

Fast Protocols for Obstruction (Diuretic Renography) and for Renovascular Hypertension (ACE Inhibition)

George N. Sfakianakis, Michael Georgiou, Felipe Cavagnaro, Jose Strauss, and Jacque Bourgoignie

University of Miami School of Medicine and Jackson Memorial Hospital, Miami, Florida

This is the fourth article in a four-part series on interventional nuclear medicine. Upon completion of this article, the nuclear medicine technologist will be able to list the available radiopharmaceuticals used in renal imaging and describe the diuretic and angiotensin-converting-enzyme inhibitor protocols.

Renal scintigraphy (SCINT) has proved to be a useful imaging modality for many renal diseases, congenital or acquired, and for the evaluation of complications of renal transplant. However, the modality has limited resolution for small morphologic changes (such as tumors) of the parenchyma and the collecting system, shows neither stones nor calcifications, and usually misses other abdominal pathology. Due to these deficiencies, SCINT never developed into a universal test and today intravenous urography (IVU) remains a useful modality for imaging many acquired renal diseases.

However, IVU is currently used less frequently, especially for congenital disorders, because of the introduction of non-invasive ultrasonography (SON) and X-ray computed tomography (CT). The new imaging modalities provided more accurate and practical approaches for studying drainage system and parenchymal morphology, renal space-occupying lesions (SOL), and trauma. The role of magnetic resonance imaging (MRI) is still under evaluation.

Despite the availability of CT, SON, and MRI, and due to its unique sensitivity in detecting regional and global functional changes of the kidneys, renal SCINT (with renography) has been accepted as the test of choice for the evaluation (diagnosis, quantitation, and follow-up) of such congenital and acquired diseases of the urinary tract, which induce focal or generalized alterations in renal function or drainage. Indeed, the most common indications for radioisotope renal studies are: obstruction of the drainage system; urinary tract infection (UTI); evaluation of renal function (including split renal function), in general and in particular, in unilateral disease, and in renal insufficiency or failure; renovascular disorders; and complications of renal transplants.

For reprints contact: G. N. Sfakianakis, M.D., Professor of Radiology/Nuclear Medicine and Pediatrics, Division of Nuclear Medicine (D-57), University of Miami School of Medicine, P.O. Box 016960, Miami, FL 33101.

Renal scintigraphy is indicated as a screening test, as the diagnostic procedure of choice, or as a complementary imaging modality in many clinical presentations. Important decisions about further work-up, mode of therapy, duration of treatment, follow-up visits, and prognosis are influenced by SCINT, which has specific advantages as a modality to study the pediatric and adult uro-nephrologic patient. Particularly important is the fact that the studies are cost effective, relatively operator independent and noninvasive, produce minimal discomfort, and have no known risk.

The purpose of this paper is to introduce a fast protocol for diuretic renography, which can be used as a screening procedure and, in most instances, as the final diagnostic test for all clinical indications, including obstructive uropathy. This protocol has been used successfully at the University of Miami/Jackson Memorial Hospital since the release of technetium-99m mercaptoacetylglycylglycylglycine ($^{99m}\text{Tc-MAG}_3$) by the U.S. Food and Drug Administration (FDA) and utilizes this tubular imaging agent and the diuretic furosemide, which is injected within 3 min after the radiopharmaceutical. With slight variations, the same protocol may be applied for angiotensin-converting-enzyme inhibitor (ACEI) scintigraphy (captopril/oral or enalaprilat/i.v.). It can be used both in children and adults with a change in dosage schedule. Very little, if any, physician participation is required (except for the injection of ACEI), no blood or urine collection is involved, and the study can be performed in any nuclear medicine laboratory. Finally, it utilizes the least possible patient/technologist/equipment time, so it is cost effective. For a review of the available methodology in general, the reader is referred to other publications (1-3).

MATERIALS AND METHODS

Instrumentation

In the adult but especially in the infant and the child, it is absolutely necessary to utilize high resolution gamma cameras, acquire sufficient counts and completely immobilize the patient, because of the small size of the kidneys and most focal abnormalities. A small field of view portable camera is needed for the neonate and the infant; this portable camera would allow imaging in the nursery, a feature which serves

unstable, ill neonates and facilitates diagnostic testing with minimal patient care disruption. A large field of view camera is necessary for the adult size patient, as it is important to include both kidneys and the bladder in the field of view. The best available resolution is necessary if the study is to provide accurate functional and anatomical diagnosis. Parallel-hole high-efficiency collimators are usually sufficient but high resolution and even pinhole imaging is recommended for detecting small lesions, such as cystic disease, hypoplasia, and focal pyelonephritis. It is important to stress that patient preparation and immobilization, as discussed further on, is more critical than switching from a high efficiency to a high resolution collimator.

Computer analysis with graph generation and quantitation of function and drainage are important features in certain disorders and in the follow-up of patients. Although these data may not be utilized in a number of studies, it is prudent to incorporate such features in the routine protocol to assure availability when clinically needed. It is therefore advisable to attach the camera to a computer and routinely obtain backup imaging for graph generation and for function, transit, and drainage quantitation. Such programs are available from most computer manufacturers, although some adjustments and improvements are needed. Electronic archiving is emerging as the proper way to store and retrieve studies.

Radiopharmaceuticals

Currently, several ^{99m}Tc -labeled complexes are in clinical use; they are pure glomerular (DTPA), glomerular with tubular fixation (DMSA, GH) and tubular secretion (MAG_3) agents. They are helpful in studying renal anatomy and function as indicated. Iodine-131 (^{131}I) or iodine-123 (^{123}I) labeled orthoiodohippurate (HIP) has been used for decades for

tubular function and drainage information. Recently, the Tc-labeled renal agent with mostly tubular handling (MAG_3) has been introduced for routine clinical use in lieu of HIP. Due, however, to its favorable characteristics, MAG_3 is the universal renal agent of choice in our laboratory.

MAG_3 is a recently introduced tubular agent (4). It is stable and strongly protein bound. Although it was initially thought that MAG_3 was a pure tubular agent, micropuncture studies have shown that it was also filtered in the glomerulus. It was found that in each pass through the kidneys, some quantity (about 5%–10% of what is presented to the glomeruli) of MAG_3 is filtered, but most is actively secreted by the tubules (50%–55%), and 40% leaves the kidneys through the renal veins, with an overall 60% extraction efficiency (Fig. 1). Due to a smaller distribution space, however, MAG_3 is excreted by the kidneys at the same rate as HIP (about 70% of the injected dose in 30 min), despite a higher extraction efficiency for HIP (80%) (Fig. 2). Thus, MAG_3 has the biologic properties of HIP and the imaging properties of a Tc-labeled agent.

As expected, experience from clinical applications in this and other laboratories indicate that MAG_3 is superior to HIP as a renal tubular agent because of the physical characteristics of ^{99m}Tc , including a larger dose: images are better and statistics for graph generation more reliable; clearance values by blood sampling are also comparable (after introducing a correction factor). In addition, MAG_3 is biologically more efficient than DTPA or GH, each of which has a renal extraction efficiency of about 20%. This advantage of MAG_3 results in higher renal accumulation, which is an advantage over DTPA or GH, particularly when renal function is decreased (5). MAG_3 has no cortical fixation, unlike GH or DMSA, and when small cortical lesions are sought, DMSA multiprojectional or tomographic images may be more advantageous (6).

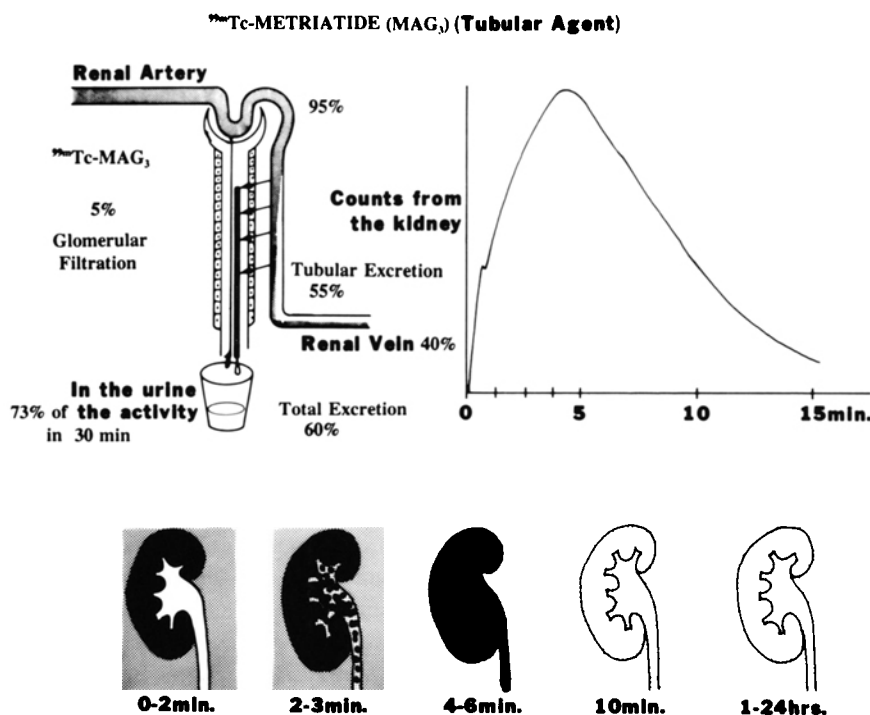


FIG. 1. MAG_3 properties, renogram, and images.

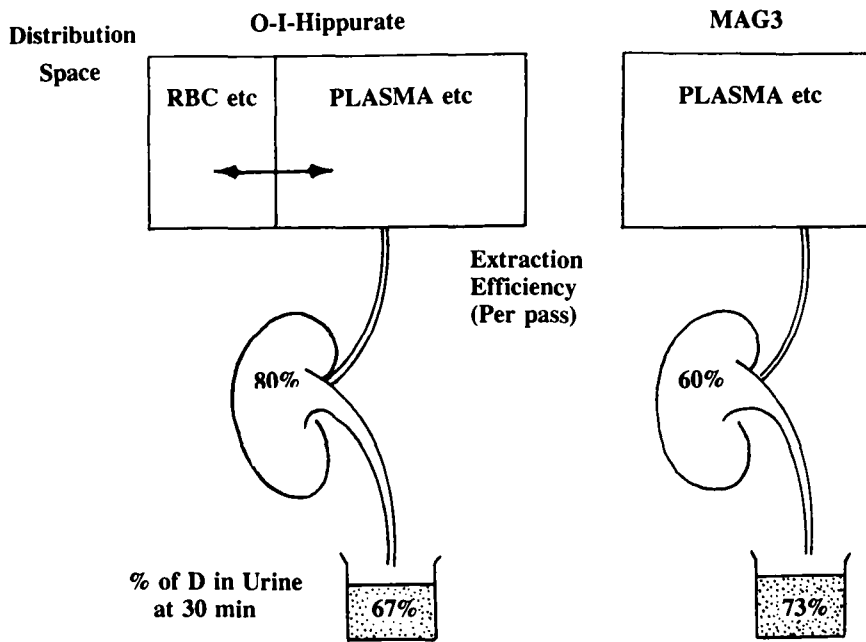


FIG. 2. MAG₃ versus HIP: Distribution space, extraction efficiency, and elimination rate.

Finally, when a specific diagnosis of a diffuse cortical disorder is needed, a combination of MAG₃ with DTPA may be the approach of choice.

Protocol

Patient preparation. A supine position is acceptable, but an upright position is preferred, for better draining of the kidneys, when the primary question is obstruction. The patient should be well hydrated unless contraindicated (orally 10 ml/kg of water or orange juice, 30 min before imaging or i.v. saline or dextrose/saline, D5.3NS or D5.25NS at a rate to deliver 15 ml/kg over a 30-min interval, beginning at least 15 min before injection of the radiopharmaceutical). The patient should be calm, comfortable, and in a warm environment, and a parent should be present when children are examined. An indwelling needle or angiocatheter should be gently inserted into a peripheral vein before injection and the absence of extravasation should be verified by infusion of 2–5 ml normal saline. Sedation may be administered if needed, and the infant or child should be carefully immobilized to assure optimal results. Adults should be informed and periodically reminded to stay still.

When intrarenal or ureteric obstruction is to be excluded, urinary bladder drainage (Foley catheter in place) may be indicated, because a full bladder may induce retention of radiopharmaceutical proximally, suggesting obstruction. The same may be true when seeking accurate cortical transit times of radiopharmaceuticals in investigation of renovascular hypertension (RVH), particularly in renal transplants.

Dose of radiopharmaceutical. MAG₃ is injected intravenously in a dose of 50–200 μ Ci/kg, (minimal ^{99m}Tc dose, 0.5–1 mCi). A maximum dose of 10 mCi assures best images and statistics; however, as low as 1–3 mCi is sufficient for drainage or for functional cortical information.

Protocol for flow, early, and late sequential imaging. Renal scintigraphy is performed in the posterior projection (in trans-

plants anterior projection) sequentially for 22 min after a bolus i.v. injection of the radiopharmaceutical, using high efficiency or high resolution parallel-hole collimators. When indicated, delayed static images may complement the study.

With MAG₃, sequential imaging starts as a 60-sec flow phase (1-sec computer and 2-sec analog images) and continues as a 21-min tissue-function/drainage phase (30-sec frames in computer and 2-min images on radiographic film). Following this phase, the patient assumes the upright position and empties the bladder. Infants are held upright for a few minutes. Following this, a postvoid image is acquired with the same settings as in the tissue phase; if activity remains in the kidneys or the ureters, a similar image is taken at 2 hr.

Diuretic. At 20 min postinjection of MAG₃, in a well hydrated patient, the intrarenal drainage system and the ureters are normally empty, with only a slight amount of tracer visible after that time. Postural pooling can be ruled out by obtaining the postvoid or postupright image described above. However, even after hydration, images may mimic obstruction due to inadequate diuresis, as a result of insufficient hydration. The routine use (at 3-min postinjection of MAG₃) of an i.v. diuretic such as furosemide (Lasix, 1 mg/kg, maximum 40 mg, or 80 mg in renal insufficiency) may alleviate confusing images, and it has been used successfully in our laboratory. Injection of the diuretic within 3 min of or simultaneously with radiopharmaceutical injection allows peak action before 10 min.

Such an approach is actually a type of diuretic renography; it certainly provides more reliable cortical images and data for quantitation of cortical function. It also empties the non-obstructed drainage system (unless function is severely diminished), thus completing a diuretic examination in 25 min. Finally, by promoting frequent urination, this method decreases the radiation exposure to the urinary bladder, which is the target organ of Tc-MAG₃.

Imaging techniques. The high extraction efficiency and the

relatively small distribution space of MAG_3 result in fast accumulation and discharge of high intensity activity by the cortex (1–3 min) and subsequently the drainage system (2–5 min) after injection. Most of this activity eventually empties into the bladder (3–10 min) and by 10–15 min, the kidneys are many times less active than the full urinary bladder. This creates a sequence of high contrast changes unique for MAG_3 and unprecedented in renal scintigraphy. Adjusting film settings to accommodate both early and delayed optimal images of the kidneys with MAG_3 is very difficult. Such settings were easily achieved with DTPA or GH, and most laboratories have their routines for these studies. When MAG_3 is used within a digital mode of operation, an exponential scale or computer multicolor scale may resolve this problem. When it is used in a laboratory with only analog imaging on radiographic film, only the early images of the kidneys need to be of optimal intensity, as they are informative and diagnostic of focal lesions. Also, if the kidney empties fast, the 10-min to 20-min images do not usually provide additional cortical information.

The most useful settings, therefore, are those that allow sufficient intensity for a faint but appreciable visualization of the body background during the first 1–2 min. Normal kidneys will dominate the image, eliminate most of the background activity, and empty themselves by 10–15 min, during which time the intrarenal collecting system and the ureters are usually visible, and after which the bladder is the dominant organ against a nearly empty background and kidneys. Abnormal kidneys will show less prominently, remain active until 20–25 min or later, and will not sufficiently clear the background (particularly the liver), which remains active until 10–25 min.

When this early part of the study is abnormal (Fig. 3A), even postvoid (Fig. 3B), delayed images (2 hr) with MAG_3 are very useful for the diagnosis of obstruction and the determination of the level of obstruction (Fig. 3C), or for the confirmation of cortical retention. For comparative purposes, such delayed images (Fig. 3C) should be acquired in exactly the same manner as the early sequential images (Fig. 3A, 3B).

Computer acquired images are used for graph generation and quantitation. They may also serve either as a backup for suboptimal direct off-the-camera images (on radiographic film), or as the sole acquisition form for computer generated hard copies on films or paper. A digital, filmless, computerized laboratory with reading sessions off the display monitors and electronic archiving on tapes, or, more recently, on laser disks and juke boxes of optical disks, is another alternative under evaluation.

Renogram generation, analysis, quantitation. Time-activity graphs of the flow or of the 22-min tissue phase (renograms) of the total kidney and of the cortex are generated using programs available in most computers. A simple routine can make two composite 30-sec images from the flow frames and place them before the frames of the tissue phase for more accurate renograms. It is imperative to select for cortical regions of interest (ROI) those that do not include collecting system activity at any time, and it is equally important to

include the entire renal pelvis in the ROI of the total kidney (Fig. 4). Renograms can then be reliable for cortical or drainage abnormalities and may be analyzed semiquantitatively.

The term renogram was introduced for HIP obtained graphs. MAG_3 graphs are identical to HIP in slopes, peak, and residual activity (cortical or total renal activity) when the same hydration and diuresis status exists (Figs. 1 and 2). The renograms from the two kidneys should be nearly identical in shape and slopes (upslope and downslope). Slight differences in height may be due to normal variation in kidney size or location, to patient positioning, or to differences in assigned ROI. Following the arrival of the MAG_3 bolus, renal activity rapidly increases, peaks at 3–5 min, and then starts declining due to the decrease in intravascular feeding-in activity (renal accumulation and extravascular distribution) and the excretion of the activity from the kidney into the ureter and bladder. From then on, MAG_3 activity falls precipitously, and at 20 min, renal activity is normally <20% of the peak. The cortical graphs are steeper and peak earlier.

Semiquantitation of the renogram alone, or in conjunction with clearance measurements, has been used as a method to quantitate disease and to help in differential diagnosis. The transit time of the radiopharmaceutical through the renal cortex (cortical renogram) provides information about cortical diffuse disease, and the renogram of the entire kidney includes information about drainage.

Many approaches for semiquantitating the renogram have been proposed such as peak time, upslope and downslope (if there is one), and the residual cortical activity (RCA) at 20 min (Fig. 5).

$$RCA = \frac{\text{cortical counts at 20 min}}{\text{cortical counts at peak}} \times 100$$

The excretory index (EI) describes the ratio between effective renal plasma flow (ERPF) and activity found in the urine. As such, EI indirectly measures activity remaining in the renal cortex (and collecting system). The RCA has been successfully utilized at our institution over the last five years to determine cortical transit of radiopharmaceuticals, as a simple index in lieu of the elaborate EI, which requires clearance measurements and urine quantitation (blood and urine sampling, etc.). It was recently shown that RCA is equivalent to EI.

When there is a plateauing or a rising renogram curve, the upslope may be utilized for semiquantitation. Another index, the original cortical activity (OCA) (Fig. 6) may be used for such cases.

$$OCA = \frac{\text{cortical counts at 2 min}}{\text{cortical counts at peak}} \times 100$$

The simple and easily calculated indices, RCA and OCA, have been very useful in the evaluation of renovascular hypertension and in the study of diffuse parenchymal diseases, including complications of renal transplants. Further work is needed, however, to confirm the validity of this experience.

The deconvolution analysis of the renogram has provided a model to mathematically quantitate renal function. Applied on ^{123}I -HIP and Tc-DTPA, it has met with little general

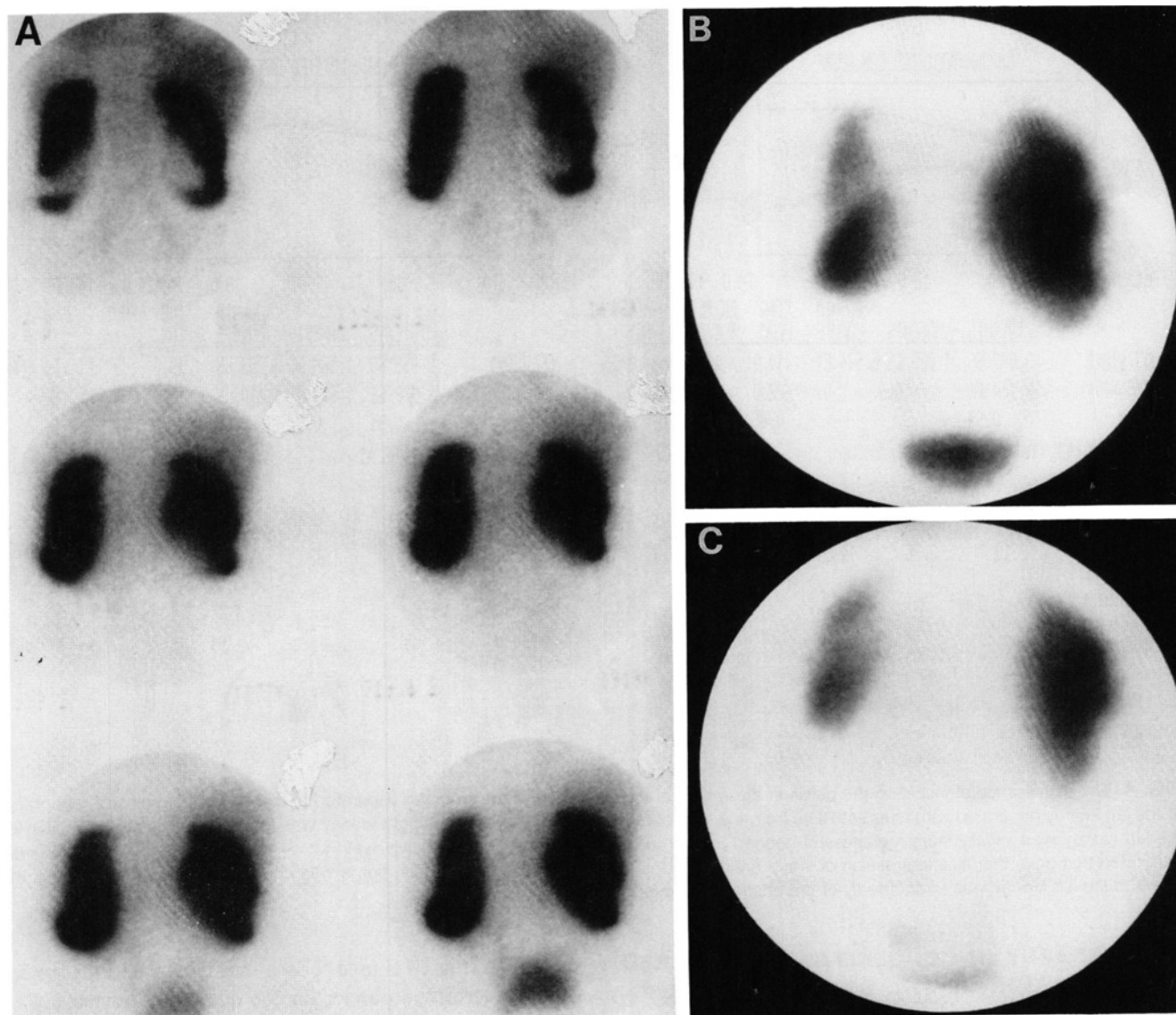


FIG. 3. Bilateral proximal (uretero-pelvic junction) partial obstruction in a 12-yr-old boy. MAG_3 study (6 mCi) with 40 mg furosemide at 3 min. (A) Selected 2-min images of the 22-min sequential study (from left to right and top to bottom, 2, 4, 10, 12, 18, and 20 min). (B) Postvoid image. (C) Delayed 2-hr image. Notice the activity within the dilated pelvis (on the right: medially and on the left: lower and laterally) appearing late and remaining until 2 hr. Graphs (Fig. 4) showed peak + $T_{1/2} > 15$ min.

acceptance. MAG_3 renography provides a better basis for such analysis and such an application is currently under study.

Semiquantitation of total renal function. Radioisotope studies can provide clearance measurements of renal function with a single (bolus) injection and one or more timely blood samples, without the need for urine collection. However, reliable and accurate results require urine collection, particularly when renal function is reduced. Finally, computer methods based on quantitation of renal uptake at 2 min, or bladder activity at 10 or 20 min by scintigraphy without blood sampling, provide useful information according to some authors.

Estimation of split renal function. Information on the function of one kidney compared to the other (split renal function) is necessary, especially when nephrectomy or corrective intervention is contemplated, or in cases of unilateral disease, evaluation or follow-up. It can be easily calculated in any

nuclear medicine laboratory with a camera and a minicomputer, obliterating the need to collect urine from each ureter. There are two techniques: quantitation of the net radioactivity present in the kidneys during the first 2–3 min after injection of MAG_3 and before activity enters the ureters and quantitation of cortical activity of DMSA after the intrarenal collecting systems are emptied.

It should be emphasized that the above protocol describes our technique and it is effective under the specific circumstances of a busy center with an adult and pediatric population. Other techniques may be better in a different environment. Most centers do not use a diuretic unless there is retention in the collecting system by 10–20 min or later. Dose schedule, imaging details, and analysis and quantitation vary significantly from center to center. Finally, many centers emphasize global renal flow and function measurements.

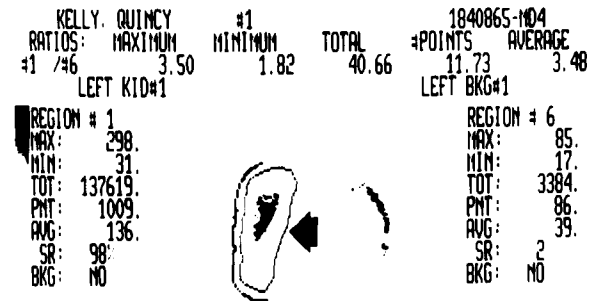
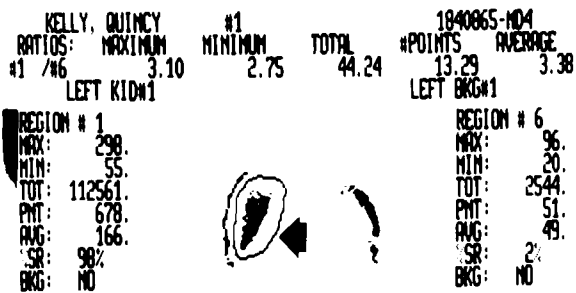
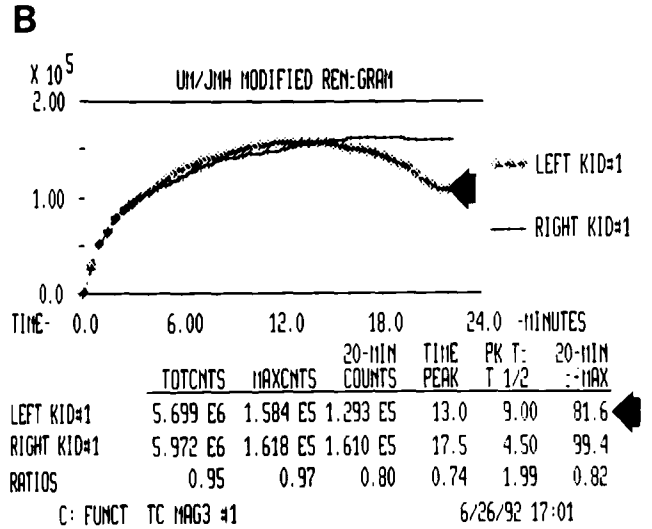
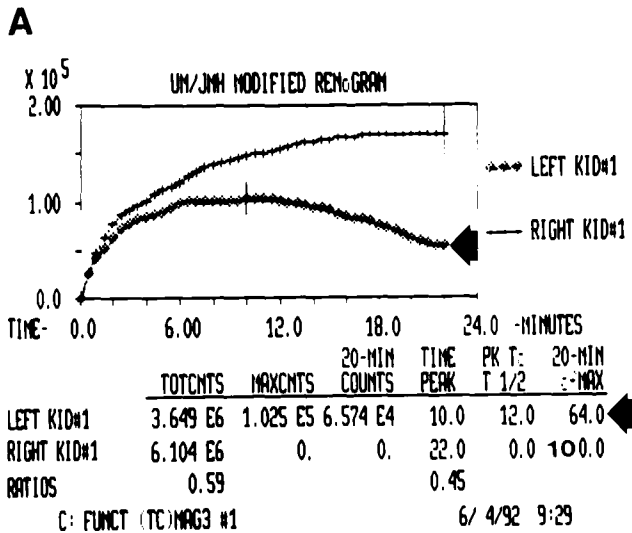


FIG. 4. The significance of including the pelvis in the region of interest (ROI) of the kidney is illustrated in these two examples of renograms of the left kidney generated with different ROIs from the same study of Fig. 3. Whereas the right kidney was treated appropriately, the ROI for the left kidney was initially inappropriate and needed to be repeated. (A) When the left pelvis was not included (ROI, arrow), a graph was generated that gave the false impression of some draining of the left kidney. (B) When the left pelvis was correctly included (ROI, arrow), the graph of the left kidney was undoubtedly of the obstructive type.

SCINTIGRAPHY IN CONGENITAL OR ACQUIRED OBSTRUCTION OF THE DRAINAGE SYSTEM

Dilatation of Drainage System and Obstruction

The most common feature of drainage system anomalies is dilatation. When associated with obstruction, the term hydro-

nephrosis (Fig. 3) is used for the intrarenal collecting system and the term hydroureter for the dilated obstructed ureter. Caliectasis, pelviectasis, and megaureter denote dilatation but not necessarily obstruction. A dilated intrarenal collecting system may be associated with a larger kidney, one that is normal size, or even a smaller kidney (relative dilatation).

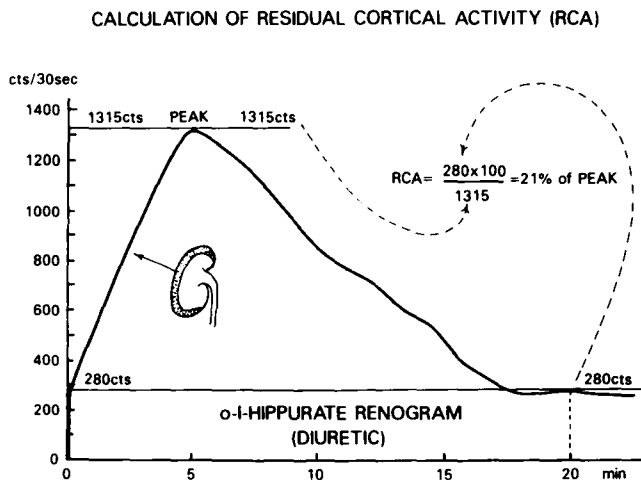


FIG. 5. Residual cortical activity.

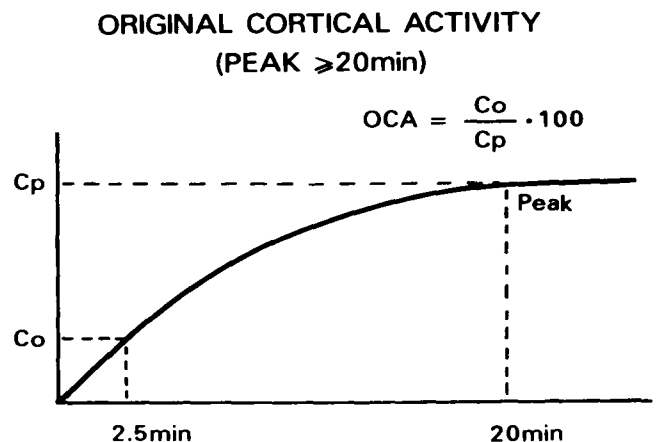


FIG. 6. Original cortical activity.

Except in the case of uncomplicated extrarenal pelvis, a dilated intrarenal drainage system is associated with parenchymal thinning of varying severity, depending on the degree and duration of the causative agent (obstruction, reflux, neurogenic problem, etc.).

Urinary tract obstruction with resultant hydronephrosis is usually congenital in a child (Figs. 3 and 4) but is an acquired process in the adult. However, associations with congenital abnormalities of the genitourinary (GU) tract and myoneurologic processes (such as meningomyelocele) occur. Acquired obstruction of the drainage system is commonly due to stones, tumors, clots, fungal balls, retroperitoneal fibrosis, or less frequently, secondary to trauma or surgery.

When obstruction is complete, the parenchyma eventually (wk to mo) atrophies completely, the size of the kidney decreases, and there is no excretion of urine. Hence, no radionuclide activity is present at any time in the collecting system. In contrast, when obstruction is partial, the degree of parenchymal thinning is directly proportional to the severity and duration of stenosis.

Obstruction may be acute or chronic (old). Acute obstruction may not be associated with dilatation of the drainage system, whereas old obstruction is characterized by dilatation.

In any type of obstruction there is delayed excretion and retention of urine with varying degrees of decreased flow and function and abnormal renograms (Fig. 4). Since delayed excretion and retention of urine are nonspecific, diuretic renography is used to diagnose obstruction. Diuresis induces fast emptying of the nonobstructed kidney but has little effect on the obstructed kidney.

Diuretic Renography

Diuretic renography is useful in confirming or excluding obstruction. The use of i.v. furosemide (1 mg/kg, maximum of 40 mg in normal function, 80 mg in renal insufficiency) is recommended by different authors, to be administered either more than 15 min before, coincident with (within 3 min), or 20–30 min after the injection of a radiopharmaceutical. DTPA or HIP, and more recently MAG_3 , have been the most commonly used radiopharmaceuticals.

To avoid duplication of effort, achieve uniformity of protocols, reliable results, and cost effectiveness, we use diuretics routinely. The rationale is that in the majority of our patients, obstruction is usually in the differential diagnosis. Likewise when cortical disorders need to be quantitated, the collecting system should not interfere with such analysis. Finally, a diuretic reduces radiation exposure to the urinary bladder. When the patient is hydrated, side effects from the diuretic are very rare. The technique followed routinely in this laboratory, for any patient referred for renal scintigraphic evaluation, is indeed a diuretic renography. The characteristic of our approach is the early injection of the diuretic, which is given intravenously within 3 min after injection of the radiopharmaceutical and has been validated for [^{131}I]HIP (7). Since the introduction of MAG_3 , this superior agent has been used instead of HIP (8).

Briefly, the patient is hydrated orally or intravenously, and

if possible is imaged in an upright position with MAG_3 . Furosemide is injected intravenously within 3 min after MAG_3 . Total sequential imaging time is 22 min followed by a postvoid view.

Criterion for obstruction is a half-time of total renal activity (including collecting system) of greater than 15 min from the injection of radiopharmaceutical (injection to peak time plus peak to half-time is greater than 15 min) (Fig. 4).

This approach is fast and accurate, except when renal function is markedly impaired, or immaturity exists (infants with very low birth weight) and insufficient urine is produced to empty the drainage system. However, such difficulties are shared by all other protocols.

The postvoid images taken after the bladder is emptied (age and training permitting) weigh heavily when function is reduced. In infants, spontaneous bladder emptying usually occurs at 10–15 min after the diuretic. In trained children and in adults, the postvoid image is taken after the 22-min course, about 25–30 min from injection. If the kidney is empty following micturition, there is strong evidence against obstruction, even if the original portion is suspicious from decrease in function. The upright position, using special chairs, is an essential improvement of diuretic renography.

The use of bladder catheterization is an issue to be considered by individual hospitals. Although frequently practiced in hospital settings, it is an invasive procedure both physically and psychologically. Introduction of pathogens, or traumatization of the tissues are serious, although infrequent, complications. Even if anatomical damage can be prevented or avoided, and antibiotics can cover for infection, for most individuals, after a certain age, catheterization is a violation of privacy, and for some it is psychologically a very traumatic experience. For these reasons, we do not routinely practice diuretic renography with a catheter in place. The use of a bladder catheter is reserved only for selected cases, such as patients with neurogenic bladder, or severely diminished function, patients with questionable obstruction studied repeatedly, or postoperatively when serious suspicion of obstruction exists. It should be underscored that sufficient hydration 30 min before the study is important.

At the present time a task force of pediatric urologists and nuclear medicine pediatric experts is evaluating diuretic renography with results to be published in the near future. The use of MAG_3 has already been approved by this group of investigators, but a standardized approach with predictable sensitive and specific results has yet to be developed (9).

RENAL ARTERY STENOSIS AND RENAL ISCHEMIA

Renal blood flow and intraglomerular pressures are regulated via the balance of (preglomerular) afferent arteriolar tone and that of (postglomerular) efferent arterioles. Efferent tone is under the influence of angiotensin II and may be inhibited by use of ACEI such as captopril, enalapril, enalaprilat, or lisinopril.

Renal artery or branch stenosis (RAS) and other ischemia-producing processes (cardiac or aortic) decrease renal blood

flow and glomerular filtration rate (GFR), proportionally for severity, unless compensation occurs. When stenosis or ischemia is severe enough to reach a critical level (about 60%–70% of the lumen), the renin-angiotensin system is activated and RVH results. The local effect (in the kidney) of the hormone, however, is a compensatory improvement of renal function (GFR).

Urography and conventional scintigraphy were not considered to be diagnostic for RVH or RAS. Invasive tests, such as aortography and differential renal vein renin levels were used, until the ACEI were introduced to clinical practice. When these agents are used in the presence of significant RAS (>60%–70%), or aortic or cardiac induced ischemia of the kidney, a clinical or laboratory (scintigraphic) decompensation of renal function usually results. Marked differences in renal function from a baseline (BSL) scintigraphic study are induced; these are considered specific for (RAS resulting in) RVH, or for renal ischemia in general, and can be readily demonstrated (10–13).

ACEI scintigraphy does not detect less than critical RAS (<60%–70%), but when positive, implies that renal ischemia is present, usually as a result of critical RAS (>60%–70%), which induces RVH. In addition to implying the presence of RAS-induced RVH, scintigraphy is useful in demonstrating the involved side.

Captopril stimulation of differential renal vein renin levels is an invasive test and results are not readily available; however, it is a reliable diagnostic approach. Less specific and sensitive are plasma renin determinations pre- and postadministration of ACEI.

At the present time, aortic and renal angiography and, less reliably, digital subtraction angiography remain the diagnostic procedures of choice in RAS. These methods visualize the anatomic lesions producing the RAS, localize it within the vessel, and help to identify the specific pathogenetic mechanism. Borderline lesions, however, need physiologic characterization (renins, SCINT) before RVH can be diagnosed, or, alternatively, confirmation by angioplasty, which results in improvement or cure of RVH. Duplex sonography is also utilized for anatomic and flow studies in RAS, but it has not been proven either specific or sensitive enough.

While nuclear studies are neither sensitive nor specific for RAS, unless RVH is present, angiography or sonography cannot specifically diagnose RVH, but can imply its presence by uncovering severe RAS. There are many examples of discrepancies between an angiographic impression of RAS (mild or severe) and the existence of RVH. Patients with RVH, angiographically mild RAS (<60%), and positive ACEI scintigraphy, responsive to angioplasty, have been encountered, while there are others with angiographically severe RAS (>80%) and negative ACEI scintigraphy who were unresponsive to angioplasty (13).

Renovascular Hypertension

RVH occurs as the result of renal hypoperfusion and may be caused by unilateral or bilateral stenosis secondary to fibromuscular dysplasia, atherosclerosis of the main renal

artery (RAS), branch arterial stenosis, whole kidney or focal renal infarction, aneurysm, or arteriovenous malformations. Clinically, RVH is believed to occur in a subset (1%–4%) of the hypertensive population and appears to be significantly less common in blacks. Early in life (<age 40), fibromuscular medial dysplasia (fibromuscular hyperplasia) is encountered in female patients predominantly and may result in RVH. Patients in age groups less likely to be hypertensive (<age 30) who develop hypertension may need to be evaluated for possible renovascular etiology. With aging, atherosclerosis becomes the most common underlying process leading to RAS and RVH and accounts for two-thirds of all cases of RVH in the fifth decade or later. A significant deterioration in renal function in the face of improved blood pressure control with ACEI also suggests the possibility of RVH. As renovascular hypertension is potentially curable, appropriate evaluation should be performed whenever RVH is a possibility (10–13).

Renal ischemia due to renal artery or aortic thrombosis in the neonate (14), or iliac artery stenosis in patients with a renal transplant also leads to RVH. The same is true for aortic stenosis, coarctation, aneurysm, dissection, or complete renal artery obstruction (RAO) with sufficient collaterals. Finally, low output heart failure may produce a physiologic response of the renin-angiotensin system without systemic hypertension.

Pathophysiology of Renovascular Hypertension and ACEI

Significant RAS, defined as involving more than 60%–75% of the lumen of the vessel, decreases afferent (preglomerular) arteriolar blood pressure, stimulates pressure receptors, and increases renin secretion by the juxtaglomerular apparatus, activating the renin-angiotensin system (Fig. 7B). A drop in the preglomerular pressure will also decrease glomerular filtration (Fig. 7B), unless compensation occurs. Indeed, as renin is secreted in greater than normal rates, angiotensin I (from angiotensinogen) and, in the presence of converting enzyme, angiotensin II are locally produced in high quantities (Fig. 7C). Angiotensin II has a preferential action on the efferent (postglomerular) arteriole and induces postglomerular vasoconstriction, thereby restoring intraglomerular pressure and maintaining glomerular filtration fraction and glomerular filtration (Fig. 7C). In the systemic circulation, however, peripheral vasoconstriction results in hypertension.

When the ACE inhibitors captopril, enalapril, enalaprilat, and lisinopril (Table 1) block the production of angiotensin II, postglomerular vasodilation takes place, resulting in a drastic decrease in (or even cessation of) glomerular filtration (Fig. 7D) and in a decrease or lack of accumulation of the glomerular agents DTPA, GH, and DMSA, as shown by scintigraphic scanning (11). At the same time, systemic blood pressure is reduced for the period of ACEI activity.

Tubular cells in this context retain, at least partially, their functional capability since blood flow to the ischemic kidney is not reduced further and may even increase after converting enzyme inhibition. Urine production is decreased or even

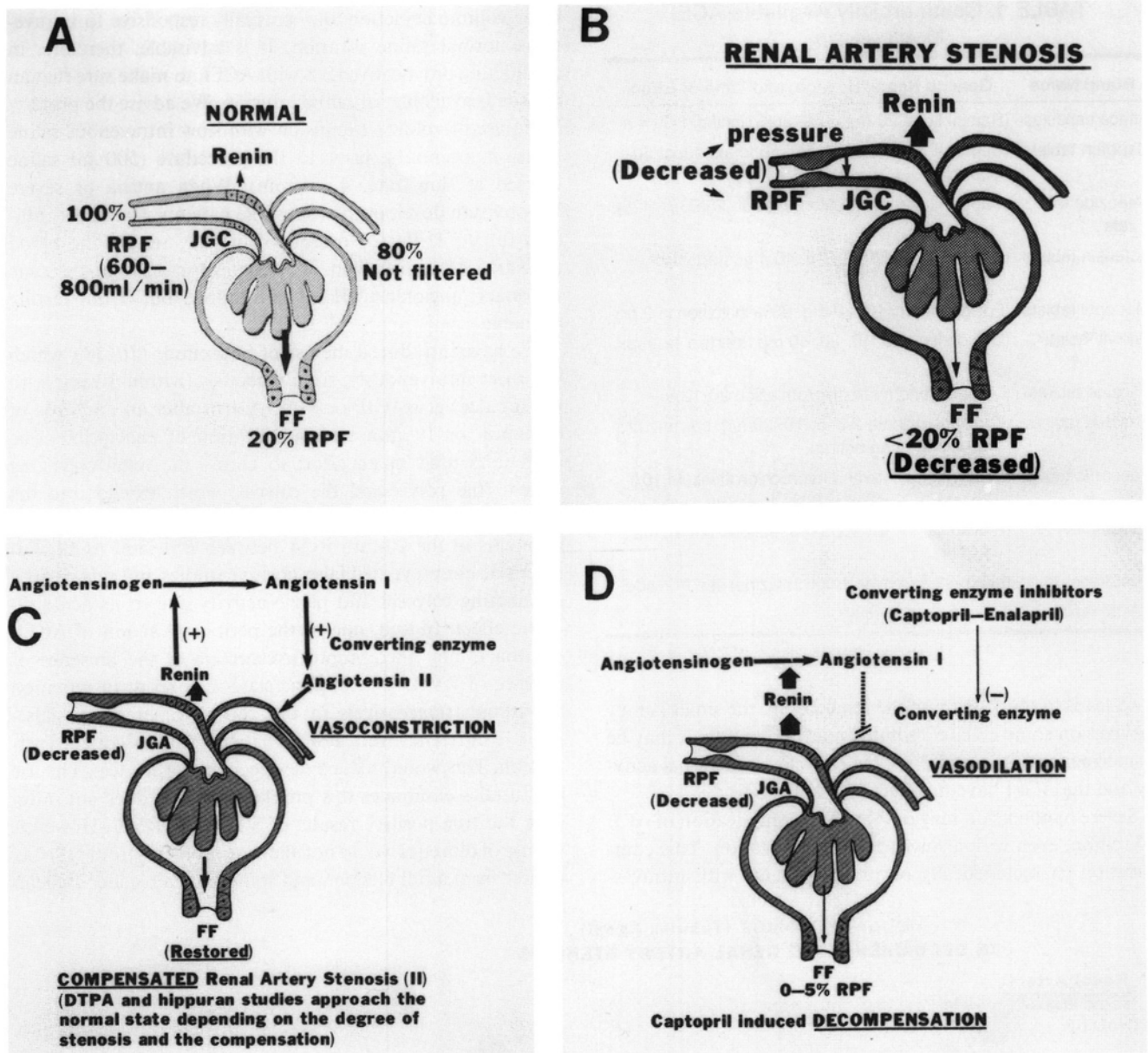


FIG. 7. (A) Normal state, (B, C) pathophysiology of renin-angiotensin II compensation of renal function in RVH, and (D) the decompensation induced by ACE inhibitors.

totally curtailed with the absence of glomerular filtration. Due to these phenomena, kidneys with RAS, following ACEI administration, do accumulate and retain tubular agents, such as HIP and MAG_3 , longer than normal (Fig. 8), although they do not accumulate glomerular agents such as Tc-DTPA or GH as efficiently as in BSL studies. Moreover, with insufficient urine production, the tubular agents (HIP, MAG_3) remain in the cortex of the kidneys for long periods of time (RCA at 20 min increases from BSL) (Figs. 5, 8, and 9) (10–13).

These effects of ACEI last only a few hours and are usually totally reversible without residual damage to the ischemic kidney. The normal contralateral nonstenotic kidney in unilateral RVH shows minimal functional changes after blockade of the renin-angiotensin system, resulting in negligible change

in its overall renal function. However, in bilateral RVH (14), in a solitary (native or transplanted) kidney with a stenotic artery (or any type of renal ischemia), or in patients with renal insufficiency and unilateral RVH, ACEI may induce acute renal failure. When a single dose of ACEI is given for diagnostic purposes, its systemic and renal effects last only a few hours, unless severe oliguria results. Then hypotension persists and recovery of renal function may be delayed for several hours (14). Enalapril administered orally and enalaprilat administered intravenously have a longer duration of action than captopril.

When RAS is very severe (>95%), the kidney is usually contracted, hypofunctioning, there is little or no compensation by the renin-angiotensin system, the renogram at BSL is rising, and the ACEI have little or no effect. Finally, when

TABLE 1. Commercially Available ACEI Medications

Brand Name	Generic Name, Dosage, and Time of Effect
Altace capsules	(Ramipril oral 20 mg 60%–80%, inhibition in 4 hr)
Capoten tablets	(Captopril oral 12.5, 25, 50 mg, max. effect 60–90 min)
Capozide tablets	(Captopril and hydrochlorothiazide 25(50)/15(25))
Lotensin tablets	(Benasepril oral 5, 10, 20, 40 mg, starts 1 hr, max. 2–4 hr)
Monopril tablets	(Fosinopril oral 10, 20 mg, 90% inhibition in 2 hr)
Prinivil tablets	(Lisinopril oral 5, 10, 20, 40 mg, starts 1 hr, max. 4 hr)
Prinzide tablets	(Lisinopril and hydrochlorothiazide 20/12.5)
Vasotec tablets	(Enalapril maleate 2.5, 5, 10, 20 mg, starts 1 hr, max. 6 hr, long acting)
Vaseretic tablets	(Enalapril maleate and hydrochlorothiazide 10/25, starts 1 hr, max. 6 hr)
Vasotec i.v.	(Enalaprilat i.v. 2 ml/2.5 mg, action 15 min, max. 1–4 hr)
Zestoretic	(Lisinopril and hydrochlorothiazide) see Prinzide
Zestril tablets	(Lisinopril) see Prinivil

RAS leads to obstruction of the renal artery, the small kidney survives on some collaterals but is not functioning. It may be visualized from its blood pool, but shows no functional activity and the ACEI have no effect (10–12).

Severe hypotension may develop as a complication of ACE inhibition, even with a single dose of medication. This complication characteristically occurs in patients with intravas-

cular volume depletion and is usually responsive to intravenous normal saline infusion. It is advisable, therefore, in conducting provocative tests with ACEI, to make sure that an i.v. site is available for saline infusion. We advise the prophylactic use of volume expansion with slow intravenous saline infusion, beginning prior to the procedure (500 ml saline infused at slow rate, 4 ml/min). When anuria or severe hypotension develops in susceptible patients, fast saline infusion (up to 1 liter or more) will usually restore the blood pressure. Administration of vasoconstrictors may become necessary; angiotensin II is the antidote, but is not readily available.

We have introduced the use of furosemide (10–13), which we inject intravenously, simultaneously (within 3 min) with the tubular agent (HIP or MAG₃), 1 hr after an oral dose of captopril, or 10 min after an infusion of enalaprilat. The diuretic is used in an effort to empty the renal collecting system (the pelvis and the calyces, which extend into the cortex) and increase the accuracy of the comparative measurements in the 20-min RCA between BSL and ACEI. Furosemide has prevented false-positive studies and acts only by eliminating calyceal and pelvic activity due to its acute diuretic effect. Indeed, due to the peripheral action of ACEI, oliguria is not uncommon, irrespective of the presence or absence of RVH. This oliguric state may result in retention of radiopharmaceuticals in the cortex, generating a false-positive difference from BSL in patients with essential hypertension. This would reduce the specificity of the test. The use of diuretics eliminates this problem, while it does not influence the true positive results of SCINT in RVH. However, the use of diuretics would not alleviate problems from obstruction or from a full bladder, and sometimes a bladder catheter

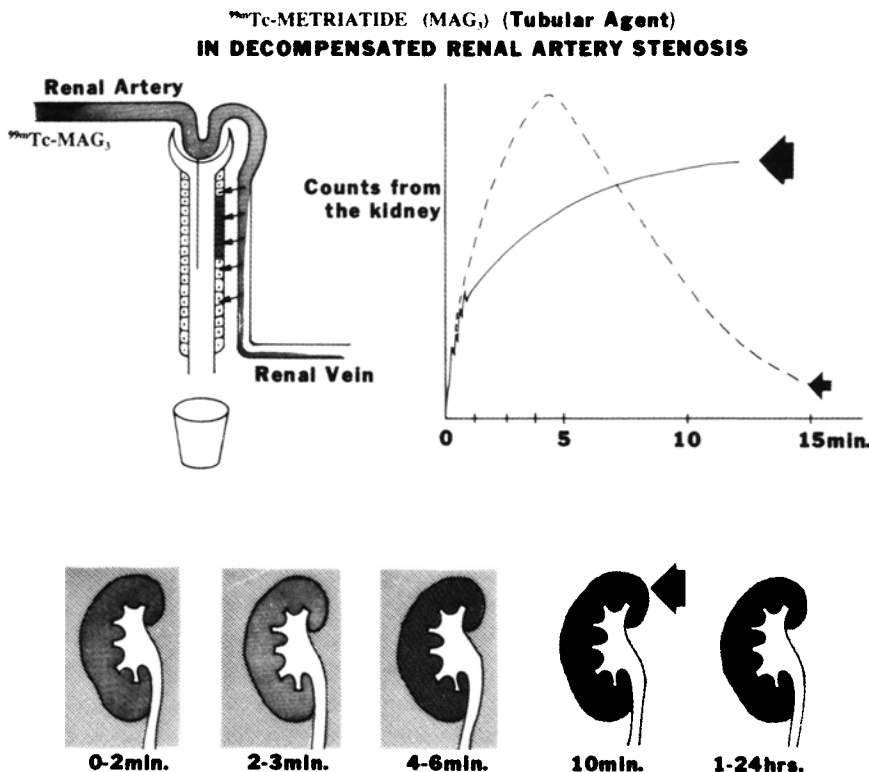


FIG. 8. In RVH, the kidney with 60%–95% renal artery stenosis has compensated (normal) function (small arrow), but ACE inhibitors decrease or block glomerular filtration and urine production, by postglomerular arteriolar dilatation. The tubular cells, however, keep accumulating MAG₃ from the postglomerular arterioles and since urine flow is reduced or curtailed, activity either remains longer in the cortex (increased residual cortical activity at 20 min) or a rising graph is generated (large arrow).

or postvoid image may be needed for confirmation, when the routine study shows evidence of bladder retention and fullness.

Current Protocol for RVH

We currently use a 1-hr protocol with a 1-mCi baseline MAG_3 study, followed by a 2.5-mg i.v. enalaprilat and, 10 min later, a 9-mCi MAG_3 study. The procedure could be performed in two different visits (each with 5 mCi of MAG_3 and diuretic, one BSL and the other after ACEI administration). If patients are on therapy with ACEI, a single study without additional ACEI may be performed and a BSL performed later if needed (if the ACEI study is abnormal).

Comparative DTPA and HIP studies were performed in our laboratory and results have been previously published (10). HIP has proved to be the superior agent for RVH in our experience (10) (Fig. 9A–D). After the introduction of MAG_3 (a tubular agent like HIP) and the i.v. ACEI enalaprilat (Vasotec), we introduced the following protocol (Fig. 9E–H).

Patient Preparation. Patients should initially have been off ACEI for at least 48 hr before we perform sequentially a BSL and ACEI study. For those on therapy with ACEI, the procedure may also be performed without interrupting treatment as a single phase study. All other antihypertensive medications and those with potential hypotensive effects should be withheld overnight.

In our laboratory, ACEI scintigraphy in hypertensives is considered contraindicated if blood pressure is not sufficiently elevated to allow for a safe reduction from the potential pharmacologic action of the drug. We routinely advise against the use of diagnostic ACEI in an adult hypertensive patient on therapy, with a systolic blood pressure below 140 mm Hg or an infant with a mean arterial pressure equal to or less than 65 mm Hg.

The patient is hydrated orally with 10 ml/kg of H_2O . An infusion of 500 ml of normal saline begins (4 ml/min). Just before the beginning of each part of the scintigraphy, the bladder is emptied. If a test starts with a full bladder, the results may be false-positive. A bladder catheter may be needed in cases with prostatic hypertrophy or in renal transplants.

A baseline scintigraphic study is first acquired for 22 min after i.v. administration of 1 mCi MAG_3 . For better sensitivity, furosemide may be injected both at BSL and after ACEI administration. However, this may result in interruptions of acquisition for micturition. It may also result in false-positive studies, due to the full bladder effect on kidney drainage during the first or, more frequently, the second part, unless a catheter is placed in the bladder. We have found it more practical and convenient for the patient not to receive a diuretic and to rely on good hydration alone for the BSL part of the 1-hr protocol.

Next, the patient empties his or her bladder and a postvoid image is taken. Monitoring of blood pressure every 5 min begins. Then a slow (over 5 min) i.v. infusion of 0.04 mg/kg (maximum 2.5 mg) of enalaprilat (Vasotec) is given. At 10 min from the beginning of infusion, the post-ACEI diuretic scintigraphy is performed for 22 min, after 9 mCi of MAG_3 and

40 mg of furosemide are administered intravenously (80 mg in renal insufficiency).

Saline is infused as above and monitoring of blood pressure is interrupted after a stabilization or rebound is observed. In case of more than a 30% drop in blood pressure, fast saline infusion to prevent complications is advised. We have performed more than 200 patient studies thus far and have not seen any problems or side effects, although in a few patients 1 liter or more of saline was used.

Acquisition of SCINT data, graph generation, and index calculation (RCA, OCA) have already been discussed. A flow study may precede function and sequential imaging, but in this case, the flow frames should be compressed and added appropriately at the beginning of the 30-sec frames.

Criteria for Interpretation of MAG_3 ACEI SCINT

Thus far, we have utilized the same criteria for enalaprilat- MAG_3 as those validated for captopril-HIP and the preliminary results indicate high specificity and sensitivity. By following up patients who were studied under the new protocol, an effort is being made to define potential differences from the HIP criteria.

Criterion 1: Evidence of ACEI effect on renogram (Fig. 9D, 9H). The shape of the graphs and the effect of ACEI are very similar whether using MAG_3 or HIP except for better count rates with MAG_3 . For peaking renograms (rising and falling graph pattern), an increase in the RCA by at least 10% from the BSL (e.g., BSL-RCA = 25%, ACEI-RCA = 35%) is considered an indication of RVH (a rising of 5%–10% may be considered suspicious). Such abnormal cases usually have RAS = 70%–95%.

Criterion 2: Rising BSL renogram (even without ACEI effect). Cases of severe stenosis (>95%) have been seen with a BSL rising MAG_3 renogram and a slight decrease in OCA or no effect (no further deterioration) by ACEI. More experience is needed to firmly establish this criterion. Severely stenotic kidneys presenting with this criterion are usually small (contracted, atrophic) and hypofunctioning (10–13).

Criterion 3: Nonvisualization of function of a kidney or part of it. Due to its high efficiency, MAG_3 allows visualization of any stenotic kidney, even if it is nonfunctioning (while nonvisualization would be typical for HIP). Kidneys with renal artery obstruction which survive on collaterals, induce RVH, do not function, are small, barely visible (blood pool), show no functional accumulation of activity, and have a renogram characteristic of the background graph shape (brief rise, peak at 1 min, slow rate of emptying). Contrary to this type of renogram, kidneys with renal failure, but without RVH, are characterized by an early upslope; they reach a plateau by 3–5 min. There is no evidence of an ACEI effect for either type of kidney (10–13).

Diagnostic Pitfalls

MAG_3 ACEI scintigraphy requires the use of furosemide and has a high sensitivity and specificity. Without furosemide, the results are not as good, because of a high incidence of (bilateral) false-positive studies.

MAG_3 and enalaprilat allow a complete study in a single

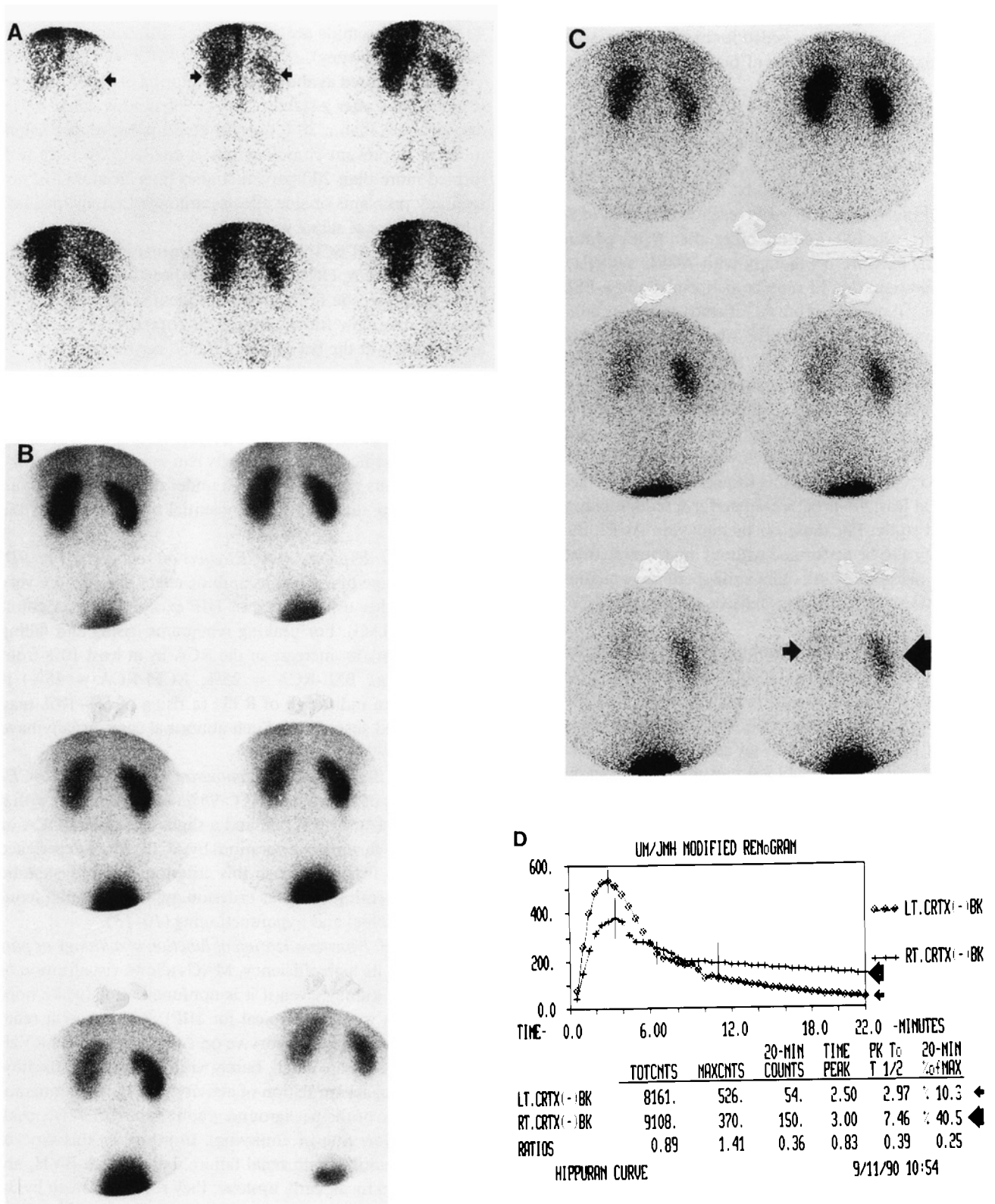


FIG. 9. Unilateral (right) renal artery stenosis (85%) inducing RVH in an adult. The patient was first studied while on therapy with captopril (oral ACE inhibitor): Whereas (A) the flow was abnormal, (B) the DTPA study did not show clear evidence of relative decreased function of the smaller right kidney. (C, D) A HIP lasix study, however, performed immediately after DTPA showed cortical retention and increased RCA on the right (large arrow), with normal function on the left (small arrow).

visit (1 hr), including BSL and ACEI, using the above protocol with furosemide as an essential part of this technique. Although the preliminary results are encouraging, more infor-

mation and further experience is necessary to ascertain that this practical approach is as specific and sensitive as is HIP with captopril.

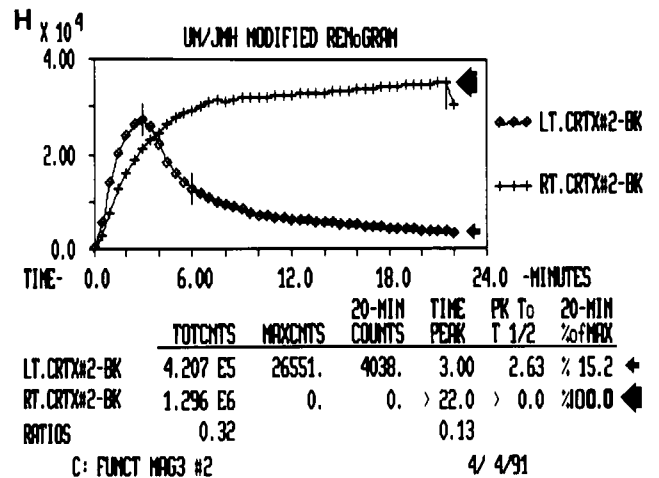
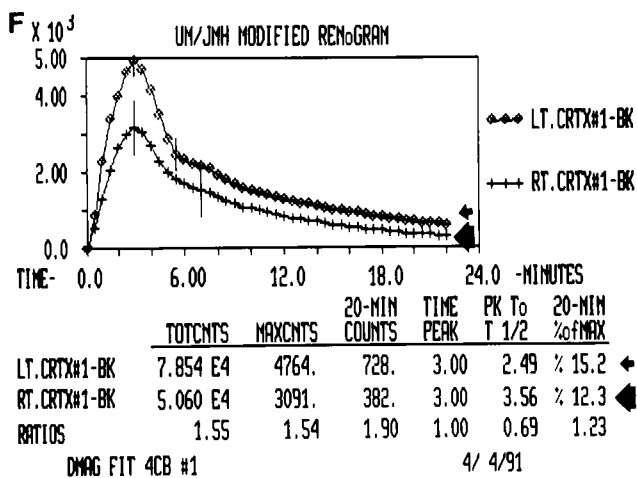
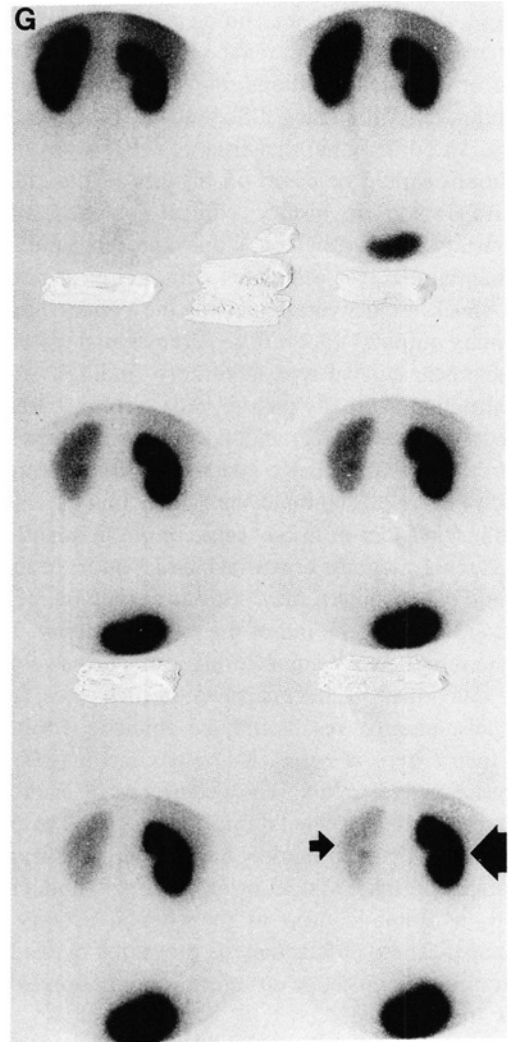
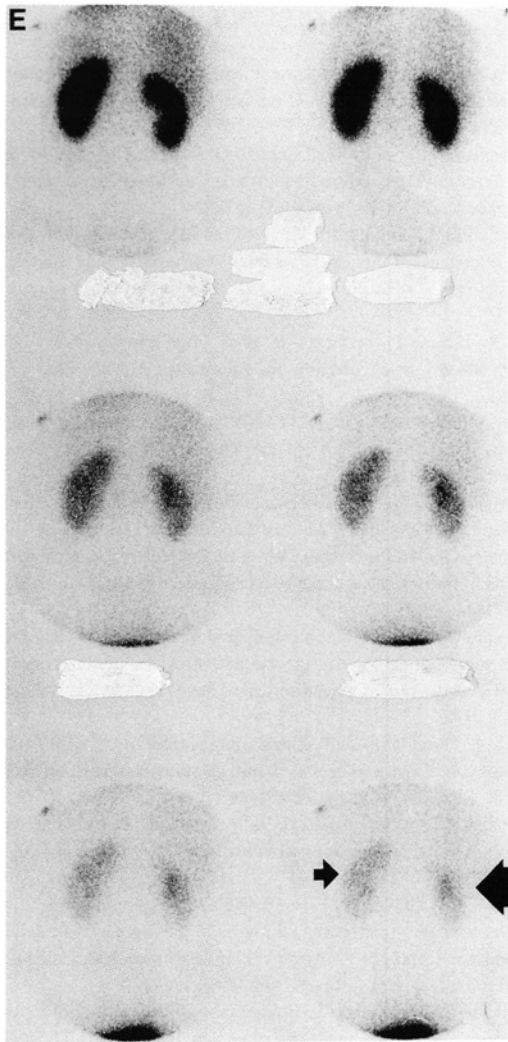


FIG. 9. (E and F) The patient returned later and a BSL MAG_3 /lasix and (G and H) an enalaprilat/ MAG_3 /lasix study were performed with the proposed protocol. The effect of ACE inhibitors on the scintigram and the renogram of the right kidney is evident (large arrows). The normal left kidney was not affected (small arrows).

It is important to review the scintigraphic images and not rely exclusively on the renographic data. Patient motion and technical problems may induce incorrect computer data and validation by correlation with images is necessary. Image

interpretation would also help in the recognition of anatomical and other pathologies and avoid false interpretations in some pitfalls.

Acute tubular necrosis (ATN), drug toxicity, interstitial

nephropathies, glomerulopathies, complete acute obstruction of the uretero-pelvic junction, renal vein thrombosis, and other acute or chronic conditions may mimic very severe RVH (criterion 2), with rising BSL and ACEI curves on scintigraphy. The differential diagnosis of RVH from these acute conditions should be based on the size of the kidney (small in RVH) and on history, clinical evaluation, and laboratory results. ATN is bilateral; kidneys are large and flow relatively maintained. It is associated with a clinical history of surgery, shock, or dehydration, with the patient having variable urinary output. Other diffuse parenchymal disorders have characteristic clinical and laboratory findings. Acute ureteral obstruction is usually painful, renal vein thrombosis is associated with hematuria, and both have predisposing factors. Chronic partial drainage system obstruction can be excluded by visual appreciation of the SCINT images.

A full urinary bladder from any cause, more frequently in patients with renal allografts or partial bladder outlet obstruction (prostatic hypertrophy), may delay the emptying of the intrarenal collecting system and of the cortical activity. This probably occurs due to a vesicopelvic reflex after urine volume exceeds the individual's bladder capacity; in such cases, false-positive or false-negative results may be obtained if tubular agents and their criteria are used. A similar effect may be the result of vesicoureteral reflux. The occurrence of such unwanted effects may be suspected if one observes a full bladder at the beginning of the examination, a persistent visualization of the intrarenal drainage system or of the ureter, and, characteristically, a dramatic drop in the cortical activity on postvoid images. These pitfalls may be prevented by bladder catheterization at the outset or on repeat examination, when such effects are suspected.

Low output heart failure, or a profound drop in blood pressure with oliguria may also result in (bilateral) false-positive results for RVH on BSL and ACEI scintigraphy. Finally, renal vein thrombosis, renal arteriolar stenosis, and vasculitis may result in images similar to those of RVH, and in the strictest sense, they may be the cause of false-positive results. Excluding these pitfalls, MAG₃-furosemide-enalaprilat scintigraphy appears to be a reliable method of screening hypertensive patients for RVH.

REFERENCES

1. Sfakianakis GN. Nuclear medicine in congenital urinary tract anomalies. In: Freeman LM, ed. *Nucl med annual 1991*. New York: Raven Press; 1991:129-192.
2. Sfakianakis GN, Vonorta K, Zilleruelo G, Jaffe D, Georgiou M. Scintigraphy in acquired renal disorders. In: Freeman LM, ed. *Nucl med annual 1992*. New York: Raven Press; 1992:157-224.
3. Sfakianakis GN. Methods. In: Van Nostrand D, series ed. *Atlas of scintigraphy in congenital and acquired renal and urinary tract disorders and complications of renal transplants*. New York: Springer-Verlag; 1992:in press.
4. Taylor A, Eshima D, Frizberg AR, et al. Comparison of I-131-OIH and Tc-99m-MAG₃ renal imaging in volunteers. *J Nucl Med* 1986;27:795-803.
5. Dubovsky EV, Russell CD. ^{99m}Tc-MAG₃: the multipurpose renal radiopharmaceutical. In: Freeman LM, ed. *Nucl Med Annual 1991*. New York: Raven Press; 1991:1-35.
6. Majd M, Rushton HG. Renal cortical scintigraphy in the diagnosis of acute pyelonephritis. *Sem Nucl Med* 1992;22:98-111.
7. Sfakianakis GN, Heiba S, Ganz W, et al. Diuretic renography with early injection of furosemide, a reliable and cost effective approach. *J Nucl Med* 1989;30:841.
8. Sfakianakis GN, Soto R, Knobloch E, et al. A routine protocol of diuretic MAG₃ renal scintigraphy in the evaluation of children and adults with congenital and acquired renal disorders: a one year experience. *J Nucl Med* 1992;33:1035.
9. Conway J. "Well-tempered" diuresis renography: its historical development, physiological and technical pitfalls, and standardized technique protocol. *Sem Nucl Med* 1992;22:74-84.
10. 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.
11. Sfakianakis GN, Sfakianaki E, Bourgoignie J. Renal scintigraphy following angiotensin enzyme converting inhibition in the diagnosis of renovascular hypertension (captopril scintigraphy). In: Freeman LM, ed. *Nucl med annual 1988*. New York: Raven Press; 1988:125-170.
12. Sfakianakis GN, Sfakianaki E, Bourgoignie J. Lasix captopril renography in the diagnosis of renovascular hypertension. In: Blaufox MD, Hollenberg NK, Raynaud C, eds. *Radionuclides in nephro-urology*. Basel: Karger; 1990;79:219-227.
13. Erbsloh-Moller B, Dumas A, Roth DR, Sfakianakis GN, Bourgoignie JJ. Furosemide ¹³¹I hippuran renography after angiotensin-converting enzyme inhibition for the diagnosis of renovascular hypertension. *Am J Medicine* 1991;90:23-29.
14. Sfakianakis GN, Sfakianaki E, Paredes A, Abitbol C, Zilleruelo G, Goldberg RN, Strauss J. Single dose captopril scintigraphy in the neonate with renovascular hypertension: prediction of renal failure, a side effect of captopril therapy. *Biology of the Neonate* 1988;54:246-253.