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A Renal Protocol for All Ages and All Indications: Mercapto-Acetyl-Triglycine (MAG_3) With Simultaneous Injection of Furosemide (MAG_3-F_0): A 17-Year Experience

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Current clinical requirements mandate the existence of a renal diuretic protocol, which is fast and easy, applicable in all ages and for all indications, convenient for both the patient and the technologist, and provides diagnostic as well as prognostic information. Seventeen years ago a 25-minute protocol, after oral hydration, with no bladder catheterization, and simultaneous injection of mercapto-acetyl-triglycine (MAG_3) and furosemide (MAG_3-F_0), was initiated. It initially was used for the evaluation of drainage and emerged as a protocol to also evaluate the renal parenchyma. Results of this protocol have been published individually, per clinical application. MAG_3-F_0 was instrumental in the evaluation and prognosis of congenital disorders. For obstruction, in the newborn, an increasing renogram mandates intervention, whereas a downsloping one predicts spontaneous resolution. In children or adults, preoperatively or postoperatively, when the cortex was visualized and drained normally, there was no obstruction, even if urine was retained within a dilated collecting system or an extrarenal pelvis. For diseases of the renal parenchyma, the protocol enabled the diagnosis of acute pyelonephritis (APN) revealing the "regional parenchymal dysfunction," diagnostic of APN. Diffuse parenchymal diseases were characterized by increased residual cortical activity (RCA), and their progression was manifested as a deterioration of RCA. End-stage renal disease was characterized by lack of accumulation and retention. Trauma and leaks were identified with specific patterns. In renovascular hypertension (RVH), an increase in RCA after angiotension-converting enzyme inhibitors is diagnostic of RVH and prognostic of the beneficial effect of angioplasty on hypertension. In renal colic, stratification was possible into (1) complete or severe obstruction requiring immediate intervention, (2) mild obstruction allowing waiting, (3) spontaneous decompression (stunned kidney), and (4) no recent obstruction. In transplants, it enabled differentiation of acute tubular necrosis, acute or chronic rejection and nephrotoxicity, and identified infarcts, RVH, leaks and obstruction. Finally, this method allows for a quick semiquantification of renal function. The clinical usefulness of the MAG_3-F_0 protocol in most congenital or acquired renal problems is proven through long-term clinical experience and has resulted in a substantial utilization of the test at our Center.
Semin Nucl Med 39:156-173

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 0001-2998/09/$-see front matter
doi:10.1053/j.semnuclmed.2008.11.001

Major technical components of the protocol for renal scintigraphy ought to be influenced by contemporary developments in imaging, including (1) the general trends of current medical practice (pursuit of a fast and simple method), (2) the clinical condition of the patient population referred for nuclear studies, and (3) the availability of competing multimodality methods for renal imaging (ultrasonography [US], x-ray tomography, and magnetic resonance imaging [MRI]). As such, the current ideal protocol for functional evaluation of the kidneys (diuretic scintirenography) should be fast, easy, and convenient for both the patient and the technologist. In addition, it should be cost effective. For practical reasons, there should be only one protocol for all indications (parenchymal and drainage), irrespective of the patient's age, the general clinical condition of the patient (portable), and the degree of impairment of the renal function. Ideally, the protocol should be capable of identifying the cause of renal problems and provide not only diagnostic but prognostic information as well. A semiquantification of renal function expressed in familiar units would be welcomed. Finally, this protocol should be completely safe and with reproducible results. Such a protocol requires the use of the most efficient clinically available radiopharmaceutical and a novel but proven approach.

The MAG_3-F_0 protocol, a 22-minute dynamic study, has been in use for the past 17 years at the University of Miami/Jackson Memorial Medical Center (UM). It replaced the o-^{131}I-hippurate (HIP) protocol by using an early injection of furosemide (F_3) instead, and it has proven to possess most of the ideal properties discussed previously. Mercapto-acetyltriglycine (MAG_3) is the most efficient radiopharmaceutical approved by the Food and Drug Administration for renal dynamic studies.[1,2] Furosemide is injected intravenously (IV), simultaneously with MAG_3-(F_0), and this combination allows for 18 minutes of dynamic imaging under the influence of the diuretic. This imaging is possible because the diuretic action of furosemide begins as early as 3 to 5 minutes after injection, (at which time the parenchyma has acquired a substantial quantity of the radiopharmaceutical). This action fulfills the purpose of evaluating the effect of the diuretic on both the renal cortical function and the drainage.[3,4] A postvoid (or postupright image in infants) complements the dynamic study and, if needed, a 1-hour delayed image can be acquired. Experience in specific clinical applications using the Hippurate or the MAG_3-F_0 protocol has been previously published[5-28] or presented in scientific meetings.[29-39] The present article serves as a review of the entire topic, following interval presentations and publications on MAG_3-F_0.[40-44]

The MAG_3-F_0 protocol was and continues to be successfully used for the evaluation of renal drainage in both congenital and acquired disorders, with renewed interest on the drainage of the cortex rather than that of the collecting system.[27,34,44] When it became evident that the MAG_3-F_0 protocol could also be used to evaluate the renal parenchyma, it was subsequently applied in all parenchymal indications: the diagnosis of renovascular hypertension (RVH) with its "deterioration" of the cortical renogram was the first such application.[19,22,23] Acute pyelonephritis (APN) with its "regional parenchymal dysfunction,"[20,25] human immunodeficiency viral (HIV) nephropathies and other nephropathies in children and adults with the "increasing residual cortical activity" as the disease deteriorates,[24,36] and the study of renal colic, including the "stunned" or spontaneously decompressed kidney,[26,28,39] followed. The MAG_3-F_0 protocol also was successful in the study and differentiation of all complications of renal transplants.[29-32] In addition, a current effort to evaluate renal function expressed in creatinine equivalent units is promising.[33,37]

A similar protocol using MAG_3-F_0 has been successfully used in children in Australia, and the results of this experience, although limited in the evaluation of drainage, have been published in a very interesting work.[45]

Methods

The MAG_3 Protocol as Applied at UM

The Choice of the Radiopharmaceutical (MAG_3)

MAG_3 is mainly a tubular agent with a high overall extraction efficiency (EE) of approximately 60%, (2-5% is filtered and 55-57% is taken up by the proximal tubular cells and excreted into the lumen of the tubules with no reabsorption). It is superior compared with the previously popular agent diethyleno-triamino-pentacetic acid (DTPA), which is a pure glomerular filtration rate (GFR) agent with an EE of only 20%. The greater EE of MAG_3 results in an early (1-4 minute) high kidney-to-background (BKG) activity, thus allowing for successful and generally acceptable cortical imaging (including, if desired, tomography with single-photon emission computed tomography [SPECT][21]), as well as providing steep renograms because of effective fast clearance of the kidneys and the BKG at 25 minutes (Fig. 1).[1,2] These characteristics assure imaging superiority and functional sensitivity.

In addition, because MAG_3 is a tubular agent, the parenchyma (cortex) can be imaged even when the GFR is minimal or absent, whereas in this setting the use of DTPA would not even be able to visualize the kidney. MAG_3 provides diagnostic and prognostic information in severe or total obstruction, in acute tubular necrosis (ATN), in angiotensin-converting enzyme inhibition (ACE-I) studies for diagnosis of renovascular hypertension (RVH), etc. Finally, because its distribution space is much smaller than that of the HIP (because of the fact that it does not enter into the red blood cells, whereas HIP does), MAG_3 is eliminated faster by the kidney and provides renograms as steep as those of HIP, even though HIP has a greater EE (80%). MAG_3 with the help of simultaneous injection of furosemide provides superior early parenchymal functional images in addition to efficiently studying the drainage system. It is for these reasons that the Society of Nuclear Medicine (SNM) recommends MAG_3 for dynamic renal imaging and functional studies.[46-48]

Patient Preparation

Routine MAG_3-F_0 studies are performed at UM without bladder catheterization. The patient is asked to empty his or her bladder before beginning the examination. For infants and young chil-

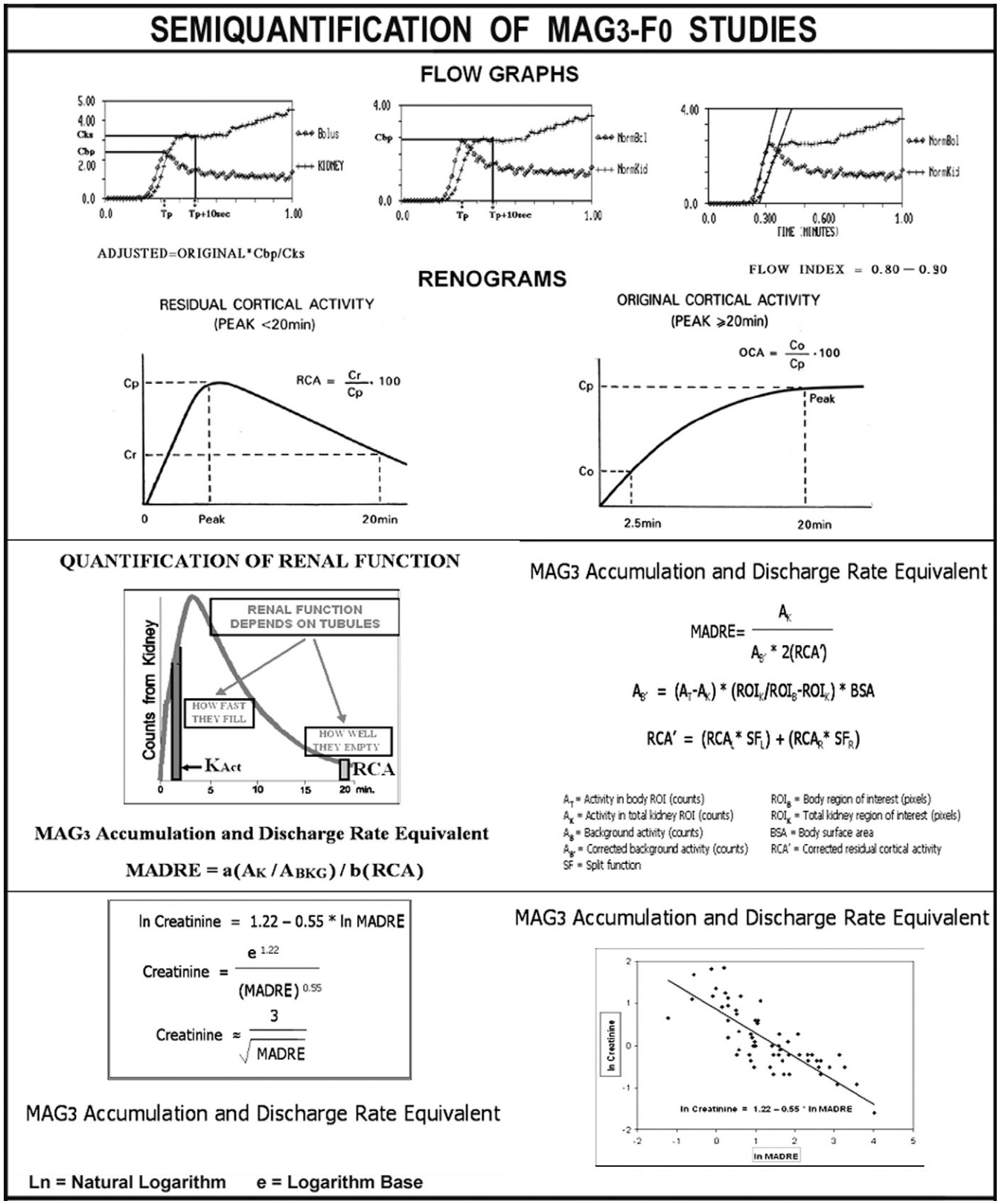

Figure 1 Semiquantification of MAG_3-F_0 studies.

dren in diapers, the study begins promptly. When intrarenal or ureteral obstruction is to be excluded and bladder or urethral abnormalities are present or suspected, urinary bladder drainage (Foley catheter in place) can be used because a full bladder may induce proximal retention of the radiopharmaceutical suggesting proximal obstruction. While seeking accurate cortical transit times in an investigation for renovascular hypertension, one may use a Texas catheter (condom type) for men or a diaper for women in lieu of catheterization, and patients are asked to empty their bladder periodically.

The patient should be well hydrated orally (10 mL/kg water or juice, or for infants/children feed milk/formula), 30 minutes before imaging. If oral hydration is contraindicated, IV saline (NS) or dextrose/saline 100 to 500 mL starting 30 minutes before imaging and continuing during the study is used; the same is used if an ACE-inhibition study is to be performed, in addition to oral hydration.

In children and adults, a supine position is preferable because it assures immobilization and avoids orthostatic hypotension. In selected cases, an upright position is preferred if gravity-assisted drainage of the kidneys is to be evaluated. Patient immobilization is essential, and in infants and children the use of a papoose board is mandatory. Adults should be instructed and periodically reminded to remain still. The patient should be calm and in a comfortable environment. When children are examined, the parent(s) should be present. Sedation may be administered exceptionally, that is, if absolutely necessary. If there is no IV running, a butterfly catheter is inserted and, before injection of MAG_3, 2 to 5 mL of normal saline (NS) is infused to ensure that there is no extravasation.

Injection of the MAG_3 and Furosemide (MAG_3-F_0)

For adults a dose of 10 mCi of MAG_3 is injected IV. In children a minimum of 1 mCi and a graduated dose ([10 mCi/70] × weight in kg) up to 10 mCi is administered. The injection of MAG_3 is fast and followed immediately by a rapid injection of 5 to 10 mL of NS to achieve flow effect in imaging; a slow infusion of 40 mg of furosemide (children 1 mg/kg) is followed immediately. In adults, if the creatinine is greater than 1.8 mg, the dose of furosemide is increased to 80 mg.

Acquisition of Data for the Dynamic Study

Native kidneys are evaluated in the posterior projection whereas transplants are evaluated in the anterior projection. The flow portion of the dynamic study is acquired during the first minute (1 frame/sec). The dynamic acquisition continues over the next 21 minutes (1 frame/30 sec) with the function/drainage part of the study. A static image, 2 minutes after bladder void (or post upright) is subsequently acquired and also, if activity remains in the kidney(s), a delayed 2-minute static image at 1 hour can be acquired. A right lateral static image after void or after delayed image completes the study; this image is useful to identify the overlying gall bladder (differentiate it from right kidney focal retention of activity). If the patient has a bladder catheter, a picture of the urine bag is acquired after the post void and the delayed images to define urine production and excretion.

Grouping of the Images

The dynamic images are grouped (the flow in 3-second images and the function in 2-minute images) to allow for easier and more accurate interpretation. The 60 1-second flow images are also grouped into 30-second images (n = 2), which are placed in front of the function images for both the renogram generation and the production of the 2-minute grouped function images.

Generation of the Graphs

Separate graphs are generated for the flow and the function, for the entire kidney and for the renal cortex. Regions of interest (ROIs) for the entire kidney include all the renal parenchyma and all the drainage system, and for the cortex are limited to a small peripheral area carefully selected and drawn far from the collecting system activity (as it develops during the entire study). Appropriate weighted background subtraction as per standard methods is performed. The resulting flow graphs and renograms are in 1-second and 30-second intervals, respectively (Fig 1).

Quantification

The blood flow to the kidney is quantified by calculating the flow velocity index (FVI) (= the slope of the curve of the kidney divided by the slope of the curve of the aorta, after equalization of the 2 graphs at the peak of the kidney activity, or 10 seconds after the peak of the aortic activity) (Fig. 1).[31,32] This FVI allows accurate and reliable data with a normal value 0.8 to 0.9, whereas other methods have unreliable results. The renograms are analyzed for their peak time and the residual cortical activity at 20 minutes (RCA) and, when the renogram is increasing, for the original cortical activity (OCA; Fig. 1).

The estimation of the split renal function is performed with the use of data acquired from the first to the second minute. Appropriate background subtraction is performed. More recently, the split renal function of an obstructed kidney may be calculated in a different way because the classic method underestimates the function of the obstructed unit (background subtraction issues).[38] The new method calculates the split renal function as the maximum of the obstructed kidney net counts by sequential per minute calculations of the function of that kidney as compared with the sum of the net activity of the normal kidney plus the activity of the bladder.[38]

The quantification of renal function (Fig. 1) is based on the MAG_3 accumulation and discharge (excretion, measured indirectly by the RCA) ratio and it is expressed as an equivalent of the serum creatinine levels (MADRE). It is calculated as the ratio of the MAG_3 weighted 2-kidney activity at 1 to 2 minutes (A) divided by the product of the weighted entire abdominal background (B) as multiplied by the average of the 2 kidneys residual cortical activity (RCA′):

$$\text{MADRE} = \text{A}/\left(\text{B} \times \text{RCA}'\right)$$

It is expressed in terms of plasma creatinine levels (Cr) using the following formula[37]:

$$\text{Cr}^2 = 9/\text{MADRE}$$

Variations of the Protocol

Single-visit baseline and ACE inhibition (ACE-I) studies for diagnosis of RVH.[22,23,42] In the adult the baseline study is performed with 1 mCi MAG_3 and the ACE-I study with 9 mCi MAG_3. The furosemide is split equally between the baseline and the ACE-I study and injected simultaneously with the 2 administrations of the radiopharmaceutical. After completing the baseline study, the patient empties the bladder, and a

Texas catheter or a diaper is applied. Provided the systolic blood pressure is at least 140 mm of mercury, a dose of 2.4 mg of enalaprilat is infused IV, followed by the provocative study 5 minute later. (In exceptional cases 50 mg of captopril is given orally and, 1 hour later, the provocative study is acquired.) The patient is supine and the blood pressure is monitored. The mode of acquisition is the same as described above. For pediatric use the minimum MAG_3 dose for the baseline study is 0.2 mCi and for the ACE-I study 2 mCi; the dose of furosemide 1 mg/kg is split equally for the 2 injections. The pediatric dose of ACE-I is 0.7 mg/kg captopril or 0.03 mg/kg enalaprilat.

SPECT-MAG_3 Study

Tomographic studies with MAG_3 can be performed with the use of a triple-head SPECT camera with a double dose of MAG_3 and an acquisition time of 4 minutes.[21] To visualize only the functioning parenchyma (analogous to DMSA images), one 4-minute acquisition suffices, and furosemide is not needed. Repeated acquisitions after Furosemide may provide 3-dimensional images of the drainage system.

Results

Clinical Experience Using the MAG_3-F_0 Protocol

When this protocol was initiated, new horizons were realized for prompt, easy, and reliable evaluation of renal drainage, but moreover for the optimal evaluation of function of the renal parenchyma. In addition, some misconceptions were exposed and challenged. Henceforth, we will discuss issues related to the application of this protocol for the evaluation of both congenital and acquired renal disorders, with an emphasis on obstruction in both children and adults. Thereafter, the evaluation of renal parenchymal disorders, including RVH, APN, HIV, and renal colic will be addressed. A brief description of the experience in renal transplants will conclude the review.

Safety Issues

During a period of 17 years, and including approximately 30,000 studies, there was only 1 episode of dyspnea after the injection of MAG_3; it occurred in an infant and resolved with the administration of oxygen. There were no serious side effects from the injection of furosemide, even in patients with reported sensitivity to sulfonamides, except for an occasional temporary mild decrease in blood pressure, which spontaneously later rebounded. After use of oral captopril, there were 4 cases of a significant decrease in blood pressure that required treatment. However, there were no problems during the use of IV enalaprilat while following the aforementioned protocol.

Comments on the Method of Diuretic Renography

Before the introduction of diuretic renography, the Whitaker test was the standard method used to diagnose obstruction. The test was invasive and required catheterization of the renal pelvis and the urinary bladder, followed by infusion of NS into the pelvis at a rate of 10 mL/min. An increase in the renal pelvic pressure greater than 10 cm of water from the pressure in the urinary bladder defined obstruction. In addition to the fact that this was quite an invasive method, it also, not infrequently, provided false-positive results because of the fact that the tested kidney had substantially reduced function and under no circumstances could produce 10 mL/min urine. The Whitaker test was replaced by noninvasive diuretic renography, which only required bladder catheterization.[3]

In literature from authors in the United States, diuretic renography is perceived to be performed by injecting the diuretic 20 to 30 minutes after the radiopharmaceutical ($F_{+20\ to\ +30}$), but in the European practice, the 15 minutes before (F_{-15}) method is favored.[46,49] Actually, O'Reilly introduced diuretic renography with injection of the diuretic 30 minutes after the radiopharmaceutical or in repeated studies as early as 4 minutes.[4] In an effort to proceed with the injection of furosemide only if the nondiuretic study showed retention, the 20- to 30-minute protocol was favored. When it was later realized that this approach produced false results, the Europeans changed the time of injection of Furosemide to 15 minutes before the injection of the radiopharmaceutical.[46]

However, in practice one can inject the diuretic simultaneously with MAG_3 (MAG_3-F_0) and obtain similar results as the other 2 methods. Moreover, the MAG_3-F_0 method is superior because acquisition time is decreased by 15 to 20 minutes, interruptions for bladder voiding are minimized (compared with F_{-15}), and radiation exposure to the patient is reduced (compared with $F_{+20\text{-}30}$). Additionally, this method only requires the temporary placement of a "butterfly" line at the time of the injections rather than the need to secure a vein catheter, a fact very important in pediatric use. Indeed, a comparative study performed at UM and presented at the annual meeting of the SNM provided proof of such advantages of MAG_3-F_0.[43] This research was based on a single injection of 40 mg of furosemide given at T = 20 minute after 1 mCi MAG_3 (F_{+20}), while at the same time (20 minutes) a regular dose of HIP was injected and a full acquisition at a different peak for 22 minutes was initiated (F_0) and finally, 15 minutes after the injection of furosemide, a large dose of 9 mCi MAG_3 was injected and acquisition was completed 20 minutes later (F_{-15}; Fig. 2). A case of such a triple study is presented in Figure 2 indicating that the F_0 method is as good as the F_{-15} and certainly much better than the F_{+20}, which in this particular case, produced a false positive renogram. The results of this research project indicated that the three protocols were equally useful for the diagnosis of obstruction; however, the time required to complete the F_{+20} was 30 to 40 minutes, for the F_{-15} was 40 minutes, whereas 22 minutes was sufficient for the F_0 (Fig. 2). A summary of the results of this study is presented in Table 1. The most important finding, however, in applying the F_0 protocol was the fact that it also facilitated functional evaluation of the renal parenchyma (Fig. 3).[43]

The Drainage of the Cortex Makes or Excludes the Diagnosis of Obstruction[27,34]

Until the present time, there has been a firmly rooted concept in the nuclear medicine literature that it is essential to study the

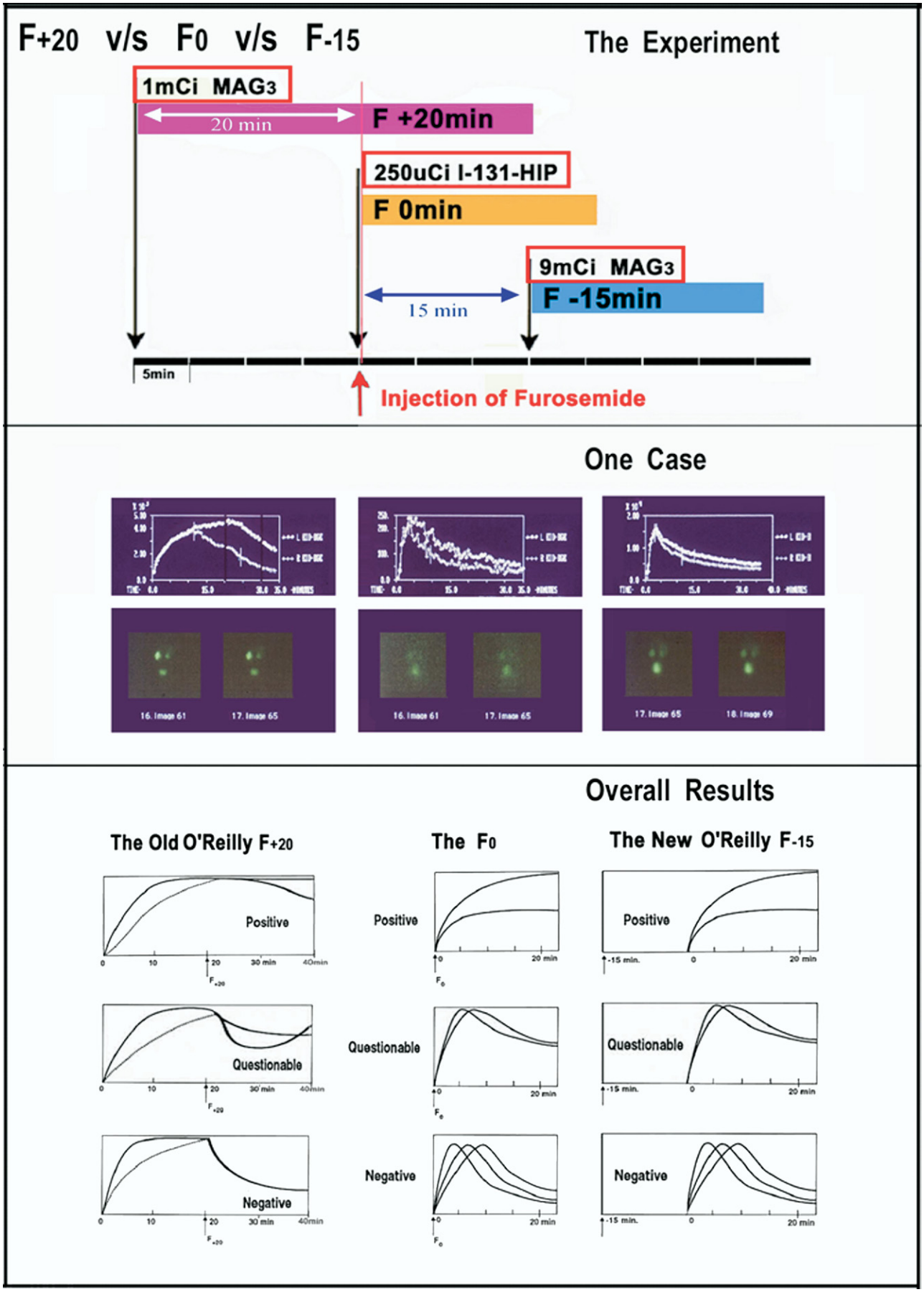

Figure 2 Experimental comparison of the three different times of injection of Furosemide (F_{+20}, F_0, and F_{-15}). (Color version of figure is available online.)

Table 1 Zero Time Injection Diuretic Renography (F_0)

It is at least as accurate as $F_{+20/30}$ and F_{-15}
Better tolerated (shorter; one injection)
Fewer interruptions in adults for voiding
Cost effective (concluded in 25 minutes)
Reduces the radiation exposure of the patient
Allows the evaluation of the parenchyma

entire drainage system of the kidney to make or exclude the diagnosis of obstruction.[3] Although the behavior of the cortex has always been evaluated, it was never considered important for the diagnosis of obstruction.[3] Even a normal renal cortical renogram was considered only tangential evidence that relief of the obstruction (when the drainage system showed retention) will result in preservation of renal function.[3,50] On the other hand it is a well-known fact that diuretic MRI studies use regions of interest placed on the renal cortex.[51]

In reviewing thousands of MAG_3-F_0 studies, however, and observing the behavior of the renal parenchyma (cortex mostly), for which this method optimally allows, and by obtaining follow-up studies in more than 100 patients, it became evident that if the cortex drains there is no functional obstruction, irrespective of the drainage of the collecting system.[27,34] Since then, more emphasis has been placed on scrutiny of the cortex: If enough of the cortex can be seen to visualize its drainage (unaffected by the imaging effect of the collecting system), its degree of emptying (in comparison to the cortex of the contralateral kidney) assumes diagnostic significance. The results were crucial especially for cases of extra-renal pelvis, in dilated ureters including vesico-ureteral reflux (VUR) and postoperatively after (endo)-pyeloplasty (Fig. 4). Careful placement of the ROIs provided diagnostic and supportive renograms of the cortices. Therefore, in cases of abnormal total kidney renograms and before diagnosing obstruction, a thorough visual analysis of the images, perhaps supported by appropriate normal cortical renograms, may save some patients from further painful evaluations and even unnecessary surgery (Fig. 4). This experience has been presented at the SNM Annual meeting and data from more than 1 year of follow-up studies in dozens of patients showed preservation of status and function of such kidneys.[34] In neonates with dilated nonobstructed pelvices, normal emptying of the cortices results in a downsloping total kidney renogram with good prognosis for spontaneous normalization (Fig. 4).[27]

Imaging the Kidneys of the Newborn, the Infant, and the Child

Normal Studies

There has been a misconception that the kidneys of a newborn cannot be imaged with MAG_3 and that we need to

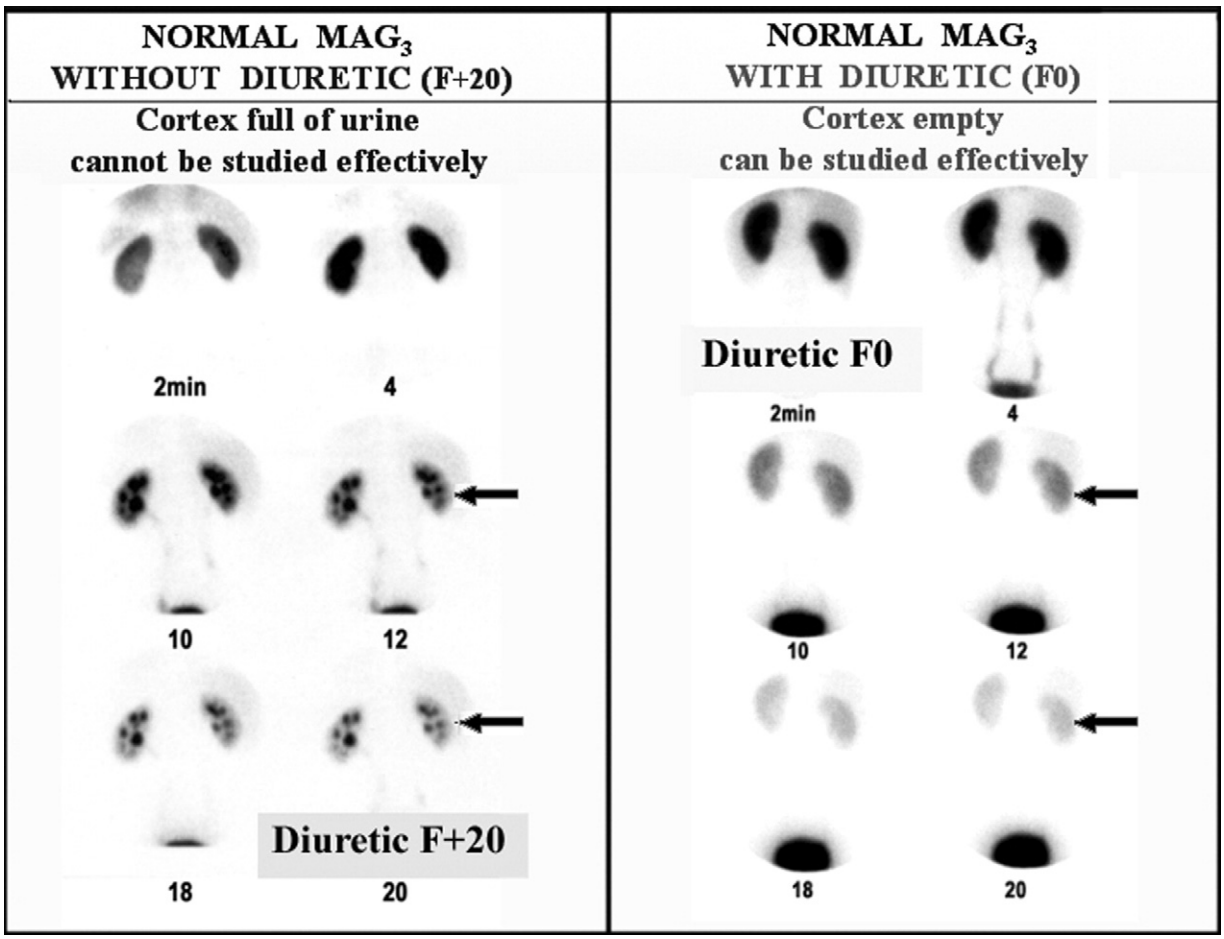

Figure 3 MAG_3-F_0 method allows the functional evaluation of the renal cortex (parenchyma).

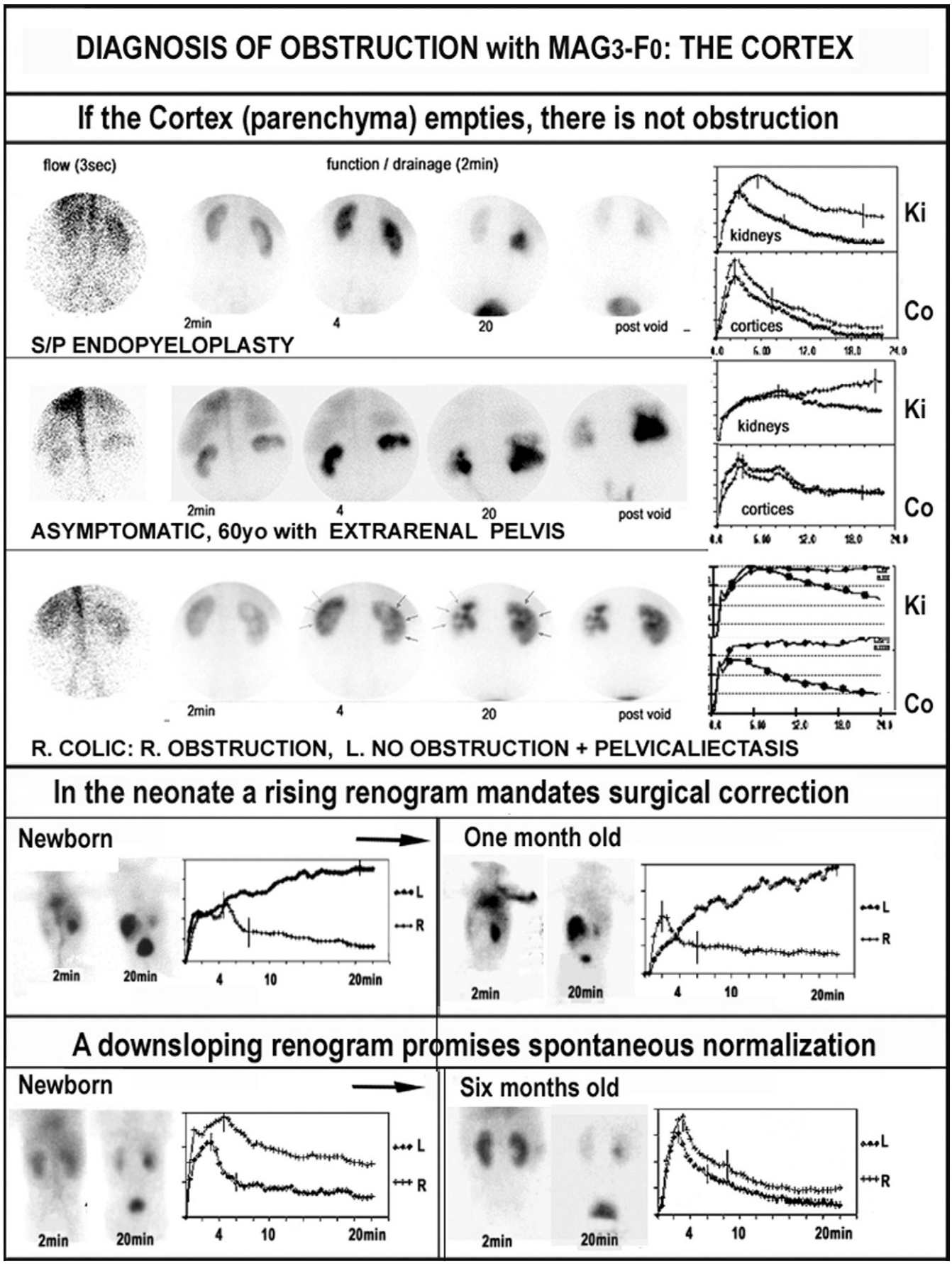

Figure 4 The behavior of the cortex makes or excludes the diagnosis of obstruction.

catheterize the urinary bladder to perform a diuretic study. The fact is that MAG_3-F_0 works in the newborn as well as in the infant and the child. The sponsoring company, however, did not pursue FDA approval for newborns and MAG_3 has to be used off label. Urinary bladder catheterization is not necessary. Observations in more than 500 newborns and in many more infants indicate that during the 22-minute period after the IV diuretic is administered, infants usually empty the urinary bladder at least once or twice. Even in cases when children with nonobstructed kidneys do not empty the bladder, the kidneys still empty entirely while the bladder remains full during the study, to empty later. Of course, normal newborn studies show increased cortical retention of MAG_3 (RCA 30-40%) due to renal immaturity. In full-term infants, the normal study with MAG_3-F_0 becomes similar to the adult by the age of 2 to 3 months (peak time 2-3 minutes and RCA <20% of the peak) (Fig. 4; 6 months old).[27]

Perinatal Complications

MAG_3-F_0 is successful in uncovering perinatal renal complications such as ATN and RVH. The case of perinatal ATN in Fig. 5 is that of a newborn delivered by a diabetic mother after a prolonged difficult labor; renal ischemia during delivery resulted in reversible renal damage, ATN, as the scan indicated. In Fig. 6, a case of RVH in a neonate is included; it was the result of renal ischemia caused by a thrombus, which developed around an umbilical artery catheter needed for therapy; this destroyed one kidney and rendered the other kidney ischemic, resulting in RVH. The baseline and the ACE-I MAG_3-F_0 study were diagnostic. Such patients, if treated for hypertension with ACE-Is, will develop renal failure.[7,10,23]

Congenital Renal Insufficiency/Failure

Cases of bilateral renal agenesis, bilateral dysplasias, and bilateral obstruction (Fig. 5) require an emergent diagnosis and appropriate treatment and MAG_3-F_0 contributes to the evaluation.[27]

Congenital Nonobstructing Renal Disorders

Usually, after an abnormal renal US, patients are further evaluated with MAG_3-F_0 to obtain an accurate diagnosis with prognostic information. Renal agenesis, horseshoe kidney, ectopia, hypoplasia, dysplasia, prune-belly cases with dilated ureters, are the most common of these conditions and MAG_3-F_0 significantly helps to establish the exact diagnosis and provides prognostic information (Fig. 5).[27]

MAG_3-F_0 in Congenital Renal Obstruction

In cases of obstruction due to uretero-pelvic junction obstruction or uretero-vesical junction obstruction, posterior urethral valves, or ectopic insertion of ureter, as discussed previously, MAG_3-F_0 experience suggests that the best way to detect obstruction is to evaluate the drainage of the cortex.[27,34] In the neonate however, because of resolution limits, when there is a dilated collecting system the renal cortex cannot be effectively differentiated from the collecting system of the kidney and the evaluation of the renal parenchyma is not usually possible. In addition, the immaturity of the kidney does not allow adequate perception of the drainage of the renal cortex in question. Therefore, the decision regarding obstruction with MAG_3-F_0 should follow the traditional manner of evaluating the overall kidney, parenchyma and collecting system together. The resulting renogram can be upsloping, plateauing or downsloping. By performing follow-up studies and evaluating the function of the potentially obstructed kidney by 3 months of age, it was possible to define whether or not the patient had obstruction. The retrospective analysis of this data indicated that all the cases with upsloping renograms at birth showed deterioration and loss of function at 3 months, with subsequent need for intervention to alleviate obstruction. The delay in intervention (3 months), however, resulted in permanent loss of renal function. Therefore, an upsloping renogram is an indication for early intervention. However, a downsloping renogram was always associated with spontaneous recovery without the need for surgery (Fig. 4). Cases with plateauing renograms need close follow up because some of them respond spontaneously while others require surgery. The results of this analysis were published in the *Journal of Urology*.[27]

Evaluation of Congenital Renal Diseases (CRD) in the Post-Newborn Age

MAG_3-F_0 is a reliable and efficient method to study patients with CRD after the newborn period. Actually, the test is more successful at this age because the kidneys are larger, more mature, and the properties of both the renal parenchyma and the drainage system can be easily appreciated, therefore allowing for a more definitive decision about kidney health or disease.[27]

Follow-Up MAG_3-F_0 Studies

MAG_3-F_0 is a reliable test to follow progression of renal disease or the effect of medical or surgical therapy on renal parenchymal function and drainage (Fig. 4).[27]

Evaluating Acquired Renal Diseases, Parenchymal, or Drainage

MAG_3-F_0 provides the unique opportunity to study the function of the renal parenchyma. At UM, the protocol has been applied in the evaluation of functional parenchymal diseases, those involving the entire kidney unilaterally (RVH, some ATN) or bilaterally (most ATN, and HIV and other nephropathies), as well as those, which involve focal areas of the cortex (APN). At the same time, drainage of the kidney is evaluated (obstruction), as well as trauma and urine leaks, Renal colic, etc, which makes the test even more clinically useful.

MAG_3-F_0 in the Diagnosis of RVH and in the Prognosis of the Effect of Angioplasty on Hypertension[6-19,22,23]

RVH is not the same entity as renal artery stenosis (RAS). RVH is induced when severe RAS exceeds a critical percentage of obliteration of the arterial lumen (>60-70%) and the renin/angiotensin system is overstimulated. Renal ischemia induces enhanced release of renin by the juxtaglomerular apparatus, resulting in overproduction of angiotensin-I from

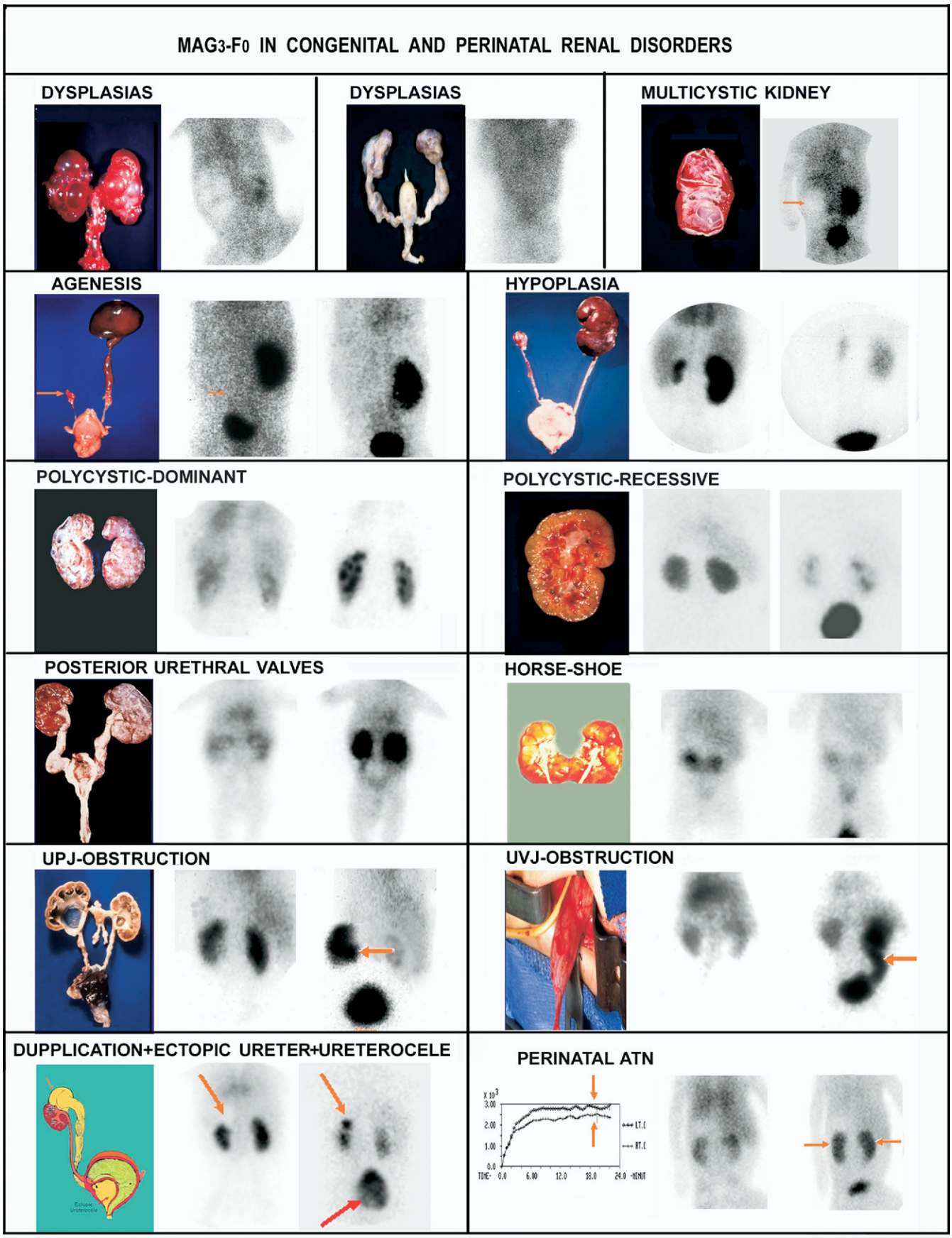

Figure 5 Cases of MAG_3-F_0 studies in congenital and perinatal renal disorders.

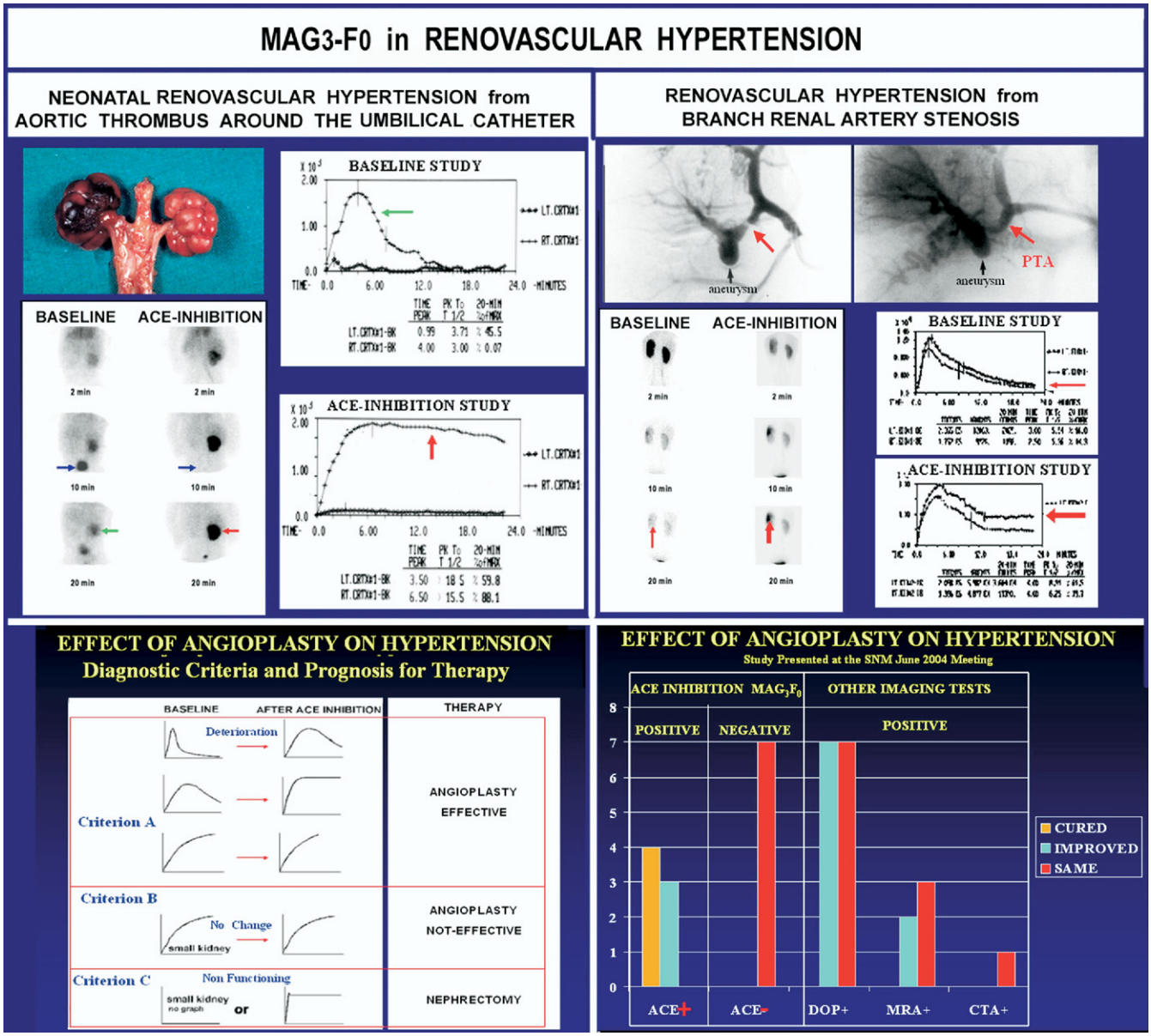

Figure 6 MAG_3-F_0 in renovascular hypertension.

the abundant angiotensinogen. This in turn produces high levels of angiotensin-II, which results in preferential efferent arteriolar vasoconstriction in an effort to maintain glomerular filtration (GF), yet peripherally this induces RVH.

ACE-I scintirenography enables the diagnosis of RVH by blocking the production of angiotensin-II and decompensating renal function (GFR reduction). A positive ACE-I MAG_3-F_0 study provides the diagnostic information for RVH and prognosticates the success of intervention in ameliorating or curing hypertension. If the patient has hypertension, which is not of renovascular etiology (essential or renal), ACE-I MAG_3-F_0 is negative.

Beyond a certain degree of arterial stenosis (>95%), there is no GFR compensation, and renal damage from long-standing severe RAS results in a small kidney, which is not compensated and hypertension is renal, not renovascular. In such cases, MAG_3-F_0 is abnormal at baseline but there is no deterioration with ACE-Inhibition, therefore the test is negative for the effect of ACE-I but with persistent unchanged abnormal renograms.

The protocol for the diagnosis of RVH requires a baseline (BSL) and an ACE-I study as discussed previously. It is performed after the discontinuation of long-acting ACE-Is for 3 days (enalapril) or overnight for short acting ACE-Is and other antihypertensives. During the examination, an IV should be in place running NS, and blood pressure should be monitored. The criterion for a positive study is determined by the effect of ACE-I on the renal function. According to the criteria established by the SNM, an increase in the RCA by 10% from the BSL is diagnostic of RVH (Criterion A). An increasing BSL renogram, however, without evident effect of ACE-I, may signify a >95% RAS (Criterion B), whereas a nonfunctioning kidney may indicate obstruction of the renal artery (Criterion C; Fig. 6). Angioplasty would not be effec-

tive in combating hypertension when ACE-I MAG_3-F_0 results in Criteria B and C (Fig. 6).[35]

Criteria A through C have been studied at UM in a retrospective review of the effect of angioplasty on hypertension in hypertensive patients, who had ACE-I MAG_3-F_0 and other tests. Results were presented at the SNM Annual Meeting 2004. On the basis of this analysis, the predictive value of MAG_3-F_0 ACE-I was found to be 100%, whereas ultrasonography, CT angiography, and MR angiography, although accurate in making the diagnosis of RAS, had less than 50% accuracy in predicting effect of angioplasty (Fig. 6).[35]

ACE-I MAG_3-F_0 is also successful in studying hypertensive neonates to diagnose RVH from umbilical artery thrombus and children with hypertension in an effort to indicate RVH, as in the child with branch RAS (Fig. 6).[22,23]

Diagnosis of Acute Pyelonephritis with MAG_3-F_0

Among nuclear practitioners not familiar with the MAG_3-F_0 protocol, there is a misconception that 3 to 5 hours delayed imaging after injection of DMSA (or even GH) must be used to detect acute pyelonephritis (defects without parenchymal loss) and scars (defects with parenchymal loss). However, in native kidneys and in renal transplants, the 22-minute protocol (MAG_3-F_0) can diagnose APN by showing a region of decreased activity at 2 minutes, which develops into an area of focal parenchymal retention of the activity at 10 to 20 minutes, ie, "regional parenchymal dysfunction" (RPD; Fig. 7). As proven comparatively at UM, MAG_3-F_0 is equally sensitive and more specific than DMSA in diagnosing APN by visualizing the RPD, which is characteristic of APN and differentiating APN from scar, which is a focal defect without RPD (Fig .7). This comparative study was performed in 85 children and published in *Radionuclides in Nephro-urology* in 1997 and in the *Journal of Nuclear Medicine* in 2000.[20,25] Characteristic cases are presented in Figure 7. There are disadvantages of DMSA and glucoheptonate in imaging for APN (eg, uncertainties about the defects, resulting in an agreement rate of only 80% among readers in the European analysis). The DMSA study requires 2 visits and 4 to 5 hours to complete, and it is difficult with DMSA to differentiate APN from scars (both appear as focal defects) because small scars may not show parenchymal loss and the size and contour of the kidneys vary. MAG_3-F_0 cannot only differentiate between scars and APN, but it may also show the coexistence of a scar and APN as well as very small areas of APN (Fig. 7).

MAG_3-F_0 in the Diagnosis of Diffuse Parenchymal Disease (DPD)

For the native kidney or the renal transplant, in children and adults MAG_3-F_0 can differentiate between ATN and acute and chronic DPDs of the kidneys and can serve this purpose in the patient who is admitted with renal failure of obscure etiology. Characteristic cases of ATN, acute renal failure caused by nephrotoxicity, chronic renal insufficiency, and HIV nephropathy are presented in Fig. 8.[24,36] The differentiation is based on the relative preservation of renal blood flow as in ATN and on the size of the kidneys (normal in acute problems: small or atrophic in chronic problems). MAG_3-F_0 is also useful in prognosis for recovery of renal function (high levels of activity retention) and for the follow-up of these patients to evaluate the effect of treatment (with quantitation of GRF).

MAG_3-F_0 in Renal Colic

A common misconception is that evaluation with noncontrast helical computed tomography (HCT) alone is sufficient to stratify renal colic patients who require emergent intervention. This is based on the HCT presence, location, and size of renal stones with some help from secondary signs such as fat stranding, dilation of the collecting system, etc. Three studies at UM, done retrospectively and prospectively, indicated that only MAG_3-F_0 could correctly identify if there is currently obstruction and its degree (total, partial [severe or mild]) or if there had been obstruction recently, but the kidney was spontaneously decompressed ("stunned kidney"; Fig. 9).[26,28,39]

The "stunned" kidney is characterized by varying degrees of decreased flow and function, continuous accumulation and retention of activity in the parenchyma and production of dilute urine; it requires an overexposure of the image to produce adequate visualization of the drainage system (Fig. 9). This condition is due to the cortical ischemia present in obstruction; post spontaneous decompression appears on MAG_3-F_0 as an image similar to acute tubular necrosis (of course unilateral); it takes approximately one week for the kidney to return to its previous state (Fig. 9).

In one of the aforementioned studies at UM (the retrospective), which included 80 patients, when HCT was positive, MAG_3-F_0 indicated that only 24% had total obstruction and 32.5% partial, whereas in 43.5% of cases there was no obstruction, either because there had never been one (21%), or the kidney was in the post spontaneous decompression state (stunned; 22.5%). However, among the cases that were negative by HCT some had obstruction (translucent stones and retroperitoneal fibrosis). Additional facts from published data show that even stones less than 4 mm may not be spontaneously discharged.[52] Patients with obstruction by MAG_3-F_0 (even without pain because of the effect of the analgesics) must be decompressed by intervention to avoid renal damage (Fig. 9).

The prospective UM study, which included 240 patients, confirmed the results of the earlier retrospective study and underscored the appropriateness of stratifying patients with renal colic using MAG_3-F_0. Again, the need for emergent intervention in the obstructed cases to avoid renal damage was demonstrated, because many discharged patients with painless obstruction are noncompliant with follow-up instructions and as a consequence often lose renal function.[39]

Renal Trauma and Urine Leak

Although renal scintigraphy can signify the presence of renal parenchymal trauma, it excels in helping in the diagnosis of urinary leak (Fig. 10).[44] Although it is routinely used for renal transplants for detecting urinary leaks, it is not used in evaluation of native kidneys in abdominal trauma, because other imaging modalities (US, CT) provide information for all the abdominal organs.

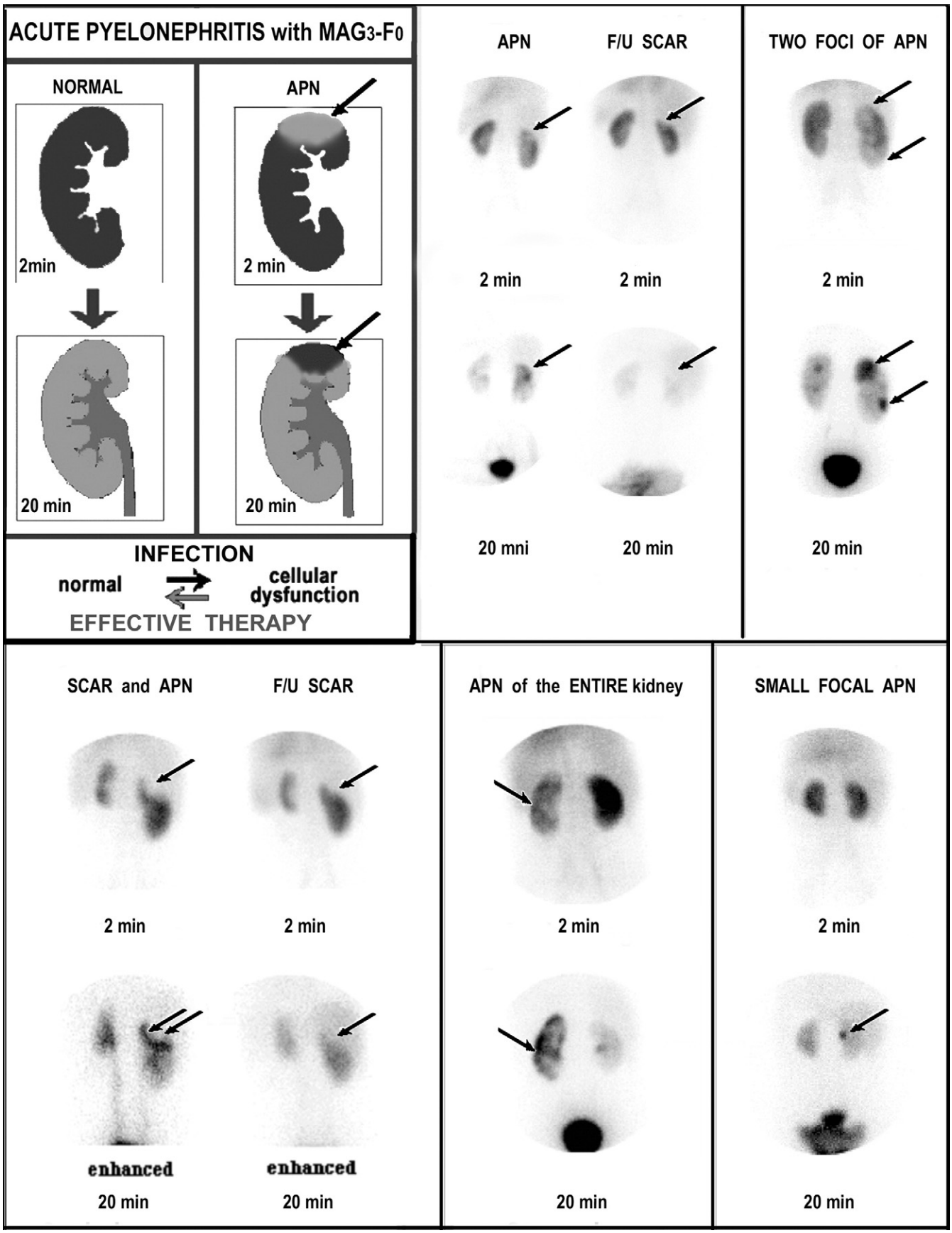

Figure 7 Acute pyelonephritis with MAG_3-F_0: the RPD.

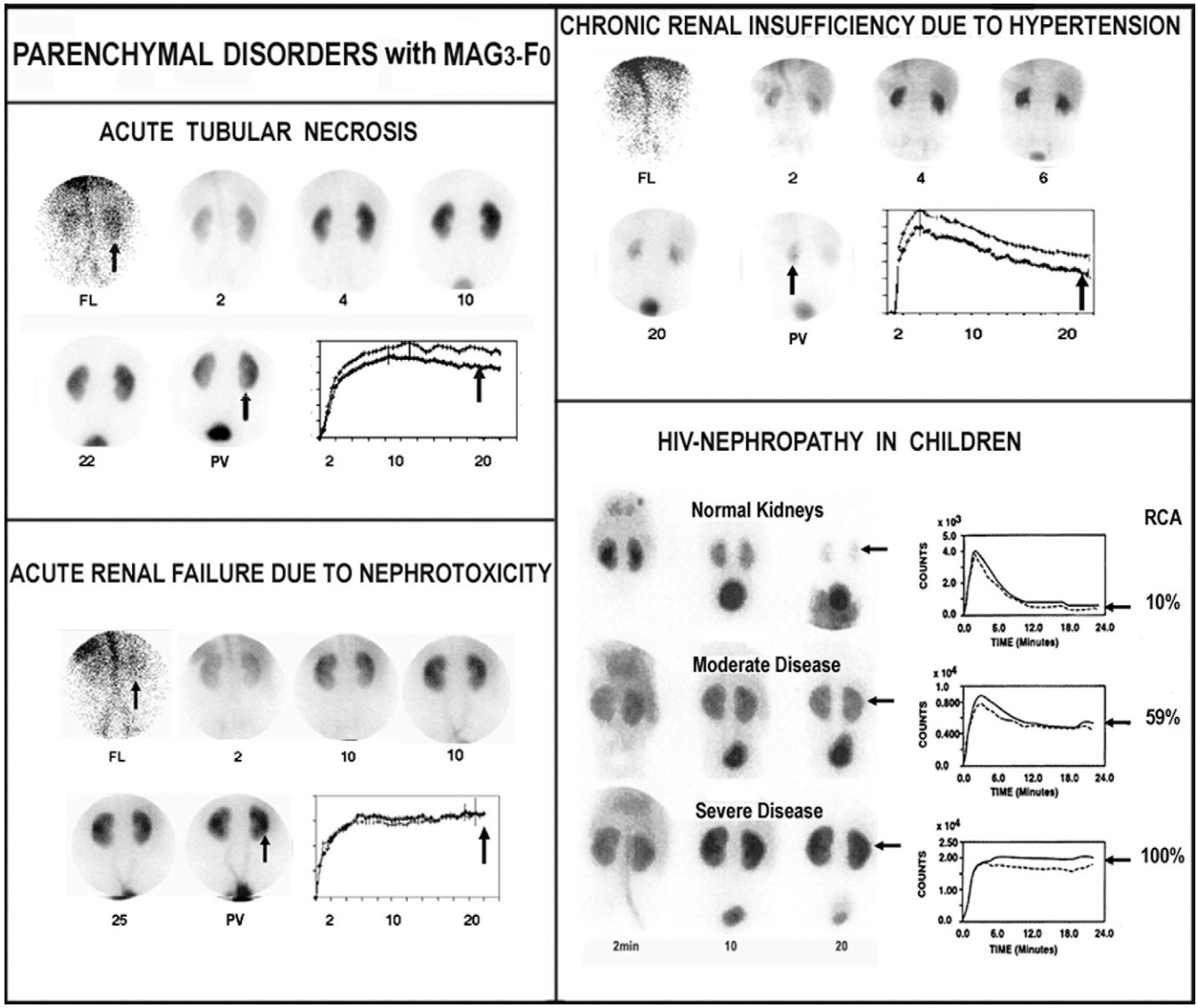

Figure 8 DPDs with MAG_3-F_0.

MAG_3-F_0 in the Evaluation of Complications of Renal Transplants

The MAG_3-F_0 protocol was applied in the study of complications of renal transplants.[29-32] The normal renal transplant is characterized by a normal flow study, with a flow velocity index (FVI) between 0.8 and 0.9, and a normal function study, with a renogram showing RCA less than 20% of the peak activity (Fig. 10: normal). The diagnostic profiles studied in the evaluation of complications of transplants included both anatomical complications as well as functional complications (Table 2).

While we were working on the differential diagnosis of functional complications (ATN, rejection, and toxicity) the different quantification parameters of MAG_3-F_0 were used, such as the FVI, the size of the transplant (number of pixels), the rate of accumulation (AI = K/BKG at 1-2 minutes), the time of the peak activity (Tp), the RCA, and the OCA. Logistic regression analysis of the data of 123 patients with complications and of 15 patients with normal transplants determined that when all parameters (FVI, S, AI, Tp, RCA, OCA) were used, differentiation could be made between the following:

Normal from abnormal (97.8%);
ATN from rejection (81.5%);
Toxicity from ATN (89.4%); and
Toxicity from rejection (81.9%).[31,32]

In current clinical practice more interest is placed on anatomical complications (Fig. 10), because history, clinical presentation, laboratory data, and biopsy are used to differentiate diffuse parenchymal complications (ATN, rejection, and toxicity). On the other hand, a careful review of the MAG_3-F_0 images can usually indicate if any anatomical complication is present (Figs. 8 and 10).

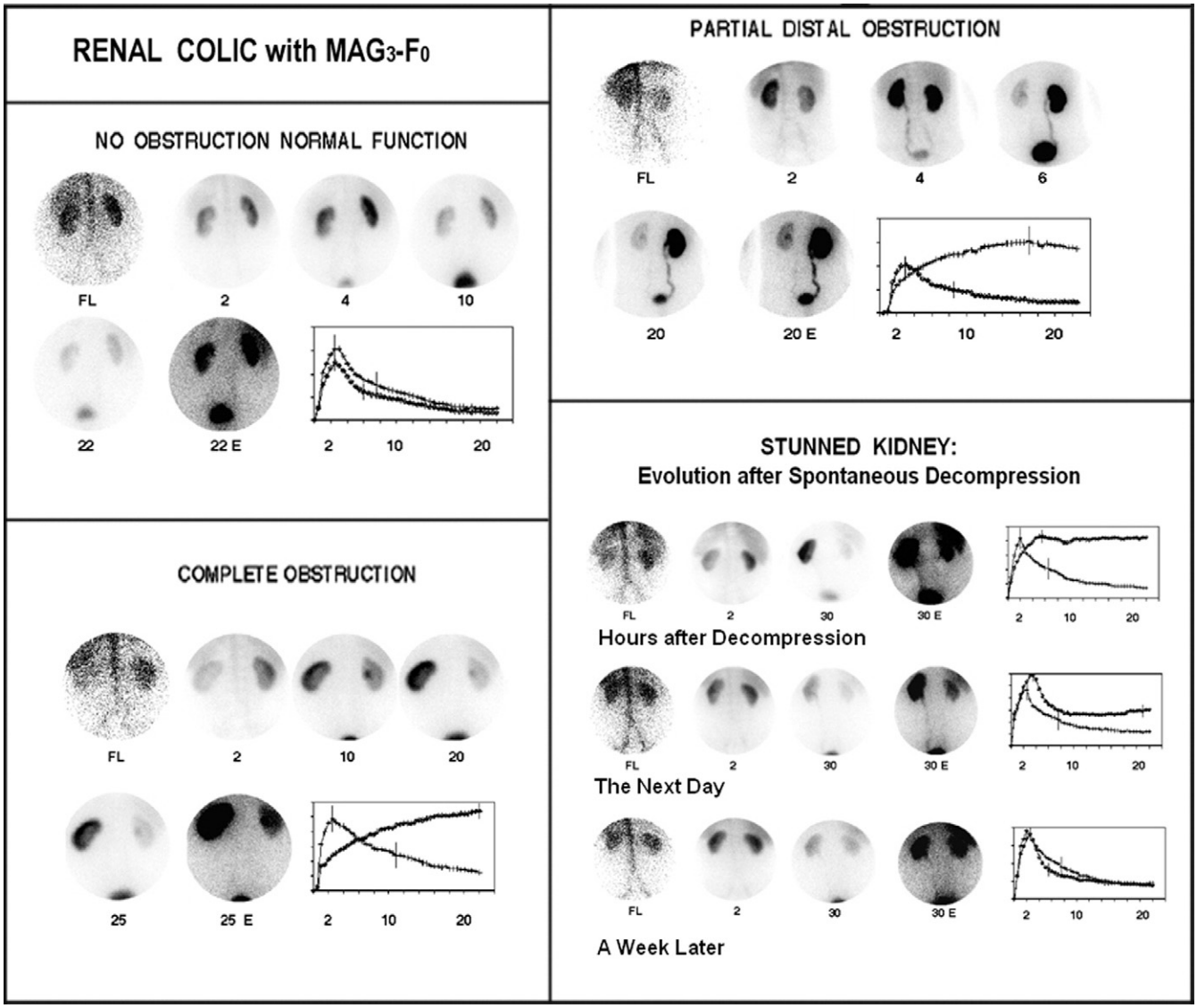

Figure 9 Studies of renal colic with MAG_3-F_0: obstruction and the stunned kidney.

Discussion

The clinical status of "traditional" renal scintirenography (DTPA or MAG_3 $F_{+20\ to\ +30}$, or F_{-15} for drainage and DMSA for APN, etc) is characterized by certain advantages because it provides reliable information about drainage and effectively excludes obstruction and offers useful, albeit limited, information about the function of the cortex.[46-49] However, there are problems associated with this diagnostic approach, which can be summarized as follows: (1) There are too many radiopharmaceuticals and complicated protocols; (2) patient preparation is painful and dangerous (especially bladder and vein catheterization)[49]; (3) the studies are too lengthy (from 40 to 60 minutes, or 4 hours for DMSA); and (4) the inherent limitations of the basic methodology (limited resolution, nondifferentiation of space-occupying lesions, nonvisualization of stones and calcifications) are persistent, whereas the correlative imaging modalities (US, CT, MRI) have substantially improved, not only providing high-resolution diagnostic images but also, more recently, using contrast functional studies of the kidneys.[51] Finally, there is a lack of familiarity about the scintigraphic studies among both referring physicians as well as some user doctors. As a result, renal scintigraphy has always been and still remains underused. Regarding patient preparation and the length of study,[49] characteristic is the testimony of a pediatric urologist, who recited what a father told him: "Better operate on my child than send us for another nuclear study." Those who practice pediatric nuclear medicine had these concerns since the 1970s and 1980s. There has always been a need for a simple and easy protocol.

Because of the aforementioned concerns and after an encouraging experience in the 1970s and 1980s with HIP and furosemide injected at 3 minutes (HIP-F_3) at the Ohio State University[5-12,40,41] the fast (22-minute dynamic), simple and easy protocol was initiated at UM as soon as MAG_3 became available (1990). MAG_3-F_0 replaced the dual protocol followed until then (HIP-F_3 for function and glucoheptonate for

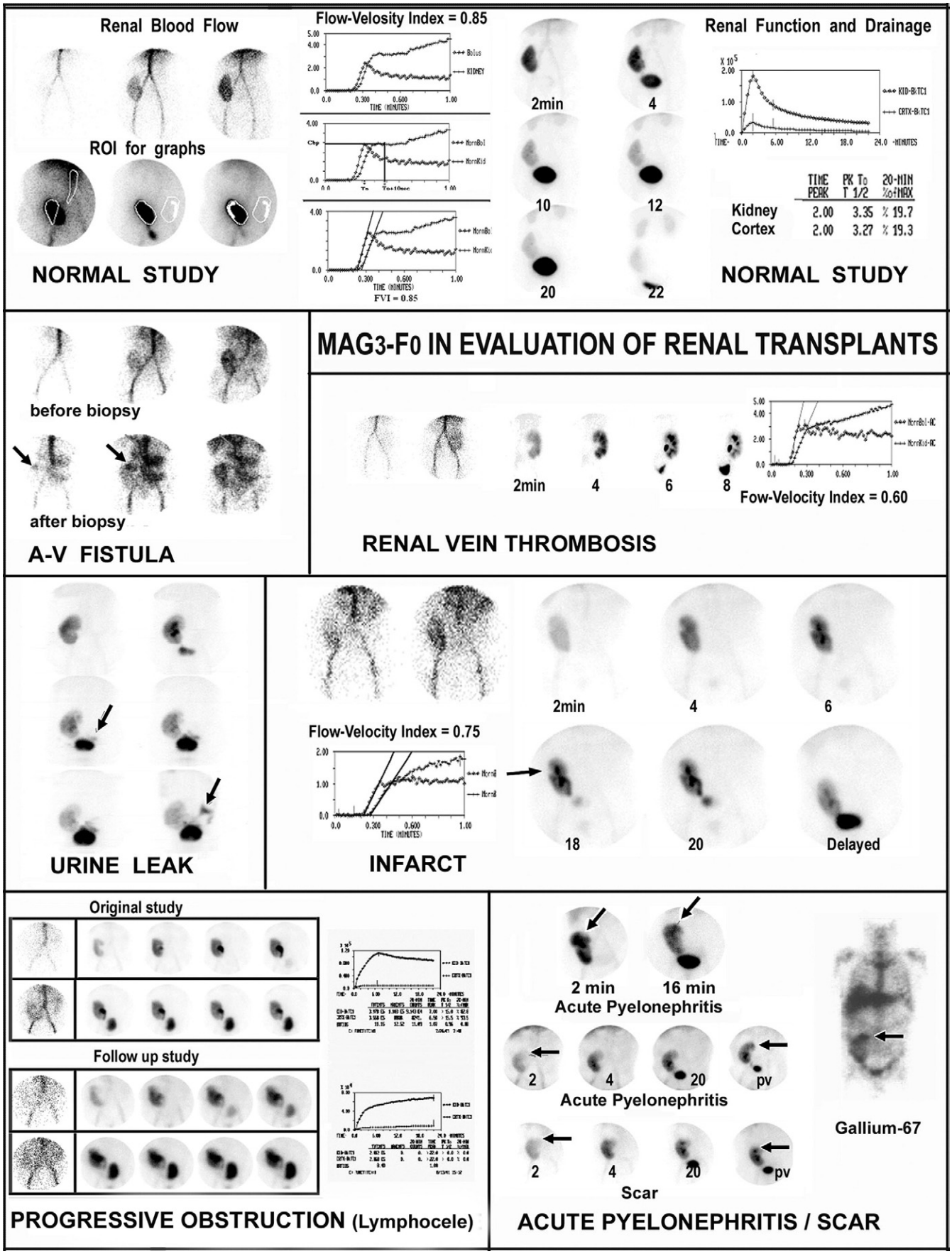

Figure 10 MAG_3-F_0 in the evaluation of renal transplants.

Table 2 Diagnostic Profiles of Complications of Renal Transplants

Anatomical complications
Vascular
Renal artery (branch) obstruction/thrombosis/stenosis
Arteriovenous fistula/pseudoaneurysm
Renal vein thrombosis/stenosis
Parenchymal
Acute pyelonephritis/abscess
Branch arterial obstruction/Infarct
Trauma, tumor, cyst, focal bleeding/hematoma
Drainage
Obstruction, urine leaks, lymphocele
Functional Complications
Postischemic and contrast media damage (ATN)
Rejection acute (interstitial, vascular), chronic
Cyclosporine and other toxicities
Recurrence of parenchymal disease
Diffuse infection (microbial and viral)
Regional dysfunction:
Infection, ATN, rejection, branch RAS, toxicities

imaging renal parenchyma).[16,17] The 22-minute dynamic protocol called for the simultaneous injection of MAG_3 and furosemide (MAG_3-F_0) after oral hydration and without bladder catheterization.[42-44]

During the next 8 years this protocol not only provided a reliable way to evaluate patients for obstruction and renovascular hypertension (RVH), thus continuing the HIP-F_3 experience,[5-18,29,40,41] but also opened a new world that facilitates the study of focal or diffuse diseases of the renal parenchyma (based on cortical activity accumulation and discharge). These new applications helped in the diagnosis and follow-up of a variety of DPD as well as that of APN, revealing the "regional parenchymal dysfunction," characteristic of APN. Since 1998, at UM, the same protocol has been employed for all indications, in all ages and renal function statuses. This helped evaluate and follow-up drainage disorders (congenital and acquired), parenchymal diseases and, of course, helped differentiate complications of renal transplants. In addition to studying APN, RVH and DPD, it has been used in the study of renal colic, unraveling the syndrome of "stunned kidney," the dysfunctioning spontaneously decompressed kidney. It served the vast majority of cases and provided diagnostic and prognostic information. It was embraced by clinicians and surgeons at UM and resulted in a large number of referrals (up to 15 studies per day), which further enriched the experience in individual applications as documented in a number of publications.[19-28,30-39,42-44]

Considering the new interest developed in the evaluation of renal obstruction by observing the behavior of the renal parenchyma, higher resolution cameras may be needed for more successful results and even sequential quantitative high resolution tomographic studies to better identify and study the renal cortex.

The MAG_3-F_0 protocol was successful in the vast majority of referrals. In some exceptional cases, results may have required follow-up studies (eg, in newborns with horizontal renograms). Given the availability of US and prophylactic treatment of infection, such a follow-up was considered "reasonable" and given the "easy" MAG_3-F_0 method quite acceptable.

The successful clinical applications of MAG_3-F_0 described herein contributed to the popularity of this protocol at UM. Patients experienced only minor discomfort having this study and parents did not complain of the suffering of their children. Referring physicians were satisfied with the broad results and promptly participated in publications about individual applications of MAG_3-F_0. Renal scintigraphy does not appear threatened by the advances of correlative imaging, because MAG_3-F_0 is fast, effective and successful in the vast majority of current cases referred to the nuclear medicine laboratory. MAG_3-F_0 is the much sought after fast easy protocol for evaluation of the "functional anatomy" of the kidneys in all ages, for all indications and under all renal functional conditions.

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