of at least 2–3 min or 40%. An increase in  $T_{\text{max}}$  from 5–8 min is much more significant than a change from 17–20 min. A decrease in relative uptake of  $^{99m}\text{Tc}$ -MAG3 or  $^{123}\text{I}$ -OIH 10% (relative uptake decreasing, for example, from 50% to 40%) after ACEI is uncommon, but, when present, represents a high probability for renovascular hypertension. Finally, it is important to distinguish parenchymal (significant) from pelvic (insignificant) retention. Cortical ROIs often are used to evaluate parenchymal retention, but cortical renogram curves may be noisy when a low dose of  $^{99m}\text{Tc}$ -MAG3 is administered for a baseline exam and renal function is poor. In this setting, the whole-kidney renogram will provide a better index of parenchymal function if there is no tracer retention in the renal pelvis or calyces.

**Specific interpretive criteria for  $^{99m}\text{Tc}$ -DTPA.** Reduction in relative uptake >10% after ACEI indicates a high probability for renovascular hypertension. Five to nine percent is considered to be an intermediate response, although a recent study performed under carefully controlled conditions suggests that smaller changes may be significant. High probability is also associated with a >10% decrease in calculated

glomerular filtration rate (GFR) of the ipsilateral kidney after ACEI. Marked unilateral parenchymal retention after ACEI compared with the baseline study also represents a high probability for renovascular hypertension.

#### I. Reporting

The post-test probability for disease cannot be determined solely by the results of the test. The test results must be combined with the pretest probability. For this discussion, a pretest probability of 10%–30% is assumed for the moderate-to-high-risk patients in whom ACEI renography should be performed. When this test is performed in lower risk patients, the post-test probability will be smaller than the numbers cited here. Test results should be interpreted as consistent with high, low, or intermediate probability of disease.

**Low probability.** Normal findings on ACEI renography indicate a low probability (<10%) for renovascular hypertension. Abnormal baseline findings that improve after ACEI also indicate low probability for renovascular hypertension.

**Intermediate probability.** Patients with an intermediate probability of disease have abnormal baseline findings, but the renogram is unchanged after ACEI. This group often includes patients with ischemic nephropathy involving 1 or both kidneys. The sensitivity of abnormal baseline findings that are unchanged after ACEI is quite high (>90%), but the specificity is poor, probably in the range of 50%–75%, depending on the pretest probability of disease and the coexistence and severity of renal dysfunction

**High probability.** The probability is considered high (>90%) when marked change of the renogram curve occurs after ACEI, compared with baseline findings.

#### J. Quality Control

Gamma camera and image display are described in the Society of Nuclear Medicine Procedure Guideline for General Imaging. Images should be reviewed in a dynamic format to evaluate for presence of patient motion. An image should be obtained over the injection site to exclude infiltration, because infiltration of the injected dose can alter the shape of the renogram curve and interfere with quantitative measures of renal function (GFR, effective renal plasma flow, <sup>99m</sup>Tc-MAG3 clearance).

#### K. Sources of Error

Sources of error include ingestion of food within 4 h of administering captopril, infiltration, pelvic retention, dehydration, hypotension, and a full bladder impairing drainage. Pelvic re-

tention is likely to be related to the patient's state of hydration but will result in an abnormal whole-kidney renogram curve, which may be incorrectly interpreted as representing renovascular hypertension. Dehydration and hypotension may lead to bilateral parenchymal retention and renogram curve abnormalities.

### V. Issues Requiring Further Clarification

A. A recent prospective investigation compared simultaneous <sup>123</sup>I-OIH and <sup>99m</sup>Tc-DTPA captopril renography with the results of angiography (not revascularization). This study included a group of patients with a high prevalence of renal dysfunction. In subjects with GFR <50 mL/min, only 15%–20% of test results could be classified as high probability for renovascular hypertension, whereas 80%–85% fell into the intermediate probability category. Among 30 individuals with high probability captopril renograms (all "correct" compared with angiography), the mean serum creatinine concentration was 1.2 ± 0.4 mg/dL. Among 30 subjects with either incorrect results (7 false-negatives and 2 false-positives) or intermediate probability results (*n* = 21), the mean serum creatinine concentration was 2.0 ± 1.2 mg/dL. The false-negative studies may have occurred because hypertensive patients with azotemic renovascular disease may no longer have a renin-dependent hypertension or because renal artery stenosis may not have been the cause of the hypertension.

Future studies need to define patient subgroups and the results of ACEI in these subgroups (e.g., azotemic versus nonazotemic patients; results in patients taking diuretics, beta blockers, calcium channel blockers, angiotensin II receptor blockers, and ACEIs versus patients not taking these medications; results in patients with normal baseline studies versus patients with abnormal baseline studies as often observed in azotemic renovascular disease; better characterization of the effects of salt loading and the state of hydration; and additional evaluation of the role of aspirin-enhanced renography and exercise renography to detect renovascular hypertension).

B. Patients with azotemia tend to have a large percentage of intermediate probability (abnormal but nondiagnostic) results. In this subset, a positive captopril test (stimulated plasma renin assay) may improve the true-positive rate without introducing false-positive results.

## VI. Concise Bibliography

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## VII. Disclaimer

The Society of Nuclear Medicine has written and approved guidelines to promote the cost-effective use of high-quality nuclear medicine procedures. These generic recommendations cannot be applied to all pa-

tients in all practice settings. The guidelines should not be deemed inclusive of all proper procedures or exclusive of other procedures reasonably directed to obtaining the same results. The spectrum of patients seen in a specialized practice setting may be quite different from the spectrum of patients seen in a more general practice setting. The appropriateness of a procedure will depend in part on the prevalence of disease in the patient

population. In addition, the resources available to care for patients may vary greatly from one medical facility to another. For these reasons, guidelines cannot be rigidly applied.

Advances in medicine occur at a rapid rate. The date of a guideline should always be considered in determining its current applicability.