

Renal Scintigraphy Following Angiotensin Converting Enzyme Inhibition in the Diagnosis of Renovascular Hypertension (Captopril Scintigraphy)

Renovascular hypertension (RVH) may be due to unilateral or bilateral stenosis of the main renal artery (RAS), branch arterial stenosis, whole kidney or focal renal infarction, aneurysms, or arteriovenous malformations. Other entities such as hydronephrosis, renal cysts, or neoplasms may produce high renal vein renin hypertension, but they do not belong to the classic group of causes of renovascular hypertension. Clinically RVH is defined as high blood pressure caused by occlusive disease of the renal arterial vasculature, which is potentially curable by surgery (renovascular intervention or nephrectomy), or transluminal renal angioplasty (1). It occurs in a subset (1%–4%) of the hypertensive population and is due to fibromuscular dysplasia or to atherosclerotic plaque(s). Renal ischemia due to renal artery or aortic thrombosis in the neonate infant (2) or from iliac artery stenosis in patients with a renal transplant also lead to RVH (3).

No historical or physical finding is specific in the diagnosis of RVH. A recent onset of hypertension after the age of 50 yr in a patient with other evidence of arteriosclerosis, or severe hypertension before the age of 30 yr may suggest the possible presence of RVH (1).

Demonstration of causality between a renal arterial lesion and hypertension is essential to the diagnosis of RVH. Angiography is the accepted method for the diagnosis of RAS, however, demonstration of an anatomic abnormality does not indicate RVH. Similarly, angiographic findings of RAS do not predict the effect of renal arterioplasty on hypertension (1).

Urography (IVP) has an unacceptably high (up to 58%) false-negative rate in diagnosing RVH. Conventional radio-nuclide scintigraphy (without pharmacologic intervention) may indicate the existence of RAS, but the sensitivity is low and the specificity unacceptable (3).

Differential renal vein renin determinations are used in the evaluation of RVH. An elevated renal-vein to arterial-renin relationship is diagnostic of RVH. However, the test has a low sensitivity (23%–74%); it is invasive and does not provide anatomical information. Measurement of renin activity in peripheral blood before and after the administration of captopril is not a specific nor a sensitive test and does not provide information about the side of abnormality (3).

The lack of discriminating clinical findings and the inability of "noninvasive" tests to establish a diagnosis of RVH led to the preferential use of the renal arteriography combined with

the measurement of renal vein renin ratio. Percutaneous, transfemoral retrograde arteriography is the standard approach to make the anatomic diagnosis of RAS (1). Digital subtraction angiography (DSA) has a sensitivity of 87.6% and a specificity of 89.5% in diagnosing RAS as compared to conventional arteriography. Measurement of renal vein renin activity (RVR) helps in establishing the causative relationship between RAS and RVH. But these invasive and expensive tests cannot always predict the potential beneficial or curative effect of angioplasty or vascular surgery.

Medical therapy for RVH is currently available and RVH can be treated conservatively. Surgical management is associated with significant morbidity and mortality. Revascularization is very effective in lowering RVH in unilateral or bilateral fibromuscular dysplasia as well as patients with atherosclerotic disease (85% and 80%).

Percutaneous transluminal renal angioplasty (PTRA) has emerged over the last several years as the interventional approach in the treatment of RVH whenever feasible. Compared to surgery, PTRA has a lower morbidity and mortality, and a diminished rate of secondary nephrectomy; it can be repeated, is less costly, and does not preclude surgical revascularization eventually.

With curative modes of therapy available, it is important to select and treat those patients with RVH. A noninvasive test sensitive and specific in predicting the outcome of interventional or surgical therapy would be invaluable for screening and diagnostic purposes. Most tests yield less than optimal results; captopril scintigraphy, however, may prove useful in this setting (5).

PATHOPHYSIOLOGY OF RENOVASCULAR HYPERTENSION AND THE ANGIOTENSIN CONVERTING ENZYME INHIBITORS

Normal renal physiology is depicted in Figure 1. In comparison, significant RAS, defined as involving more than 60%–75% of the lumen of the vessel, decreases afferent arteriolar blood pressure, stimulates pressure receptors and increases renin secretion by the juxtaglomerular apparatus (Fig. 2). A drop in the preglomerular pressure will also decrease glomerular filtration (GF), unless compensation occurs. As renin is secreted, angiotensin I and (since converting enzyme is present) angiotensin II are locally produced; angiotensin II with its preferential action on the efferent arteriole induces post-glomerular vasoconstriction, thereby restoring filtration fraction and glomerular filtration rate (GFR) (Fig. 3) (5).

When angiotensin converting enzyme inhibitors (ACEI) such as captopril or enalapril block the production of angio-

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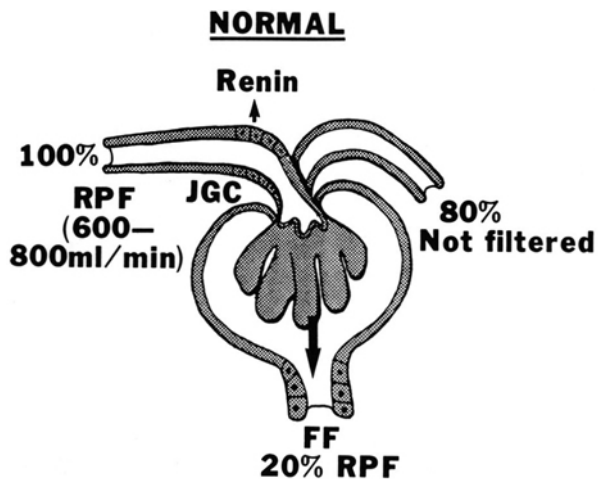


FIG. 1. Normal renal function. Approximately 20% of the renal plasma flow (RPF) is filtered for a filtration fraction (FF) of 0.2. Cells in the juxtaglomerular apparatus (JGE) secrete renin, which maintains homeostasis.

RENAL ARTERY STENOSIS (1)

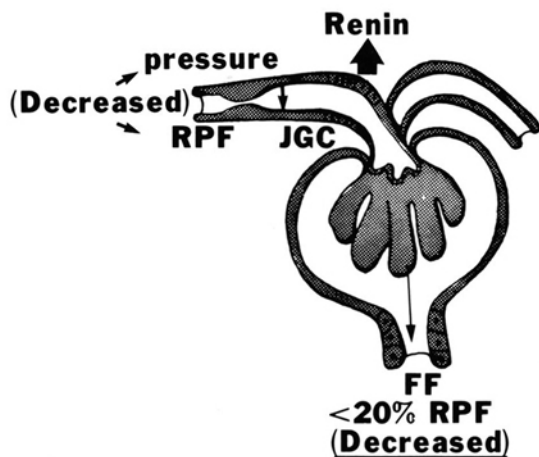
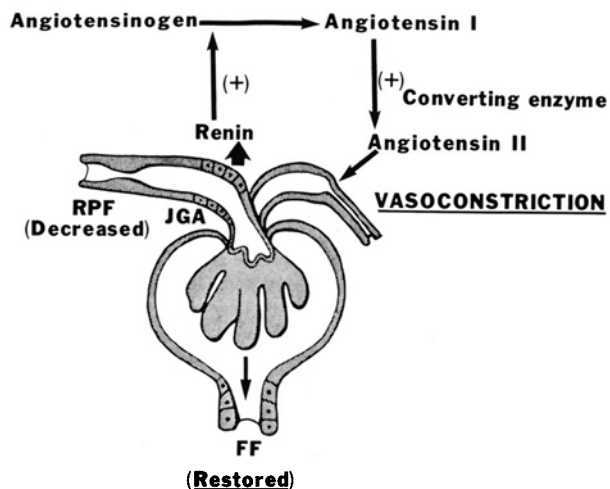


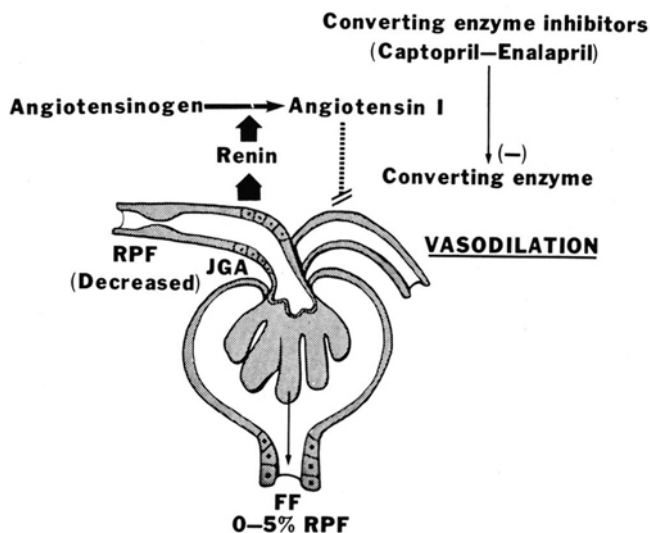
FIG. 2. When RAS occurs (> 60%–70% of the lumen), RPF and pressure distal to stenosis both decrease. This leads to a temporary reduction of FF. Baroreceptors stimulated by the decrease in pressure induce increased renin secretion, which eventually results in compensation (see Fig. 3) if the stenosis is not too tight (> 95%).

tensin II, a further increase in renin secretion and in angiotensin I formation occurs. Lack of angiotensin II results in a post-glomerular vasodilation, a decrease in filtration fraction and a decompensation of renal function, with a drastic decrease in GF (Fig. 4). When ^{99m}Tc -DTPA imaging is performed there is decreased accumulation by the stenotic kidney. Similarly, ^{99m}Tc -glucoheptonate and ^{99m}Tc -DMSA are not filtered and are not available for reabsorption; therefore, they do not accumulate after captopril in kidneys with stenotic arteries, which is evidence that their cortical fixation in normal kidneys takes place primarily or exclusively by reabsorption (5). The magnitude of GFR reduction (or cessation) depends upon many factors such as the systemic blood pressure, the severity of the renal arterial stenosis, the degree of



COMPENSATED Renal Artery Stenosis (II) (DTPA and hippuran studies approach the normal state depending on the degree of stenosis and the compensation)

FIG. 3. The renin angiotensin system compensates renal function by postglomerular vasoconstriction. This restores FF. Angiotensin II, however causes systemic hypertension (RVH).



Captopril Induced DECOMPENSATION

FIG. 4. Converting enzyme inhibitors decompensate renal function by blocking angiotensin II production, which results in postglomerular vasodilatation. Filtration is curtailed or blocked (DTPA not accumulated and/or excreted). The tubular cells accumulate OIH but the activity is delayed or kept in the cortex because of the reduced or interrupted filtration and urine production (see Fig. 6).

the previously effective compensation, and the integrity of the renal vessels.

The tubular cells in this context retain, at least partially, their functional ability since blood flow to the ischemic kidney is not reduced and may even increase after converting enzyme inhibition. Urine production is decreased or even totally curtailed in the absence of GF. This explains why stenotic kidneys do accumulate tubular agents (^{131}I or ^{123}I -OIH or ^{99m}Tc -MAG3). Since there is not sufficient urine production,

the tubular agents remain in the cortex of the kidneys, which explains their cortical retention by stenotic kidneys on captopril scintigraphy (Figs. 5 and 6). These effects of ACEI last only a few hours and are totally reversible without residual damage to the ischemic kidney (5).

In contrast, the contralateral nonstenotic kidney in RVH shows minimal functional changes which are not overall significantly changed after blockade of the renin-angiotensin system.

In bilateral RVH, however, or in a solitary (native or transplanted) kidney with a stenotic artery, and in patients with renal insufficiency and unilateral RVH, ACEI may induce acute renal failure. This side effect lasts while sufficient levels of ACEI circulate. When a single dose of ACEI is given for diagnostic purposes their systemic and renal actions last only a few hours unless severe oliguria is induced when they last longer (2).

There is a variable frequency and severity of impairment of renal function following ACEI in susceptible patients (bilateral disease, single kidney), the degree of which seems to be dictated by the severity of the arterial stenosis.

Severe hypotension may develop as a complication of the ACEI inhibition, even with a single dose of ACEI. This complication occurs in patients with intravascular volume depletion and is responsive to intravenous normal saline infusion. It is advisable, therefore, in conducting provocative tests with ACEI that a vein be available for saline infusion. When anuria develops in susceptible patients (bilateral RVH, single stenotic kidney), administration of vasoconstrictors may rarely become necessary. Angiotensin II is the antidote, a drug very difficult to use and not available commercially (3).

We have introduced the use of furosemide (lasix), which we intravenously inject simultaneously with the tubular agent ^{131}I -orthoiodohippurate (OIH) one hour after an oral dose of

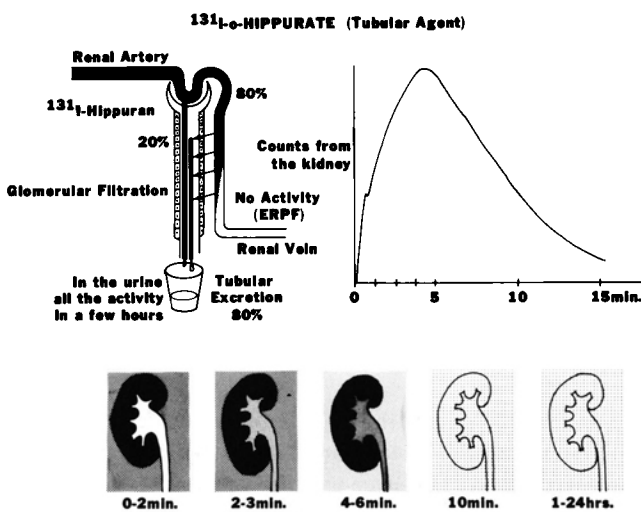


FIG. 5. Normal OIH renography. This may be a normal kidney, a kidney with a subcritical ($> 70\%$) RAS, or a kidney with compensated significant RAS (80% – 95%) in a patient with RVH as in the BSL study of Figure 7.

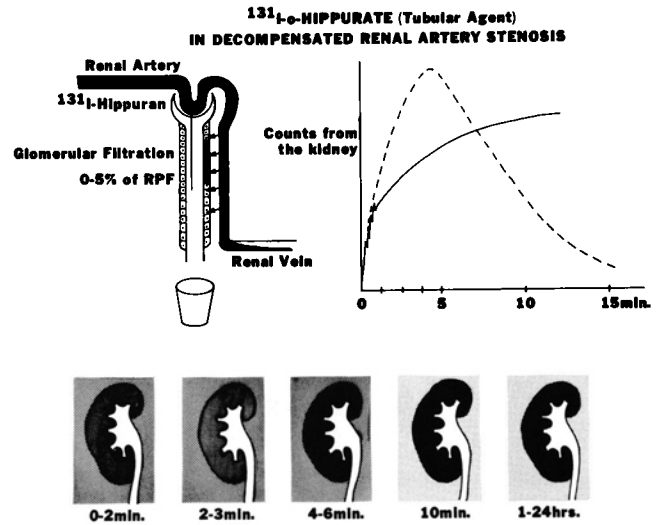


FIG. 6. Abnormal OIH renography (continuous line as compared to normal interrupted line). This can be a captopril decompensated kidney with RAS 80% – 95% (Figure 7) or a BSL study of a kidney with very severe ($> 95\%$) RAS. In the latter case, captopril may further deteriorate the study.

captopril (3). The diuretic is used in an effort to empty the collecting system of the kidney and increase the accuracy of our method. Furosemide, as given in our protocol, acts only by eliminating calyceal and pelvic activity due to its acute diuretic effect (3). This action of furosemide is entirely different from its reported volume depletion effect when injected intraperitoneal in rats 6 hr before performing CAP scintigraphy (6).

TECHNIQUES OF RENAL SCINTIGRAPHY AND RENOGRAPHY

Technetium-DTPA studies performed using 5–10 mCi usually include both a flow and a functional phase. The flow study consists of 1–2 sec images obtained for 1 min and the function study of 2-min images, 30 sec/point graphs, for 20–30 min. Split renal function or split GFR clearance has been used for quantitation of Tc-DTPA studies.

Iodine- ^{131}I -OIH studies (200 – $300 \mu\text{Ci}$) are conducted for 20–30 min with 2-min images and 30 sec/point renograms. Function curves (renograms) for the entire kidney and for the cortex are analyzed by computing upslope, peak and downslope data; a more sophisticated approach employs deconvolution analysis to calculate transit times. We found it sufficient in the investigation of RVH to compute the percentage of the peak cortical activity remaining at 20 min (residual cortical activity, RCA). For both the captopril (CAP) and the baseline (BSL) study, we suggest the use of furosemide (40 mg i.v.) at the beginning of the study (within 3 min of the injection of OIH) to induce diuresis and clear the collecting system, thus decreasing the occurrence of false-positive studies (3,5).

Computation of RCA is performed as follows: A cortical region is carefully assigned for each kidney. The cortical graphs are obtained for a 22-min period. Each cortical graph

consists of 44 points since the acquisition is at 30 sec/frame. For better statistical results, a line is fitted from point 20 (10 min) to point 44 (22 min). The peak activity is found and noted as peak counts (PC). The activity at 20 min is found and noted as residual counts (RC). The 20-min RCA is then calculated using the formula:

$$RCA = \frac{RC \cdot 100}{PC} \% \quad \text{Eq. 1}$$

When the curve is ascending or plateauing, the RCA is 100% and any effect of ACEI can only be determined by calculating the original cortical activity (OCA) using the formula:

$$OCA = \frac{OC \cdot 100}{PC} \% \quad \text{Eq. 2}$$

where OC is the activity of the cortex (counts) at 2.5 min (the fifth point of the cortical graph).

A captopril effect is defined as an increase in the RCA or a decrease in the OCA. The magnitude of a diagnostic effect has yet to be determined for the RCA is currently considered >10% increase from BSL to captopril study.

Technetium-MAG3 studies follow similar protocols and can be analyzed in the same manner as OIH studies.

Technetium-GH studies (5–10 mCi) follow in general the technique of Tc-DTPA with additional delayed images obtained at 4–6 hr. Tc-DMSA (< 5 mCi) is reserved for delayed imaging exclusively (4–24 hr).

Split renal function can be calculated from the computer-generated data by using any one of the above radiopharmaceuticals. GFR and/or ERPF can be measured by established methodology during or following the scintigraphic studies.

CAPTOPRIL PROTOCOL

The efficacy of a single dose of captopril (CAP) for scintigraphic evaluation of RVH has been established (3). In practice, a BSL (without CAP) study can be performed which is followed by CAP scintigraphy; alternatively the CAP study can be performed first. When the BSL study is done first, CAP scintigraphy can be performed the same day (morning-afternoon). When CAP is done initially, then the BSL study should be delayed for at least 48 hr to make certain that captopril is excreted and no longer effective. In either approach, a deterioration of the BSL Tc-DTPA renal function or increase in ¹³¹I-OIH cortical retention associated with ACE inhibition is characteristic of RVH. Scintigraphy can also be performed if the patient is on chronic ACEI therapy without any change any medication; a baseline study then may be performed, if needed, after withdrawal of the medication for 48 hr.

Our approach for CAP scintigraphy is as follows: Medication withdrawal overnight is advisable, and the study should not be initiated if blood pressure is below 140 mm Hg. If captopril is given to patients with low starting pressure (< 140 mm Hg), hypotension with serious consequences may occur. Following oral hydration (10 ml/kg), in patients not receiving ACEI, an intravenous infusion of normal saline is established at the rate of 4 ml/min. Blood pressure is recorded and 50

mg captopril is given orally. Blood pressure is monitored and recorded every 15 min. Scintigraphy is performed one hour after medication when captopril has been absorbed and angiotensin II is not present. If blood pressure falls below safe levels, the administration of normal saline is increased (one liter, or more may be required). Most patients receive 500 ml saline. Approximately 5% of patients may need quicker and larger infusions. Out of 300 studies, we have observed only one newborn baby with bilateral renal ischemia and persistent hypotension after captopril, who required the use of vasopressor drugs, and three patients with orthostatic hypotension at the end of the study, who responded to i.v. saline (5). Lack of appropriate treatment may cause unwanted complications.

CAPTOPRIL SCINTIGRAPHIC PATTERNS

Scintigraphic findings before and after ACE depend on the severity of the disease, on the effectiveness of ACEI in decomensating renal function, and on the functional integrity of the kidneys.

Subcritical Renal Artery Stenosis

Approximately 60%–75% of the renal arterial lumen must be occluded before clinical hypertension (RVH) develops. Subcritical, asymptomatic RAS is associated with normal baseline scintigraphy, which is unchanged by ACE inhibition.

Technetium-DTPA and ¹³¹I-OIH scintigraphy are abnormal in many patients with long-standing essential hypertension and chronic renal insufficiency (CRI) or failure, however, angiotensin converting enzyme inhibition does not affect scintigraphy and may even improve ERPF (3). It is important, to distinguish kidneys whose function is severely impaired due to other than RAS causes from RVH kidneys whose function is reduced because of nearly complete renal arterial occlusion; this distinction is difficult because neither responds to ACEI. Iodine-131-OIH BSL renography is characteristic in that the nuclide continues to accumulate in the cortex resulting in a rising cortical curve in RVH as opposed to plateauing renogram seen in CRI (see below).

Renin-Angiotensin Compensated RAS

With RAS obliterating 60%–90% of the arterial lumen, a rather recent onset of hypertension, and an otherwise normal kidney, BSL scintigraphy may be entirely normal due to a complete compensation of renal function under the local influence of the renin-angiotensin system (Figs. 3 and 5). After administration of ACEI, however, a dramatic suppression of GFR occurs (Figs. 4 and 6).

In these patients, renal blood flow is not further reduced and may often increase, after ACEI. Thus, flow studies of the RVH-associated kidney do not deteriorate and may even improve; the renal blood pool also remains unchanged or is slightly increased (3).

With Tc-DTPA or Tc-GH the effect of ACEI is manifested at 4–6 min by a striking decrease, compared to the BSL study, in the accumulation of renal activity reflecting a marked reduction in filtration of the radioactive material.

With ¹³¹I-OIH studies, the effect of ACEI is manifested by an early (2–4 min) decrease in activity and by a characteristic, pronounced, cortical retention of the radiopharmaceutical at

20 min, at which time the image of the cortex is prominent and the residual cortical activity (RCA) exceeds 30% of its peak value (Figs. 7 and 8); in many cases, the renogram shows a late plateau or may be slowly and continuously rising (RCA = 100%) (Fig. 9). Usually images at 20 min are more intense than at 4 min.

Technetium-GH and Tc-DMSA delayed images are characterized after ACEI by a suppression or lack of any cortical renal radioactivity in this group of patients with RVH (5).

In unilateral RVH the contralateral kidney remains normal, and split renal function changes in favor of the normal kidney. In bilateral RVH there may be positive findings on both sides as clearances decrease in both kidneys. In branch stenosis there are focal findings (3). Technetium-DTPA scintigraphy may occasionally be better than ¹³¹I-OIH for the diagnosis of RVH due to branch arterial stenosis because of better resolution, although ACE inhibition is manifested on OIH studies more convincingly (5).

When renal insufficiency exists, the effects of ACEI are less prominent and difficult to appreciate with Tc-DTPA, because of the associated decreased BSL renal accumulation of the radiopharmaceutical and the high background activity, which make a further decrease difficult to appreciate visually or quantitatively. Similarly, in borderline cases, with a stenosis between 60%–80%, particularly when there is associated im-

pairment in renal function, ACEI induce only a mild reduction in filtration that is difficult to appreciate with Tc-DTPA. OIH has a higher sensitivity because the cortical retention of the activity (RCA) is more easily recognizable and quantitated. A change in OIH RCA >10% suggests RVH (3). Bilateral RAS causing RVH can be missed on Tc-DTPA scintigraphy, but it is easily recognized as bilateral increase in RCA >10% from the baseline values on OIH captopril scintigraphy.

Severe RAS

Severe, (> 90% RAS), RVH is nearly always associated with a significant decrease in renal function and in the size of the affected kidney. Despite a powerful activation of the renin-angiotensin system, its effectiveness in compensating GFR is only partial and incomplete. BSL studies are then abnormal, reflecting that part of the renal function which renin-angiotensin do not compensate (Fig. 9). Technetium-99m-DTPA studies show a decrease in function of the stenotic kidney; OIH renography shows abnormal cortical retention at 20 min (RCA > 30% of the peak or even a rising graph). Following ACEI, there still is a change from the BSL scintigraphy but the magnitude of the change is diminished. Although both Tc-DTPA and OIH show differences, OIH appears more sensitive than Tc-DTPA in detecting small changes from BSL.

As RAS approaches 100%, the BSL renal function may be

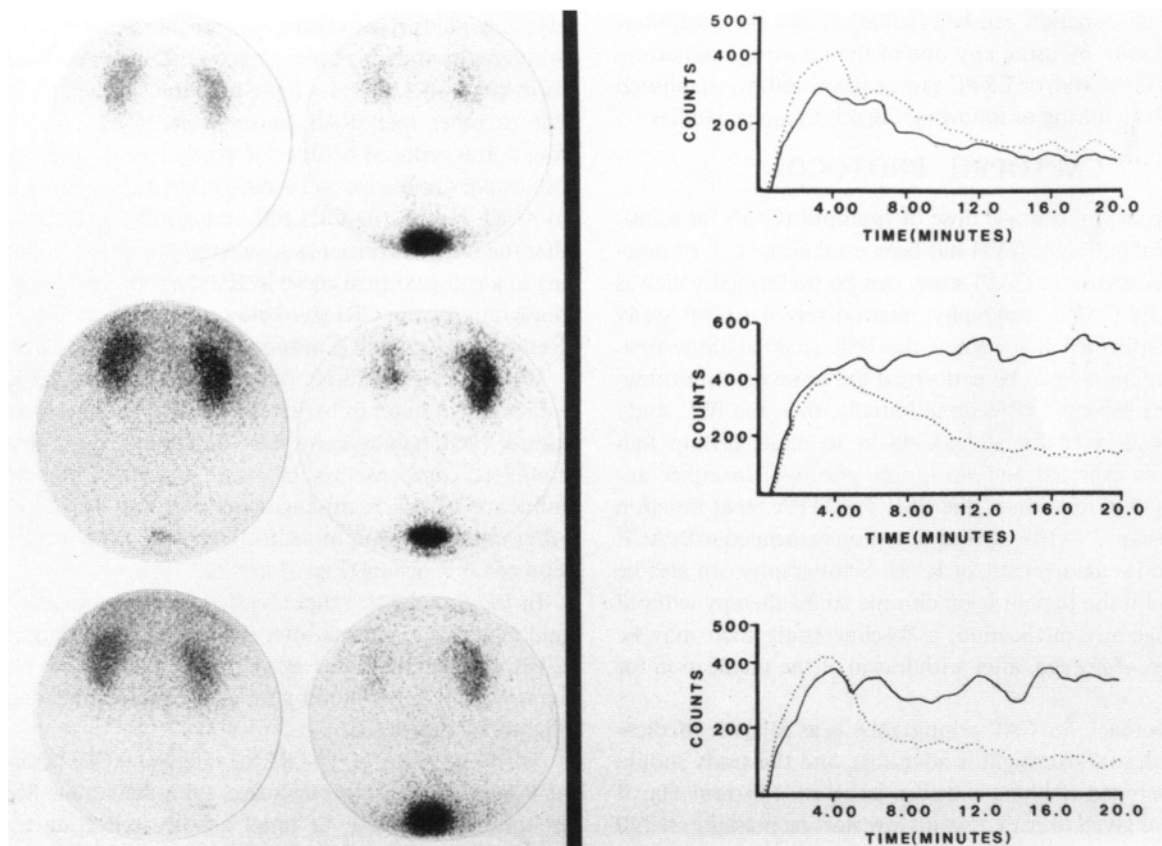


FIG. 7. Iodine-131-OIH renography in a patient with right renal artery stenosis. Left: 2 min, and right: 20 min images. Upper = BSL study; Middle = captopril study; and Lower = captopril and lasix study. Lasix does not influence the true-positive study, but it has diminished the number of false-positive studies by washing out collecting system activity on captopril scintigraphy in patients without RVH. In this patient, ^{99m}Tc-DTPA studies were borderline positive.

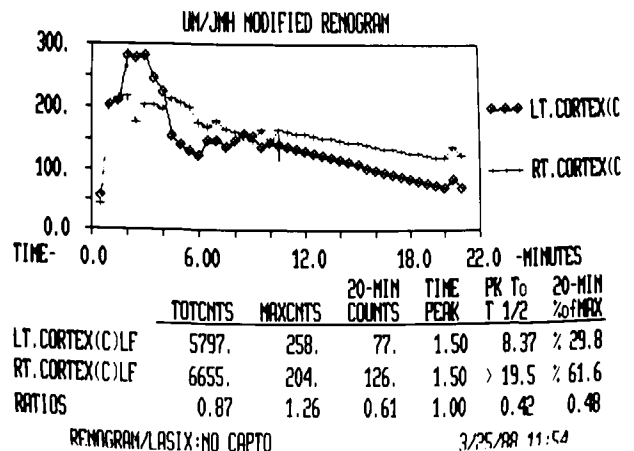
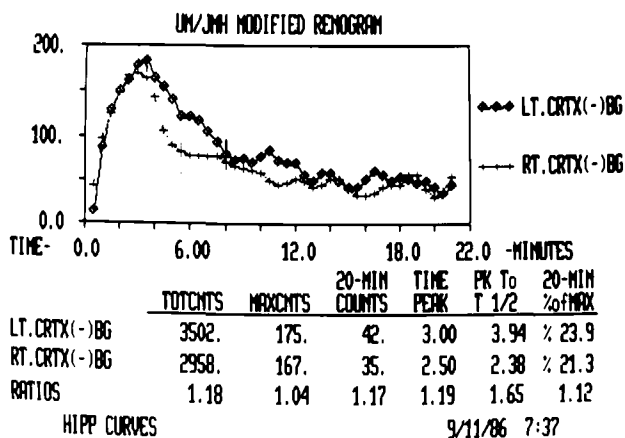
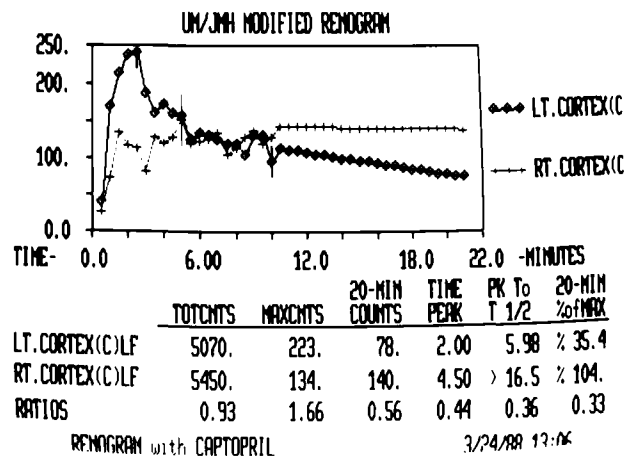
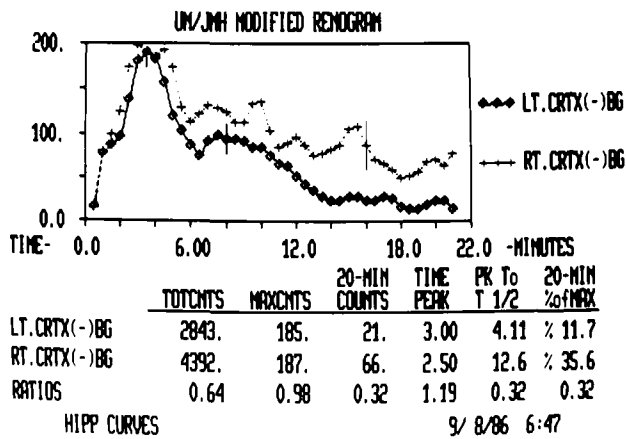


FIG. 8. Cortical renogram with ¹³¹I-OIH (post-captopril, upper, and baseline lower) in a patient with RVH due to unilateral 80% right RAS. BSL was normal and there was a slight but recognizable change after captopril. Notice the statistical fluctuation, which made it necessary to introduce the manipulations of the curves seen on Fig. 9. Technetium-99m-DTPA studies were normal at BSL and after captopril.

FIG. 9. Captopril ¹³¹I-OIH renography (upper) in a patient with severe right RAS (> 90%). Notice the abnormal baseline unilateral curve (lower) and the deterioration after captopril (upper). The distal portion of the curves have been manipulated by a least square fitting of a straight line, thus eliminating statistical fluctuations. In this patient, ^{99m}Tc-DTPA studies were not performed.

severely impaired, the kidney shrinks, and ACEI effects are less evident (Fig. 9). Technetium-DTPA studies are abnormal, and it may be impossible to appreciate any further suppressing effect of the ACEI. Eventually, BSL and ACEI studies are indistinguishable; when CRF is established, stenotic and non-stenotic kidneys look alike with Tc-DTPA. OIH BSL scintigraphy of the severely stenotic kidney is also abnormal. Cortical accumulation is slow and continuous, unlike in kidneys with other causes of failure (i.e., CRF), where a low intensity and an early plateauing curve is characteristic. Thus, in extreme cases of RAS, the diagnosis of RVH can be based on BSL findings, even though there may be no appreciable deterioration of OIH scintigraphy after ACEI (5). When BSL and ACEI studies give continuously rising graphs, the slopes rather (cts/min) than the RCA should be compared. If the slope after captopril increases, the study is positive and some response to angioplasty is expected. It appears that a lack of response in such instances predicts poor or no response probably because of established renal parenchymal damage.

Of all cases of RVH, only this type with an abnormal BSL study could be diagnosed by scintigraphy before the introduc-

tion of angiotensin converting enzyme inhibition thereby explaining the low sensitivity of conventional scintigraphy in RVH.

Available evidence suggests that in general ACEI effect on renography correlates with improvement of HT after revascularization (4,5,7). On the other hand, lack of renographic response to ACEI appear associated with a lack of PTR effect on hypertension (4,5).

Angiographically Complete Occlusion of the Renal Artery

When RAS progresses to angiographically complete obstruction, the kidney may be kept alive by collateral blood flow; renal ischemia is severe, high levels of renin-angiotensin are produced, and RVH ensues. Nevertheless, the kidney is not functioning enough to be visible as a functioning organ on scintigraphy. Technetium-99m-DTPA may show a trace of flow and faint blood-pool activity which is not modified by ACEI; on OIH scintigraphy the kidney simply does not visualize (3). No effect on RVH is expected in this group of

patients even when revascularization is technically feasible. The kidney has developed such sclerotic changes that renal parenchymal hypertension is rather predictable. Treatment with ACEI or nephrectomy may be indicated to correct RVH (1).

USES IN THE PEDIATRIC POPULATION

Umbilical artery catheterization may be a life saving procedure in newborn infants. An occasional complication thereof is aortic thrombosis, which can lead to renal ischemia and RVH because of either impingement of the thrombus on the ostium of renal arterie(s), or propagation of the thrombus into renal arterie(s). Kidney ischemia and the hypertension may resolve spontaneously after dissolution or retraction of the aortic thrombus or total destruction of the kidney. Neonates with RVH have been treated with ACEI successfully, but when ischemia was bilateral or associated with a solitary functioning kidney captopril therapy precipitated renal failure. BSL and single dose captopril scintigraphy is important for the diagnosis and prevention of this complication by demonstrating the reversible effect of the single dose (2).

In children and adolescents, we have found single dose captopril scintigraphy with both DTPA and OIH effective in diagnosing RVH; in one patient OIH predicted the results of subsequent angioplasty although Tc-DTPA scintigraphy did not change after ACEI (5).

SENSITIVITY-SPECIFICITY

No accepted criteria have been established for a positive Tc-DTPA or OIH test. We found it practical and sensitive in OIH scintigraphy to express the captopril effect as the change in the 20-min RCA. A RCA post-captopril exceeding 30% of peak activity with a 10%, at least, increase over the BSL study is associated with RVH (Figs. 7-9). If the BSL study has a rising renogram, then an increase in the slope would indicate CAP effect. Kidneys, however, with complete RA obstruction do not visualize. Kidneys with nearly complete obstruction (> 95% RAS) showed no change in the RCA after captopril, but the BSL study was already characteristic, as discussed above. In our series, if nonvisualizing kidneys are excluded, characteristic studies for RVH, either at BSL or after captopril, were seen in every one of 25 patients with RVH. No false-

positive studies were encountered among 20 patients with normal angiography or no hypertension. Technical reasons (lack of lasix injection, wrong lateralization of abnormal kidneys) and superimposed or resolving complications between BSL and CAP studies (rejection, acute tubular necrosis in transplants) have resulted in four false-positive interpretations in our group of studies in patients with essential hypertension.

Although the method is still under development, it appears that OIH captopril renography has advantages against Tc-DTPA and it is the preferred method, at least until Tc-MAG3 is better studied (7).

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