

Pharmacologic Interventions in Nuclear Radiology: Indications, Imaging Protocols, and Clinical Results¹

CME FEATURE

See accompanying test at http://www.rsna.org/education/rg_cme.html

LEARNING OBJECTIVES FOR TEST 2

After reading this article and taking the test, the reader will be able to:

- Discuss the indications and adverse effects of pharmacologic interventions in nuclear radiology.
- Recognize the scintigraphic manifestations of the physiologic changes induced by drugs.
- Describe the imaging protocols in drug-augmented scintigraphy.

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Nuclear radiology is valuable in assessing pathophysiology of a variety of organ systems. Pharmacologic interventions are often employed in radionuclide imaging to monitor the physiologic changes, which in turn facilitate the diagnosis. Metoclopramide, erythromycin, and cisapride have been used for gastric emptying studies. To overcome false-negative results, cimetidine, pentagastrin, and glucagon have been used in imaging of Meckel diverticula. Pharmacologic intervention with either cholecystokinin-8 or morphine is used primarily for the assessment of diseases of the gallbladder, common bile duct, and sphincter of Oddi. Pharmacologic interventions performed during renography include diuretic administration, angiotensin-converting enzyme inhibition, and aspirin renography. Recombinant thyrotropin can be used in patients with previously treated thyroid carcinoma who require lifelong follow-up for recurrent disease. Cardiac pharmacologic stress agents fall into two categories: coronary vasodilating agents, such as dipyridamole and adenosine, and cardiac positive inotropic agents, such as dobutamine and arbutamine. Measurement of hemodynamic responses to pharmacologic flow augmentation with carbon dioxide or acetazolamide is valuable in cerebrovascular perfusion studies.

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Abbreviations: ACE = angiotensin-converting enzyme, CCK-8 = cholecystokinin-8, HIDA = hepato-iminodiacetic acid, MAG3 = mercaptoacetyl-triglycine, rTSH = recombinant thyrotropin, TSH = thyroid stimulating hormone, SPECT = single-photon emission computed tomography

Index terms: Radionuclide imaging, technology, 10.12172, 273.12172, 51.12171, 70.1217, 81.12174 • Radionuclide imaging, transit studies, 70.1217, 81.12174

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Table 1
Gastrokinetic Agents for Pharmacologic Gastrointestinal Scintigraphy

Drug	Dose	Side Effects	Mechanism
Metoclopramide	10 mg orally 30 min before meal, four times per day	Common: nausea, diarrhea, drowsiness, fatigue Rare: extrapyramidal symptoms, tardive dyskinesia Contraindications: mechanical obstruction, pheochromocytoma	Dopamine antagonist that stimulates gastric motility independently of vagal innervation
Erythromycin	500 mg orally in a single dose	Common: nausea, vomiting, diarrhea Rare: jaundice, transient auditory impairment	Binds to antral and duodenal motilin receptors and initiates phase III of the interdigestive motor complex

Introduction

The great strength of nuclear radiology continues to be its use in the assessment of organ function. This capability often is enhanced by a pharmacologic intervention that permits observation of dysfunction, which may not appear under basal conditions (1). Common examples of pharmacologic interventions include use of gastrokinetic agents in imaging of gastroparesis; cimetidine and pentagastrin in imaging of the Meckel diverticulum; cholecystokinin-8 (CCK-8) and morphine in hepatobiliary imaging; diuretics, angiotensin-converting enzyme (ACE) inhibitors, and aspirin in renography; recombinant thyrotropin (rTSH) in thyroid scintigraphy; vasodilating agents and myocardial inotropic agents in cardiac perfusion scintigraphy; and acetazolamide in the evaluation of cerebrovascular functional reserve.

In this article, we review the indications, mechanism of action, and adverse effects of these drugs and present imaging protocols and examples of their use in nuclear radiology.

Pharmacologic Gastrointestinal Scintigraphy

Gastric Emptying

Gastric emptying is a complex process controlled by the autonomic nervous system and a variety of hormones, both gastrointestinal and nongastrointestinal in origin, as well as by factors related to the physical state, caloric content, and volume of the meal. Over the past 10 years, refinement in the mathematical analysis of gastric emptying curves, compartmentalization of the stomach into two major portions, introduction of dynamic digital gastric scintigraphy, and availability of new gastrokinetic agents have provided new tools for evaluating the pathophysiology of most gastric motor disorders (2,3).

The most common indication for performing dynamic digital gastric scintigraphy is diabetic gastroparesis (4), with the three main agents available for gastrokinetic studies being metoclopramide, erythromycin, and cisapride (Table 1). All have proved beneficial in improving gastric emptying and symptoms (Fig 1), although metoclopramide and cisapride have significant limitations. The gastrokinetic agent is administered in a meal of solids, as solids are more sensitive than liquids for detecting abnormal gastric motility. Eggs mixed with technetium-99m sulfur colloid before cooking is the meal most commonly used (3). The normal time for the stomach to empty halfway is 77 min \pm 32 (mean \pm 2 SD) for a solid meal. Values vary with gender, time of day, body position, and physical activity (2).

Metoclopramide was one of the first drugs found to have an effect on gastroparesis. Metoclopramide is a dopamine antagonist that stimulates gastric motility independently of vagal innervation. Radionuclide gastric emptying studies performed before and after metoclopramide treatment have shown that the drug shortens the gastric emptying time for solids with little effect on the time for liquids (2). Unfortunately, the use of metoclopramide is limited by a significant incidence of side effects, and results in patients have been variable.

Erythromycin, a well-known macrolide antibiotic, has been shown to increase gastric emptying of both solids and liquids dramatically and (5,6) (Fig 1). There is strong evidence from both animal and human studies that erythromycin mimics the effect of the gastrointestinal hormone motilin. Motilin induces the stomach to contract with the strong phase III contractions of the interdigestive migrating motor complex. Erythromycin is thought to bind to the antral and duodenal motilin receptors and thereby induce the same phase III activity as motilin. The results with oral forms of erythromycin are less dramatic. In one study,

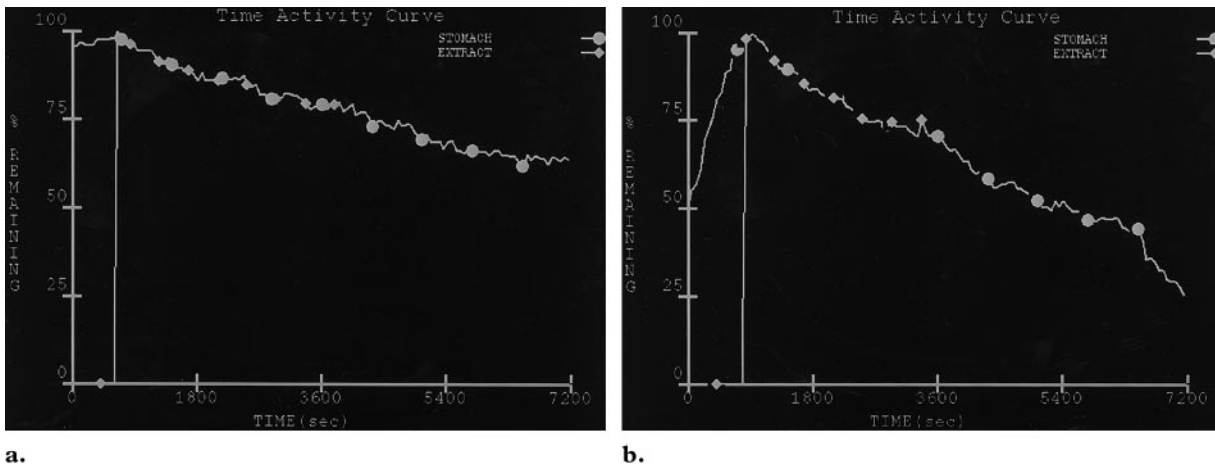


Figure 1. Effect of pharmacologic intervention in a patient with diabetic gastroparesis. **(a)** Time activity curve before treatment shows prolongation of gastric emptying time (emptying halftime, 168 minutes). **(b)** Following oral administration of erythromycin, the gastric emptying is accelerated (emptying halftime, 92 minutes). Erythromycin mimics the effect of the hormone motilin by binding to the antral and duodenal motilin receptors, which enhances the rate of gastric emptying.

after a single oral dose of amorphous erythromycin ethylsuccinate (500 mg) and crystalline erythromycin ethylsuccinate (1,000 mg), the two erythromycin preparations significantly shortened the gastric transit time of solids and liquids (30% and 20%, respectively) when compared with the effects of a placebo (7).

Both oral and intravenous administrations of cisapride, a gastrointestinal prokinetic agent without antidopaminergic properties, accelerate gastric emptying of solid and liquid meals in patients with diabetes, after gastric surgery, and with idiopathic gastric stasis syndrome (2,8). Cisapride promotes gastric motility by enhancement of acetylcholine release at the myenteric plexus (8,9). It is less potent than metoclopramide in its dopamine receptor blocking effects. Acceleration of gastric emptying following a radiolabeled meal is greatest when 10 mg of cisapride is given both in the morning and again before the test meal (9). However, cisapride has been associated with many reports of heart rhythm abnormalities, and marketing of this agent has been stopped in the United States.

Meckel Diverticulum

Meckel diverticulum is the most common congenital anomaly of the gastrointestinal tract and occurs in 2% of the population. In approximately 25% of cases, the diverticulum contains ectopic gastric mucosa (10). In a study of Meckel diverticula in children, ectopic mucosa was present in 61% of the resected specimens from asymptomatic patients (11). The most common ectopic tissues were gastric (88% of cases), pancreatic (7%), and gastric with pancreatic (3%) mucosa. Gastrointestinal bleeding is the most common manifestation of the Meckel diverticulum.

Scintigraphic studies use Tc-99m pertechnetate to demonstrate the ectopic gastric mucosa of the Meckel diverticulum. It appears that mucus secretory cells, rather than the parietal and chief cells, concentrate the Tc-99m pertechnetate. To overcome false-negative rates as high as 50%, pharmacologic interventions with cimetidine, pentagastrin, and glucagon have been tried (2,12) (Table 2).

Cimetidine is a potent histamine H₂-receptor blocker that decreases the gastric output of basal hydrochloric acid by 50% (3). The exact mechanism by which cimetidine enhances the visualization of Meckel diverticulum is not clear (13). Cimetidine inhibits pertechnetate secretion by mucus cells without impairing the uptake, and it increases the sensitivity of the imaging study to more than 90% (14). For adults, the dose with the oral form is 300 mg four times daily for 24 hours before the study. Cimetidine may be administered intravenously, with 300 mg in 100 mL of 5% dextrose in water given over 20 minutes followed by imaging in 1 hour. In children, a dose of 20 mg/kg per day is recommended. Some institutions have switched to ranitidine, which may have fewer side effects. The recommended dose is 1 mg/kg, with a maximum dose of 50 mg infused intravenously over 20 minutes followed by imaging in 1 hour (Table 2).

Pentagastrin, similar to gastrin, stimulates gastric mucosal blood flow (13). Acting on the parietal cells, pentagastrin is a potent stimulator of gastric acid secretion. It stimulates uptake and secretion of pertechnetate in both the Meckel diverticulum and the stomach. Pentagastrin is administered subcutaneously at a dose of 6 μ g/kg. Pentagastrin should not be combined with cimetidine

Table 2
Agents for Pharmacologic Meckel Diverticulum Imaging

Drug	Dose	Side Effects	Mechanism
Cimetidine and ranitidine	Cimetidine: for adults, 300 mg orally, four times per day for 24 hours; for children, 20 mg/kg/d Ranitidine: 1 mg/kg intravenously over 20 min	Common: headache, dizziness, diarrhea, muscular pain Rare: hallucination, confusion	Histamine H ₂ -receptor blocker that impedes secretion of Tc-99 pertechnetate by mucus and parietal cells
Pentagastrin	6 µg/kg subcutaneously	Nausea, vomiting, tachycardia	Stimulates uptake and secretion of Tc-99m pertechnetate in the gastric mucosa in the Meckel diverticulum and stomach
Glucagon	0.25–2.00 mg intravenously	Common: nausea, vomiting, weakness, dizziness Contraindications: hypersensitivity, pheochromocytoma, insulinoma, glucagonoma, poorly controlled diabetes	Reduces peristalsis, which allows accumulation of the radiotracer at the site of Meckel diverticulum

Table 3
Agents for Pharmacologic Tc-99m HIDA Cholescintigraphy

Drug	Dose	Side Effects	Mechanism
Cholecystokinin-8	Intravenous infusion of 10 ng/kg/3 min	Abdominal pain, urge to defecate, nausea, flushing, dizziness, allergic reaction	Stimulates contraction of the gallbladder wall and initiates and sustains bile emptying; simultaneously relaxes the sphincter of Oddi
Morphine	0.04 mg/kg intravenously, slowly over 1–2 min	Respiratory depression, hypotension, vomiting, dysphoria, urinary retention Contraindications: should be used with caution in chronic obstructive pulmonary disease, chronic liver disease	Constricts the sphincter of Oddi and increases pressure within the sphincter and common bile duct
Phenobarbital	5 mg/kg orally for 5 days in divided doses	Sedation, anxiety	Induces hepatic enzymes, thereby increasing radiotracer uptake and biliary excretion

because the latter antagonizes pentagastrin's stimulation of pertechnetate uptake (15,16).

Glucagon is a peptide hormone and directly relaxes smooth muscle of the stomach, duodenum, distal small intestine, and colon (2,11). The intravenous administration of 0.5 units (0.5 mg) of glucagon causes inhibition of gastric motility by 1 minute, with a peak activity at 2–4 minutes and duration of 9–17 minutes. Studies in mice indicate that glucagon reduces pertechnetate uptake in the stomach by 39% (11). For this reason, glucagon has been used with pentagastrin (12). With

this combination, pentagastrin stimulates pertechnetate uptake and secretion in the Meckel diverticulum and stomach, but the glucagon reduces peristalsis, thus allowing the uptake in the Meckel diverticulum to continue to accumulate at the abnormal site. The typical dose is 0.25–2.00 mg given intravenously.

Pharmacologic Hepatocholescintigraphy

Radionuclide imaging with Tc-99m hepato-imi-nodiacetic acid (HIDA) is a well-established technique for the evaluation of various hepatobiliary diseases (17). Images obtained during the first 6 minutes after an injection of Tc-99m HIDA pro-

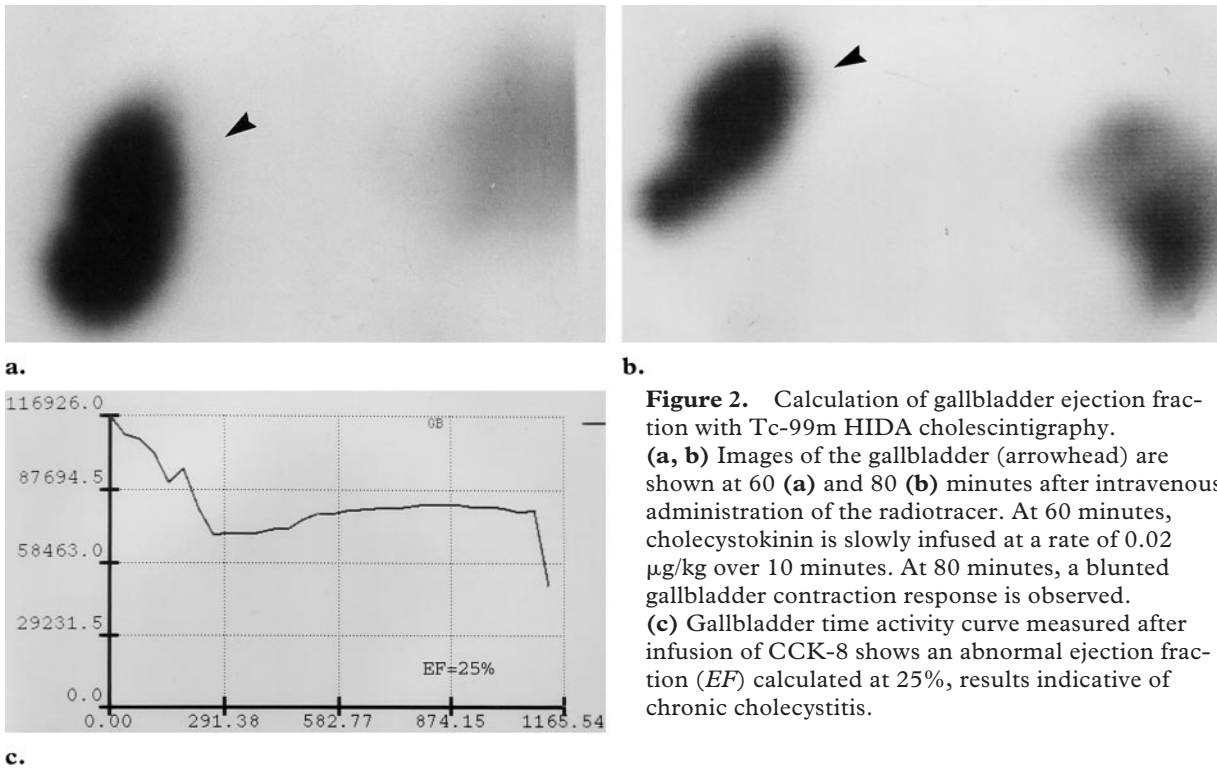


Figure 2. Calculation of gallbladder ejection fraction with Tc-99m HIDA cholescintigraphy. (a, b) Images of the gallbladder (arrowhead) are shown at 60 (a) and 80 (b) minutes after intravenous administration of the radiotracer. At 60 minutes, cholecystokinin is slowly infused at a rate of 0.02 $\mu\text{g}/\text{kg}$ over 10 minutes. At 80 minutes, a blunted gallbladder contraction response is observed. (c) Gallbladder time activity curve measured after infusion of CCK-8 shows an abnormal ejection fraction (EF) calculated at 25%, results indicative of chronic cholecystitis.

vide information about liver morphology. Images obtained between 6 and 10 minutes reflect canalicular bile transit. Images obtained between 10 and 30 minutes provide information about the major hepatic ducts and the gallbladder. Images obtained between 30 and 45 minutes provide information about the sphincter of Oddi and the common bile duct. The residual activity in the liver between 45 and 60 minutes provides information regarding bile stasis (17).

The pharmacologic agents currently used with Tc-99m HIDA scintigraphy include CCK-8, morphine, and phenobarbital (Table 3).

Either CCK-8 or morphine is used primarily to assess diseases of the gallbladder, the common bile duct, and the sphincter of Oddi (17,18). The CCK hormone stimulates contraction of the smooth muscle of the gallbladder wall and initiates and sustains bile emptying. CCK simultaneously relaxes the sphincter of Oddi by acting directly on the sphincter smooth muscle. During fasting, the serum level of CCK is at its lowest, which promotes simultaneous maximum relaxation of the gallbladder wall and maximum constriction of the sphincter of Oddi.

CCK is used primarily to induce bile emptying before the gallbladder ejection fraction is measured in the assessment of biliary dyskinesia, chronic cholecystitis, and cystic duct syndrome. The ideal patient preparation for a Tc-99m HIDA study is to maximize bile entry into the gallbladder by allowing maximum relaxation of the gallbladder and maximum contraction of the

sphincter of Oddi. This state is accomplished simply by having the patient fast overnight. It appears reasonable not to pre-empty bile from the gallbladder by administering CCK-8 because it takes several minutes for the gallbladder to empty bile after the injection of CCK-8 and it takes several hours for the gallbladder to refill, primarily because of slow pressure build-up as the sphincter of Oddi narrows gradually (17).

CCK-8 is a synthetic preparation that consists of only the last eight peptides of its parent molecule CCK-33. Most of the injected CCK-8 molecules occupy the receptors in the normal gallbladder, which enables it to empty bile almost completely. In patients with chronic cholecystitis, the total number of receptors is reduced, which accounts for the decreased bile emptying that results when these patients receive CCK-8 (Fig 2). The widely used normal ejection fraction value of 35% or greater is established by infusing 3.3 $\text{ng}/\text{kg}/\text{min}$ of CCK-8 for 3 minutes. Larger doses (20–40 ng/kg) often cause severe abdominal pain, with decreased or no bile emptying in healthy subjects. For gallbladder ejection fraction protocol, images are obtained up to 60 minutes after radiopharmaceutical injection or until the gallbladder is visualized. Data are collected for 20 minutes after slow (3 minutes) intravenous infusion of CCK-8. An ejection fraction of less than 35% is indicative of chronic cholecystitis with a greater than 90% positive predictive value (17,18). Compared with a 3-minute infusion,

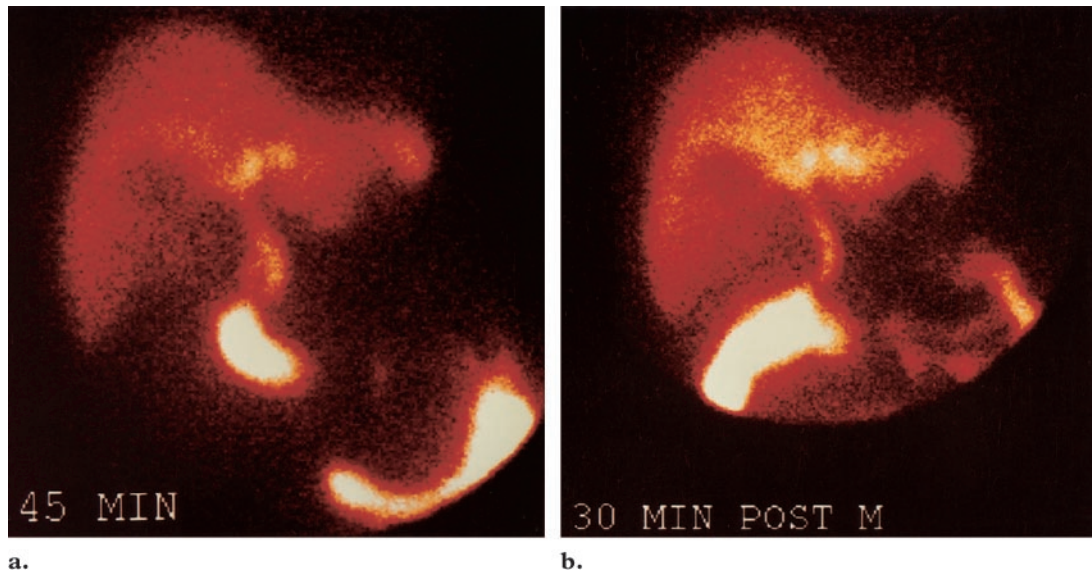


Figure 3. Utility of morphine in the diagnosis of acute cholecystitis with Tc-99m HIDA cholescintigraphy. On images obtained 45 minutes after radiotracer administration (**a**) and 30 minutes after intravenous administration of morphine (**b**), the gallbladder is not visualized. Nonvisualization of the gallbladder after administration of morphine is diagnostic of acute cholecystitis in the appropriate clinical setting.

Table 4
Agents for Pharmacologic Renal Scintigraphy

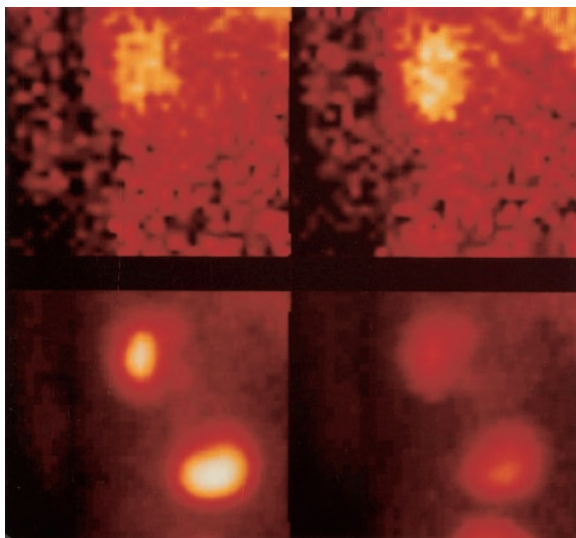
Drug	Dose	Side Effects	Mechanism
Furosemide	1.0 mg/kg intravenously	Tinnitus, allergic reaction Contraindications: anuria, hypersensitivity to furosemide	Inhibits primarily the absorption of sodium and chloride not only in the proximal and distal tubules but also in the loop of Henle
Captopril and enalaprilat	Captopril: 25–50 mg orally Enalaprilat: 40 µg/kg intravenously up to 2.5 mg	Dry cough, postural hypotension, anaphylactoid reaction, angioedema Contraindication: pregnancy	Prevents conversion of angiotensin I to angiotensin II, which ultimately reduces the glomerular filtration rate
Aspirin	20 mg/kg orally	Epigastric distress, nausea, gastrointestinal bleeding, hypersensitivity	Inhibits prostaglandin synthesis and reduces renin

slower infusion (30–60 minutes) of the same total dose is shown to have a lower false-positive rate with fewer side effects (19).

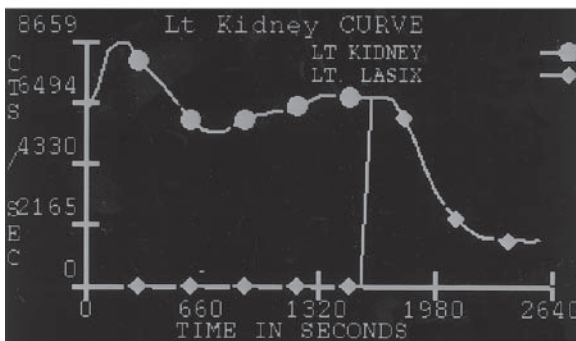
Opiates cause the sphincter of Oddi to constrict. CCK-8 administered after a morphine injection elicits an ejection fraction that is much lower than the value obtained without morphine. Therefore, caution should be exercised in interpreting the gallbladder ejection fraction values in patients receiving narcotics (20–22). Intravenous morphine is used when the gallbladder is not seen by 60 minutes after radiotracer administration, since morphine constricts the sphincter of Oddi and increases the pressure within the sphincter and the common bile duct, forcing the hepatic bile to enter the gallbladder (17). The usual intra-

venous dose of 0.04 mg/kg administered slowly over 1 minute is safe and well tolerated by the patient. Imaging is continued for an additional 30 minutes. Nonvisualization of the gallbladder by 90 minutes (ie, 30 minutes after the morphine injection was started) is diagnostic for acute cholecystitis in an appropriate clinical setting (Fig 3). A diagnosis of abnormal gallbladder function may be made when the gallbladder is not observed by 60 minutes but is seen after morphine administration (17,22). Morphine also causes alterations in duodenal muscle activity, and many patients may demonstrate enterogastric reflux (22).

Phenobarbital is used to increase the accuracy of Tc-99m HIDA scintigraphy in the differentiation of extrahepatic biliary atresia from neonatal hepatitis. In patients with hepatitis, administra-



a.



b.

Figure 4. Diuretic renography. (a) Renogram of the left kidney demonstrates a dilated collecting system with no evidence of obstruction. (b) The time activity curve gradually rises until administration of the diuretic, at which time there is prompt decline in activity. Clearance half-time is normal at 6 minutes.

tion of phenobarbital induces the hepatic enzymes, which in turn enhance radiotracer uptake and increase biliary excretion (23). However, it is not possible to differentiate very severe hepatitis from biliary atresia, as both entities demonstrate delayed blood clearance, increased renal excretion, and hepatic tracer retention without biliary excretion. The typical dose is 5 mg/kg administered orally in divided doses for 5 days.

Pharmacologic Renal Scintigraphy

Pharmacologic interventions performed during renal scintigraphy include diuretic renography, ACE inhibition, and aspirin renography (24) (Table 4).

Diuretic Renography

A frequent clinical request is to evaluate for obstructive uropathy. Although the Whitaker test remains the standard for determining an obstruction, diuretic renography is a much less invasive procedure and an excellent means of investigating

possible obstructive uropathy. Attempts have been made to standardize the protocols for the procedure (25). In general, it is recommended that the patient be well hydrated. In children, bladder catheterization may be used to ensure drainage.

Tc-99m mercaptoacetyltriglycine (MAG3) is the preferred radiotracer for renal scintigraphy because of its higher renal extraction (intravenous 10 mCi [370 MBq] or 0.1 mCi/kg [3.7 MBq] in pediatrics with minimum dose of 1 mCi [37 MBq]). Scintigrams should be obtained at 3- to 5-minute intervals for the study duration. Regions of interest are drawn around each renal pelvis, with the consensus being to draw the background regions as crescent shapes lateral to each kidney (24). Furosemide is administered intravenously (1 mg/kg, with higher doses given in cases of renal insufficiency) when the renal pelvis and ureter are maximally distended. The injection of furosemide may occur as early as 10–15 minutes and as late as 30–40 minutes after radiotracer administration.

After furosemide administration, rapid emptying of the collecting system with a subsequent steep decline in the renogram curve is compatible with dilatation without obstruction (Fig 4). Obstruction can be excluded if the clearance half-time of renal pelvic emptying is less than 10–15 minutes. Many factors, including hydration state, renal function, pelvic volume, and fullness of the bladder, must be considered (26). It is necessary to evaluate the scintigrams as well as the renographic curves before making a final diagnosis. A curve that reaches a plateau or continues to rise after administration of furosemide represents an obstructive pattern with a clearance half-time of greater than 20 minutes. An apparent poor response to diuresis may also be seen in severe pelvic dilatation (reservoir effect).

Pitfalls of diuretic renography include poor injection technique of either the diuretic or the radiotracer and dehydration in which delayed transit and excretion of the radiotracer may not be overcome by the effect of a diuretic. In neonates, the kidneys may be too immature to respond to furosemide and caution should be exercised in study interpretation.

ACE Inhibition Renography

ACE inhibition prevents conversion of angiotensin I to angiotensin II. In renal artery stenosis, angiotensin II constricts the efferent arterioles as a compensatory mechanism to maintain glomerular filtration rate, despite lowered afferent renal blood flow. Therefore, the principal effect of ACE inhibition in renal artery stenosis is to reduce glomerular filtration rate (24). The affected kidney

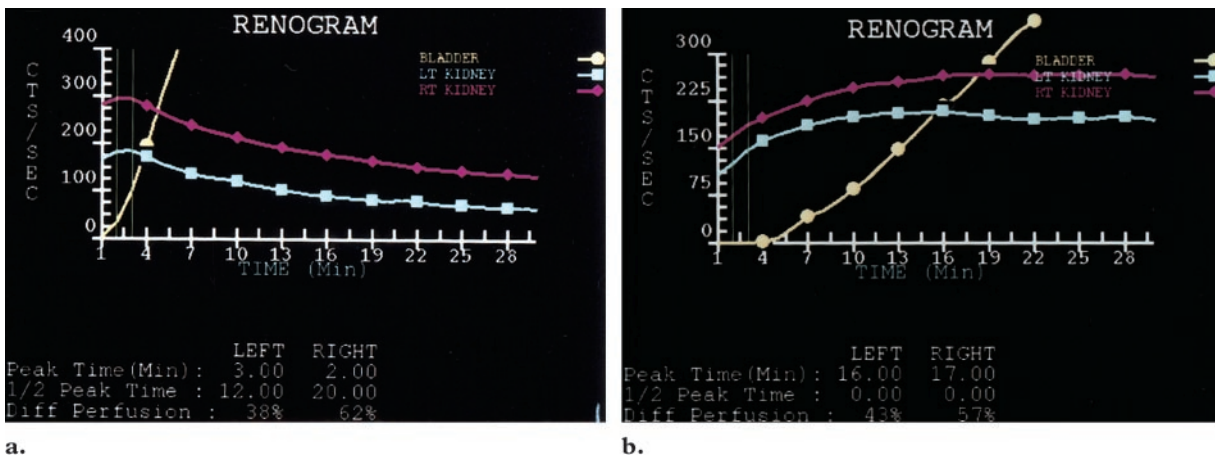


Figure 5. ACE inhibition renography. Tc-99m MAG3 renal studies were performed before (a) and after (b) administration of captopril for evaluation of renovascular hypertension. (a) Renogram shows a relative decrease in renal function on the left side. The time to peak activity is otherwise normal for both kidneys. (b) Renogram demonstrates reduced initial slope, delayed time to peak activity, and a plateau following the peak, characteristics that all reflect markedly slowed transit of radiotracer in both kidneys after the administration of captopril. These findings, which are compatible with a high probability for hemodynamically significant bilateral renal artery stenosis that is more severe on the left side, were later proved with angiography.

in renovascular hypertension often has a renogram curve with reduced initial slope, a delayed time to peak activity, and a slow downslope following the peak (Fig 5b), all of which reflect slowed transit of the renal radiotracer owing to increased solute and water retention in response to ACE inhibition (27). Reduced urine flow causes delayed and diminished washout of radiotracer into the collecting system in Tc-99m MAG3 and iodine-131 orthoiodohippurate studies. Quantitatively, there is increased time to peak activity and mean transit time. Tc-99m diethylenetriamine pentaacetic acid (Tc-99m DTPA), a glomerular agent, principally demonstrates reduced uptake on the affected side. There is little evidence to support distinction between glomerular or tubular (MAG3 or orthoiodohippurate) radiotracers in their usefulness for detection of renovascular hypertension (24).

ACE inhibition should produce no asymmetries of efferent arteriolar tone in patients with chronic pyelonephritis, obstruction, or other conditions that might otherwise mimic renal artery stenosis at baseline renography. Visual changes observed at scintigraphy, supplemented by quantitative changes in the renogram curve, are the interpretive criteria most commonly used for making a diagnosis of renal artery stenosis (27).

A 1996 consensus report (28) about methods and interpretation of ACE renography elaborates on a scoring system of renogram curves adapted by Taylor, Nally, and colleagues (27–29). It was recommended that high (>90%), intermediate (10%–90%), and low (<10%) probability categories be applied to the change in renogram curve

scores before and after the administration of captopril. Among quantitative measurements, those of relative renal function, the time to peak activity, and the ratio of 20-minute renal activity to peak activity are used more commonly than other parameters. For Tc-99m MAG3 renal scintigraphy, a 10% change in relative renal function, an increase of 2 minutes or more in the time to peak activity, and a parenchymal increase of 0.15 in the ratio of 20-minute renal activity to peak activity after the administration of captopril represent a high probability of renovascular hypertension (24).

It is difficult to assess precisely the diagnostic accuracy of captopril renography because of the differences that persist in protocols, interpretive criteria, and patient populations. Nonetheless, in most studies, both sensitivity and specificity approach 90%. In cases of bilateral renovascular stenosis, the detection of stenosis by using captopril renography may be more complicated (30). Although it is more the exception than the rule for bilateral renovascular stenosis to have symmetric findings at captopril renography, the exaggerated degree of asymmetry of renal function in response to captopril usually seen in renograms may be diminished in the presence of bilateral renovascular stenosis (Fig 5). Studies of a canine model with bilateral renal artery stenosis demonstrated that captopril produced striking changes in the time-activity curve of each kidney that were more pronounced in the more severely stenotic kidney (30). These studies imply that captopril renography may be a suitable noninvasive tool to replace the invasive renal vein renin measurements used to determine the more severely stenotic kidney in patients with bilateral renal artery stenosis (30).

The procedure guideline recommendations (28) for ACE inhibition renography provide a concise protocol. Patients should be well hydrated. ACE inhibitors should be discontinued (captopril for 2 days, enalapril or lisinopril for 4–5 days), since otherwise diagnostic sensitivity may be reduced. Diuretics should be discontinued preferably for 1 week. Dehydration resulting from diuretics may potentiate the effect of captopril and contribute to hypotension. Captopril (25–50 mg) crushed and dissolved in 250 mL water is administered orally followed by blood pressure monitoring every 15 minutes for 1 hour. Alternatively, enalaprilat (40 µg/kg up to 2.5 mg)—not to be confused with oral enalapril—is administered intravenously over 3–5 minutes. A baseline scan can be obtained before captopril renography (1-day protocol) or the next day, only if results of the captopril study are abnormal (2-day protocol).

Aspirin Renography

The synthesis of prostaglandin E2 is increased in response to a reduction in renal blood flow, which in turn stimulates renin release. It is hypothesized that inhibition of prostaglandin synthesis would decrease renin (31). Preliminary studies suggest that aspirin renography is more sensitive than captopril renography in the evaluation for renovascular hypertension (32). Aspirin has the advantage of having no effect on blood pressure and does not require that ACE inhibitors be discontinued. The results have not yet been validated in large studies; therefore, its use has not yet become clinically widespread.

Thyroid Imaging

Initial surgical excision of thyroid cancer is often followed by radionuclide ablation of remnant normal and tumor tissue with subsequent long-term therapy with thyroid stimulating hormone (TSH) and suppressive thyroid hormone. Despite the efficacy of these treatments, patients with previously treated thyroid carcinoma require lifelong monitoring for recurrent disease.

The accuracy of the two diagnostic tests that play a central role in follow-up of these patients (radionuclide whole-body scanning and measurement of serum thyroglobulin) depends on their stimulation by TSH (33,34). Periodic withdrawal of thyroid hormone therapy has been the traditional approach to provide the thyrotropic stimulus. However, hormone withdrawal is associated with hypothyroidism and occasional tumor progression (33). The introduction of rTSH offers an alternative approach (35). Recent clinical trials have shown that the sensitivity of combined

rTSH-stimulated radionuclide scanning and serum thyroglobulin measurement is equivalent to that of testing conducted after thyroid hormone withdrawal (33,36,37).

Doses of rTSH from 10 to 40 U given intramuscularly for 1–3 days have been shown to stimulate both radioiodine uptake in residual thyroid tissue and a rise in the serum thyroglobulin concentration. In a two-dose 2-day regimen, two doses of 10 U of rTSH are administered intramuscularly 24 hours apart. Twenty-four hours after the second rTSH dose, 2–4 mCi (74–148 MBq) of I-131 is administered orally and whole-body scintigraphy will be performed after 48 hours. The rTSH injections are generally well tolerated. The only adverse effect commonly associated with rTSH is mild nausea in 16% of patients (33). No detectable anti-TSH antibodies have developed following rTSH injection. Use of rTSH is generally not indicated for patients who are already known to have residual thyroid cancer.

For patients with low risk of tumor recurrence (eg, younger patients with small, encapsulated, and well-differentiated lesions without evident local recurrence or distant metastases), it may be reasonable to use rTSH for the first cycle of scintigraphy and thyroglobulin measurement 6–12 months after postoperative I-131 ablation. However, for patients at moderate to high risk of harboring residual or recurrent thyroid cancer (eg, older patients with larger, more invasive, or less well-differentiated tumors), it seems prudent to recommend obtaining at least one set of negative I-131 scintigraphic and serum thyroglobulin test results after thyroid hormone withdrawal before using rTSH-stimulated testing for long-term follow-up. In general, it now seems reasonable in low-risk patients to recommend two cycles of rTSH-stimulated testing 1–2 years apart, followed up by testing every 3–5 years. For moderate to high-risk patients who have undergone one round of hormone withdrawal testing with negative results, two cycles of rTSH-stimulated testing at 6- to 12-month intervals, followed up by testing every 1–3 years for at least the first decade of follow-up seems appropriate.

Pharmacologic Stress in Cardiac Perfusion Scintigraphy

Pharmacologic stress in conjunction with radionuclide myocardial perfusion imaging has become a widely used, noninvasive method of assessing patients with known or suspected coronary artery disease (38,39). Exercise testing is universally

Table 5
Agents for Pharmacologic Stress in Cardiac Perfusion Scintigraphy

Drug	Dose	Side Effects	Mechanism
Dipyridamole	0.142 mg/kg/min intravenously over 4 min	Chest pain (20%), headache (12%), dizziness (12%), ST segment changes (8%) Contraindication: severe bronchospasm	Blocks cellular reuptake of adenosine via inhibition of deaminase, thus increases the amount of endogenous adenosine available for cell membrane receptor binding, causing vasodilatation
Adenosine	Intravenous infusion at a dose of 140 µg/kg/min over 6 min; radiotracer is injected at the end of the 3rd min	Chest, throat, or jaw pain; headache; flushing; arteriovenous block, ischemic electrocardiographic changes	Vasodilatation
Dobutamine	5–40 mg/kg/min intravenously in 3-min stages with radiotracer injected at peak infusion rate	Chest pain, palpitation, headache, flushing, dyspnea, hypersensitivity reactions	Synthetic catecholamine with a plasma half-life of 2 min that acts through the alpha-1 and beta-2 adrenoreceptors
Arbutamine	Administered with a closed-loop delivery device that modulates the rate on the basis of physiologic feedback	Arrhythmias, angina, hypotension, ST segment depression, tremor, flushing, headache, dizziness, hot flashes	Mixed beta-1 and beta-2 agonist with a mild affinity for alpha-1 receptors

avored because it provides important blood pressure and electrocardiographic data. With exercise testing, the aim is to induce myocardial ischemia, whereas with pharmacologic testing, the aim is to provoke myocardial perfusion heterogeneity (40). Like patients who undergo exercise stress testing, patients who undergo pharmacologic stress testing and who have normal perfusion images have a less than 1% annual incidence of cardiac events (38). The likelihood of an event increases with the extent and severity of perfusion abnormalities.

Pharmacologic myocardial stress testing may be appropriate in elderly and debilitated patients with significant peripheral vascular disease, disabling arthritis, previous stroke, orthopedic problems, chronic pulmonary disease, extremity amputation, severe obesity, sick sinus syndrome, pacemakers, and aortic stenosis. It may also be appropriate in patients receiving heart-rate-limiting medications such as propranolol. In a 1997 American Society of Nuclear Cardiology survey, 34% of perfusion imaging studies were performed after administering pharmacologic stress agents (39).

Pharmacologic stress agents fall into two categories: coronary vasodilating agents, such as di-

pyridamole and adenosine, and cardiac positive inotropic agents, such as dobutamine and arbutamine (38,41,42) (Table 5). Vasodilating agents work directly on the coronary vessels and increase blood flow, whereas inotropic agents work indirectly by increasing myocardial workload, which then leads to an increase in coronary blood flow. There is some concern that dobutamine may interfere with the uptake of Tc-99m sestamibi and thus lower the sensitivity of the study for detection of disease; therefore, the vasodilating agents are generally preferred (38). Pharmacologic stress testing has high clinical use for classifying the risk of patients with known or suspected coronary artery disease, in select patients after myocardial infarction, and in patients needing noncardiac surgery. Use of vasodilating agents is particularly advantageous in assessing patients after myocardial infarction, as the agents allow testing as soon as 2 days after the event.

Dipyridamole and adenosine share a common mechanism of action that lead to coronary vasodilation. Vasodilating agents increase myocardial blood flow three to five times above the resting level. Overall, dipyridamole myocardial perfusion imaging has an average sensitivity of 90% and a specificity of 85% for the detection of coronary

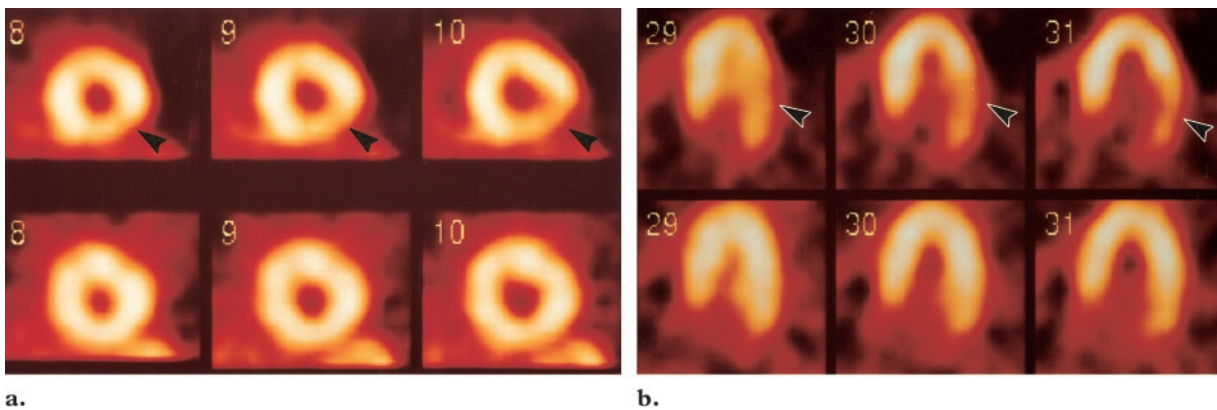


Figure 6. Pharmacologic myocardial perfusion imaging. Short axis (**a**) and horizontal long axis (**b**) views of a thallium-201 myocardial perfusion SPECT study. Dipyridamole stress images (upper) show a moderately large perfusion abnormality involving the posterolateral wall of the left ventricle (arrowheads) that improves significantly on the redistribution images (lower), compatible with myocardial ischemia.

artery disease (Fig 6) (38). Diagnostic accuracies for adenosine are similar to those of dipyridamole. Numerous studies have reported improved diagnostic accuracy with vasodilator pharmacologic stress compared with exercise in patients with a left bundle branch block. It is thought that the increased heart rate and myocardial workload associated with exercise decreases septal blood flow, which would not occur with vasodilator stress.

Methylxanthines, such as theophylline or caffeine, antagonize the effect of dipyridamole and adenosine. Patients must be off caffeine, aminophylline, theophylline, chocolate, and nicotine for 24 hours before the test. The maximal vasodilating effect of dipyridamole occurs 5 minutes after intravenous administration and lasts for 10–30 minutes. Most patients experience an increase in heart rate and a decrease in systolic blood pressure (43). There is no change in the pressure-rate product. Chest pain is fairly common during vasodilator stress, occurring in approximately 10%–20% of patients. Chest pain during dipyridamole testing is not related to the severity of coronary artery disease and has little diagnostic value (44). Severe side effects are extremely rare. Should bronchospasm occur, the antagonist aminophylline is administered intravenously, generally in a bolus dose of 50–75 mg, followed by, if necessary, a second dose at 20 minutes.

Adenosine has a serum half-life of 2–10 seconds with a maximal coronary vasodilating effect after 2 minutes. Adenosine causes side effects more commonly (83% of cases) than does dipyridamole, and they include chest, throat, or jaw pain; headache; flushing; and arteriovenous block

(43,45). They can be reversed immediately by terminating the infusion. Contraindications for using the agent are severe bronchospastic disease and sick sinus syndrome.

Positive inotropic agents are reserved for patients who are unable to exercise adequately and who have contraindication to dipyridamole infusion, such as those with bronchospastic pulmonary disease. These agents work by stimulating beta-receptors in the heart, augmenting both the contractility and the heart rate (46–48). There is a two- to threefold increased coronary flow comparable with that occurring during physical exercise, but the peak heart rate is usually lower than that achieved with exercise.

Dobutamine hydrochloride is a synthetic catecholamine with a plasma half-life of 2 minutes that acts through the alpha-1 and beta-2 adrenoceptors. Dobutamine mimics exercise physiology because it significantly increases the heart rate and blood pressure at doses greater than 20 $\mu\text{g}/\text{kg}$ per minute. A sensitivity of 82% and a specificity of 75% for detection of coronary artery disease have been reported (46).

Arbutamine, a recently approved pharmacologic stress agent, is a mixed beta-1 and beta-2 agonist with a mild affinity for alpha-1 receptors (48). It is delivered by a closed-loop computerized delivery system that constantly monitors the heart rate response to the arbutamine infusion. Arbutamine has an inotropic and chronotropic activity similar to that of dobutamine, but it has less peripheral vasodilating activity. Arbutamine simulates exercise more closely than does dobutamine.

Table 6
Agent for Pharmacologic Stress in Cerebral Perfusion Scintigraphy

Drug	Dose	Side Effects	Mechanism
Acetazolamide	1 g intravenously over 2 min, followed 20 min later by radiotracer	Transient numbness, tingling of the fingers, allergic reactions, light headedness Contraindications: cardiovascular instability, renal or hepatic insufficiency, a history of allergy to sulfa drugs	Carbonic anhydrase inhibitor that causes cerebral vasodilatation, probably by reducing pH in the brain tissue

Evaluation of

Cerebrovascular Functional Reserve

Cerebral autoregulation compensates for reduced cerebral perfusion pressure by vasodilation until further response is not possible. Patients with cerebral or carotid artery disease may show blunted or absent response to vasodilating agents (49,50). The poor response to vasodilating agents occurs if the autoregulatory capacity is exhausted by reduced perfusion pressure distal to stenosis and by poor collateral circulation. With the administration of vasodilating agents, the affected hemisphere or vascular distribution cannot dilate further, whereas unaffected areas respond. This produces asymmetries in the distribution of the radiopharmaceutical, with an increase in radiotracer retention in normally perfused areas. Cerebrovascular reserve can be assessed by measuring hemodynamic response to pharmacologic flow augmentation with carbon dioxide or acetazolamide (Table 6) and by using a variety of imaging methods, such as positron emission tomography (PET), single-photon emission computed tomography (SPECT), transcranial Doppler ultrasonography, xenon computed tomography, and magnetic resonance imaging (51).

Acetazolamide is a carbonic anhydrase inhibitor that causes cerebral vasodilatation, probably by reducing the pH in brain tissue. The increase in blood flow is dose dependent and ranges from 30% to 50% approximately 20 minutes after intravenous injection of acetazolamide (52–54). An acetazolamide challenge test has been used to measure cerebrovascular reserve in patients with carotid artery stenosis greater than 70%, patients with moderate nondisabling stroke, and patients with a history of transient ischemic attacks (52). Perfusion studies performed after an acetazolamide challenge test provide objective evidence of the deleterious effects of carotid stenosis on cerebral blood flow. They also help to give an esti-

mate of the integrity of collateral vessel circulation to the affected hemisphere. The loss of reactivity in patients with symptoms who have greater than or equal to 70% carotid stenosis is an important predictor of impending cerebral infarction (49).

The acetazolamide protocol consists of administering 1 g intravenously over 2 minutes, followed 20 minutes later by intravenous administration of 20 mCi (740 MBq) of Tc-99m hexamethylpropyleneamine oxime (HMPAO) or Tc-99m ethylcysteinate dimer. Not infrequently, patients report transient numbness and tingling of the fingers. Allergic reactions and light-headedness have also been reported (54). Contraindications to an acetazolamide challenge test are cardiovascular instability, renal or hepatic insufficiency, and a history of allergy to sulfa drugs.

It is essential that a baseline cerebral perfusion SPECT study be performed for comparison (52). Some patients with virtually normal results from an acetazolamide examination may have a global reduction in perfusion reserve. It is possible to detect this by measuring the uptake of HMPAO after the administration of acetazolamide compared with that on the baseline scan (54).

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