Diagnosis of Angiotensinogenic Hypertension: The Complementary Roles of Renal Scintigraphy and the Saralasin Infusion Test

J. G. McAfee, F. D. Thomas, Z. Grossman, D. H. P. Streeten, E. Dailey, and G. Gagne

State University Hospital, State University of New York, Syracuse, New York

A recently developed 1-day screening procedure for angiotensinogenic ("high-renin") hypertension is based on (A) a fall in blood pressure in response to intravenous infusion of the angiotensin antagonist, saralasin (P-113), and (B) peripheral venous renin assays by radioimmunoassay, in a sodium-depleted state. Out of 700 hypertensive patients screened by these tests, 160 had renal imaging performed with technetium-99m glucoheptonate and iodine-131 Hippuran. The P-113 infusion test proved superior to peripheral venous renin assays for the detection of angiotensinogenic hypertension. Positive infusion tests correlated well with renal vein renin assays. Frequently, however, both these tests were positive with bilateral renal disease and/or malignant hypertension. While renal imaging proved valuable in indicating which patients had a unilateral abnormality, it frequently could not distinguish unilateral renovascular disease from unilateral parenchymal disease unrelated to angiotensinogenic hypertension. Twenty-five patients in this series had arteriographic renal artery stenosis, of whom 3 had false negative P-113 infusion tests, 9 had negative peripheral renin assays, and 3 had no imaging abnormalities. This study indicates that scintigraphy is a useful procedure for the investigation of hypertensive patients when the initial P-113 infusion test is positive, or discordant with other findings. By imaging, angiotensinogenic hypertension due to bilateral renal disease can be distinguished from unilateral renovascular disease, and the site of the ischemic renal tissue can usually be identified.

J Nucl Med 18: 669–675, 1977

In the Cooperative Study of Renovascular Hypertension of 1972 (*1*) two principal "nonoperative" screening methods were available: intravenous urography and Hippuran renography. Their effectiveness in the diagnosis of bilateral renal vascular disease and of segmental lesions was not described. The detection rate for unilateral vascular lesions was 78% by intravenous urography (*2*), but there was an 11% incidence of false positives. With Hippuran renography (*3,4*), the detection of unilateral renal vascular disease was 85%, but the false-positive rate was 10% (*3*). A combination of these two methods proved too expensive for use as a routine screening procedure for a large series of hypertensive patients. The value of routine intravenous urography for the detection of renal vascular lesions associated with hypertension has been seriously questioned (*6*). Moreover, Hippuran renography with dual probes has been abandoned at many centers, chiefly because errors in positioning these detectors have produced false-positive results.

A new diagnostic test, highly specific and accurate for angiotensinogenic hypertension, has been devel-

Received Sept. 21, 1976; revision accepted Feb. 11, 1977.

For reprints contact: John G. McAfee, Div. of Nuclear Medicine, SUNY Upstate Medical Center, Syracuse, NY 13210.

oped, and is suitable for screening relatively large groups of hypertensive patients at reasonable cost (*7–9*). The specific angiotensin—II antagonist saralasin (P-113) (an octapeptide)—is infused intravenously under conditions of sodium depletion, and serial blood pressures are measured. Only in patients with "high-renin" (angiotensinogenic) hypertension do the systolic and diastolic pressures decrease. In patients with "low renin" hypertension, the blood pressure increases; in the majority of patients with "essential" hypertension, the blood pressure response is insignificant. Hence, by this test hypertensives may be classified as "high renin," "normal renin," or "low renin" (*10,11*). In view of the efficacy of this test, the need and future role of radiotracer studies in hypertensives must be re-examined. Heretofore there has been no simple screening test, other than intravenous urography, to assess the incidence of false negative radiotracer tests in renal vascular hypertension. In this paper, renal scintigraphy is compared with the P-113 test, renin assays, urography, and renal arteriography in a series of hypertensive patients. In addition, the relative values of different segments of the scintigraphic study are examined.

METHODS

Over a period of 20 months ending May 1975, 700 hypertensive patients were screened by the P-113* test and peripheral renin assay using methods reported previously (*9*).

Renal scintigraphy was performed in 160 patients out of 700 who had the P-113 test. Almost all of this group also had a peripheral plasma renin assay. When the P-113 test was positive, or when its results conflicted with the peripheral renin assay, clinical history, or other laboratory findings, radionuclide imaging was performed. Ninety-three patients had intravenous urography. Renal vein renin assays (*9*) and renal arteriography were performed selectively.

Renal scintigraphy was performed with a scintillation camera,† positioned posteriorly over the kidneys with the patient sitting in a special chair,‡ the back being inclined at 45°. After fasting overnight, the patient ingested 250 ml of water half an hour before the study. Fifteen mCi of Tc-99m glucoheptonate were rapidly injected i.v. Serial images with a window setting of 20% were made every 2 sec for 30 sec, beginning 12 sec after injection. A series of 5 "early" scintiscans was obtained at 1-min intervals. The first of these, beginning 1 min after injection, was exposed for a preset count of 300,000; the subsequent exposures were for a preset time equal to that of the first "early" one. The pulse-height analyzer was then centered on the principal gamma emission of iodine-131. Two hundred microcuries of [^{131}I] so-

TABLE 1. SUMMARY OF LABORATORY, NUCLEAR, AND RADIOGRAPHIC RESULTS

	P-113 & scintigraphy	P-113	Scintigraphy	Peripheral renin assay		Renal-vein renin		IVP		Arteriogram*	
Final diagnostic classification	No. of patients	No. +	No. +	No. of studies	No. +	No. of studies	No. +	No. done	No. +	No. done	No. +
Angiotensinogenic	51	43	40	46	25	41	35	31	14	34	24
Renal artery stenosis	24	16	21	20	9	20	17	13	10	24	24
Bilateral renal disease	16	16	16	15	8	13	12	10	1	6	0
Obstructive uropathy	3	3	3	3	2	1	1	3	3	1	0
Misc. & unknown diag.	8	8	0	8	6	7	5	5	0	3	0
Nonangiotensinogenic	109	6	44	106	5	29	1	62	22	14	1
Essential hypertension	59	0	0	59	5	10	1	28	1	7	0
False-positive P-113	5	5	0	5	0	3	0	4	0	1	0
Renal artery stenosis	1	0	1	1	0	0	0	1	0	1	1
Unilateral renal lesions	22	0	22	22	0	11	0	16	15	3	0
Misc. & unknown diag.	17	0	17	15	0	5	0	11	6	2	0
Renal transplant	1	1	0	0	0	0	0	0	0	0	0
Bilateral renal disease	4	0	4	4	0	0	0	2	0	0	0
Totals	160	49	84	152	30	70	36	93	36	48	25

* Arteriographic findings of renal artery stenosis only.

dium ortho-iodohippurate (Hippuran) were rapidly injected intravenously. Two-minute images were obtained every 2 min for the first 10 min, and then at 15, 20, and 30 min. At 1 hr after the injection of the glucoheptonate, the pulse-height analyzer was reset for the Tc-99m gamma energy and the kidneys were imaged with a preset count of 300,000. When there was evidence of pelvocalyceal retention of activity, additional erect and delayed images were obtained at both Tc-99m and I-131 settings. Lateral and anterior views were obtained with any evidence of renal ptosis or displacement. Additional images were obtained— at the Tc-99m setting, with high-resolution or pinhole collimators—when segmental or focal lesions were suspected. The total time for the procedure, using both renal radiopharmaceuticals, averaged 75 min.

The renal scintiscans were reviewed retrospectively by three nuclear-medicine physicians independently, without benefit of clinical or laboratory information, and the recorded results were compared with the original interpretation. The abnormalities noted on each portion of the radiotracer study were graded as none, minimal, moderate, marked, gross, or nonfunctioning. Differences in renal size, segmental, or focal defects, or pelvocalyceal abnormalities were also tabulated. Likewise the intravenous urograms and renal arteriograms were "blindly" reviewed by three diagnostic radiologists using criteria of interpretation similar to those of the Cooperative Study (*1*).

TABLE 2. SARALASIN INFUSION TEST VS. SCINTIGRAPHY

	No. of patients		
	Angiotensinogenic	Non-angiotensinogenic	Total
A. P-113 —, scintigraphy —	0	59	59
B. P-113 —, scintigraphy +	8	44	52
RA stenosis	5	1	6
RA stenosis; post-op P-113 only	3	0	3
Unilateral renal chronic pyelonephritis	0	7	22
postobstructive atrophy	0	5	
hydronephrosis	0	4	
cysts	0	4	
infarcts	0	2	
Bilateral renal disease	0	4	4
Miscellaneous and unknown	0	17	17
C. P-113 +, scintigraphy —	11	6	17
RA stenosis	3	0	3
Fine vessel disease, unilateral	1	0	8
Renal failure	2	0	
Cushing's	1	0	
Diag. unknown	4	0	
False + P-113	0	5	5
Transplant in failure	0	1	1
D. P-113 +, scintigraphy +	32	0	32
Renal artery stenosis	13	0	14
Bilateral parenchymal disease	16	0	16
Obstructive uropathy	3	0	3
Total	51	109	160

RESULTS

Tables 1 and 2 compare the results of saralasin infusion and scintigraphy with the final diagnosis. Fifty-one patients were finally classified as having angiotensinogenic hypertension. The saralasin test was positive in 43 and scintigraphic abnormalities were present in 40 (Table 1). The assays of renal vein renin correlated much better with the final diagnosis of angiotensinogenic hypertension than the peripheral venous renin assays. Twenty-four of these 51 patients had renal artery stenosis, 16 had bilateral parenchymal disease, three had obstructive uropathy, and the remaining eight had other conditions without scintigraphic abnormalities.

Six patients with positive saralasin tests and negative scintigrams were finally classified as nonangiotensinogenic because of negative renin assays, negative repeat saralasin tests, or subsequent clinical response. Two-thirds (111) of all scintigraphic studies were performed in patients with normal saralasin tests and conflicting results of other laboratory procedures (Table 2). In this group, scintigraphy detected five patients with renal artery stenosis and angiotensinogenic hypertension, and repeat saralasin tests in two of these became positive. A much larger number of renal abnormalities (44), unassociated with angiotensinogenic hypertension, were detected scintigraphically, half of which were unilateral. By imaging alone, we were unable in twelve instances to distinguish these unilateral parenchymal lesions (such as chronic pyelonephritis) from unilateral vascular lesions. This differentiation was eventually made on the basis of intravenous urography and occasionally by renal vein renins and arteriography. Fifty-nine patients in this group had both a negative saralasin test and normal scintigraphy, and were finally classified as essential hypertensives. False-positive tests in these patients included five peripheral renins, one renal vein renin and one intravenous urogram.

Scintigraphic findings. Of 25 patients with ar-

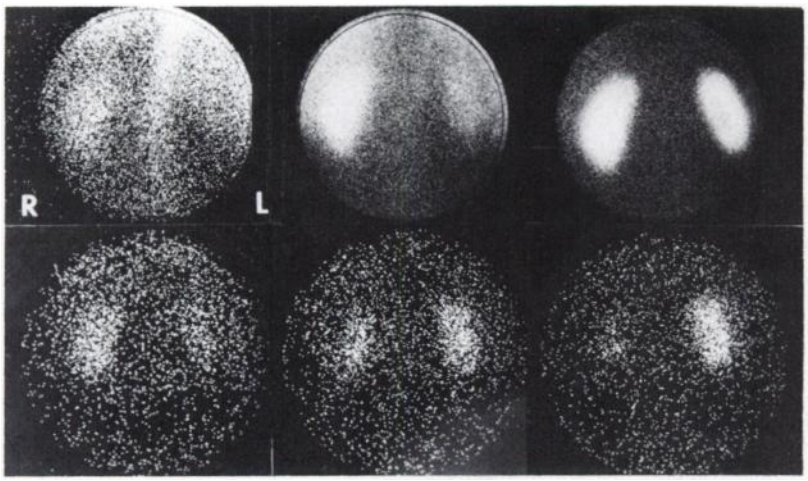

FIG. 1. Forty-four-year-old male with antiotensinogenic hypertension and left renal artery stenosis, eventually treated by nephrectomy. Renal scintigraphy: upper row—Tc-99m glucoheptonate images at 18 sec, 1 min, and 1 hr. Impaired concentration in left kidney is most obvious at 1 min. Lower row—[^{131}I] Hippuran 2-min images at 1, 10, and 30 min. Left renal concentration is decreased initially, but later is increased due to prolonged parenchymal retention.

teriographically proven renal-artery stenosis, all except one had angiotensinogenic hypertension. The scintiscans were positive in all except three, and there was an equal number of false-negative saralasin tests. There were, however, no instances in which both the infusion test and scintigraphy were negative.

Technetium-99m glucoheptonate generally demonstrated the abnormality better than [^{131}I] Hippuran (Fig. 1). Four segmental lesions were best demonstrated on delayed images with the Tc-99m agent (Fig. 2). Of the three parts of the study performed with Tc-99m glucoheptonate (namely, the rapid serial images, the five early images, and the 1-hr images), each showed the abnormality best with about equal frequency. In six instances the relative concentrations of the Tc-99m agent in the two kidneys appeared equal on the 1-hr images; consequently, if only this portion of the study had been obtained, the incidence of false-negative examinations would be high. In nine of these patients there was no renal atrophy.

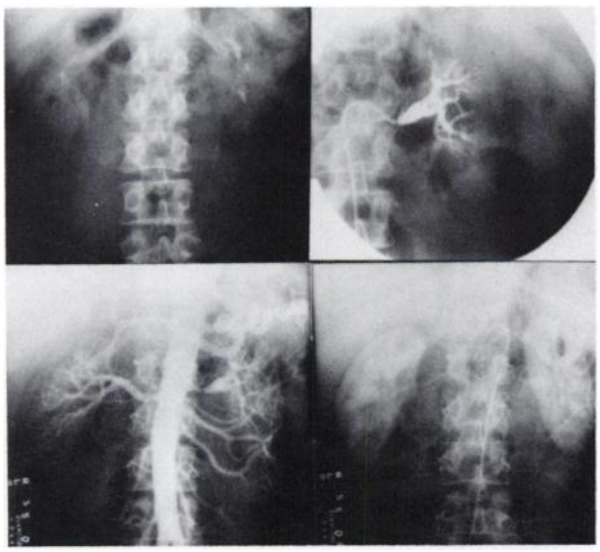

FIG. 1B. Left upper: intravenous urogram, read as normal, but shows minimal left hyperconcentration. Aortogram and left renal arteriogram show tight arteriosclerotic stenosis of left renal artery without significant atrophy.

In the [^{131}I] Hippuran studies, the portions that best demonstrated the unilateral abnormality were the delayed images obtained at 25–30 min, and the second best were the earliest images obtained within the first 2–4 min of injection. There was no instance in which Hippuran detected an abnormality that was not also detected with the Tc-99m agent; on the other hand, two patients showed abnormalities with the technetium agent that were not demonstrated with Hippuran. With either radiotracer, neither the differences in concentration between the two kidneys, nor the differences in renal size, correlated with the duration or severity of the hypertension.

In this series, 18 patients with angiotensinogenic hypertension and positive saralasin infusion tests had bilateral renal disease without stenosis of the major renal arteries. Sixteen of these had abnormal scintigrams. The technetium images showed asymmetric renal concentration in 11, and 4 had marked unilateral atrophy. In late images obtained at 30 min, an abnormally high retention of [^{131}I] Hippuran in the parenchyma of both kidneys was found in all but three patients. This was the most valuable sign showing the bilateral nature of the disease (see Fig. 3).

DISCUSSION

In many respects our study of 700 hypertensive patients is not comparable with the series of 2,442 in the Cooperative Study (*1*). Nevertheless, the proportion of studies of the total patient population by radiotracer methods (22%) is the same. Compared with the older dual-probe Hippuran renogram,

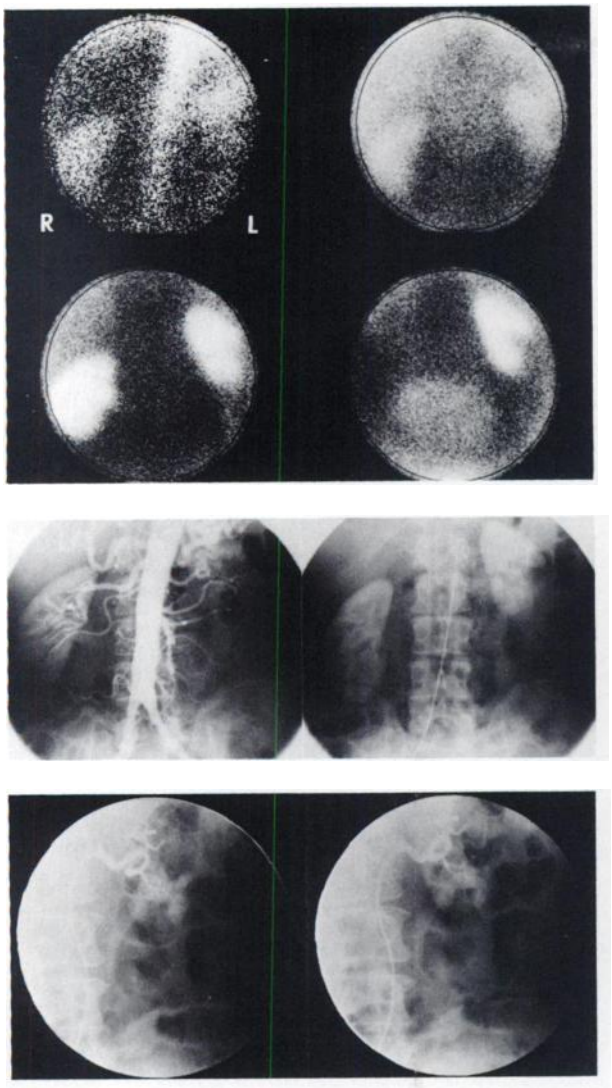

FIG. 2. Fifty-nine-year-old male with angiotensinogenic hypertension and segmental lesion, left lower kidney. Top, Tc-99m glucoheptonate images. Decreased perfusion in left lower kidney at 16 sec (left upper), less striking at 1 min (right upper). Large defect in inferolateral segment of left kidney, more obvious in left posterior oblique (right lower) than in posterior view (left lower). Center, aortogram in same patient as in top image. Bottom, selective injection of left upper renal artery. Left lower renal artery is blocked. Nephrogram phase again shows segmental defect. Arteriosclerosis of lower aorta. (Films courtesy of Dr. Edward G. Bell, Crouse-Irving Memorial Hospital.)

scintillation-camera imaging apparently does not markedly improve the detection rate for renovascular disease. Nonetheless, the camera method does avoid false positives due to errors of detector positioning. In this series the three false-negative gamma-imaging findings in renal-artery stenosis occurred in the presence of extensive collateral renal circulation.

The saralasin infusion test, performed under standardized conditions, has few false positives, is economically acceptable as a screening procedure, and only infrequently fails to detect angiotensinogenic hypertension. From this study, the infusion test appears to be much more reliable than peripheral renin assays. The saralasin test correlates well with the renal vein renin levels. The latter assays also indicate the side involved in unilateral renal disease, but they obviously cannot be employed for screening because of the necessity of renal vein catheterization. Although saralasin infusion is a screening procedure that specifically indicates angiotensinogenic hypertension, it can neither differentiate between the many causes of this type of hypertension (Table 3), nor indicate unilateral or bilateral renal involvement.

Renal scintigraphy appears most useful in hyper-

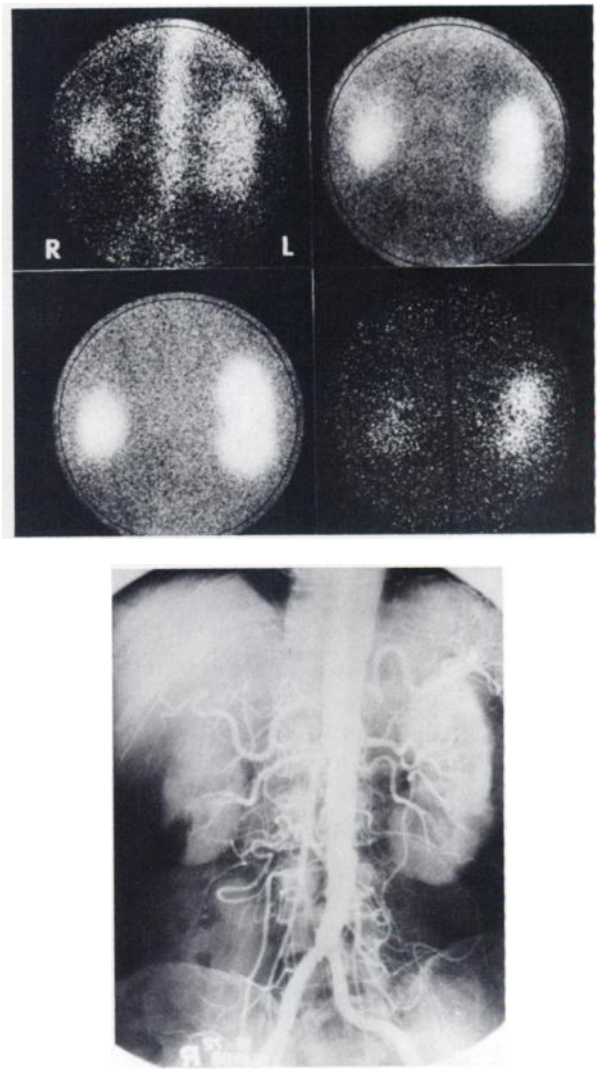

FIG. 3. Sixty-two-year-old white male with angiotensinogenic hypertension and bilateral arterial disease. Very high absolute renin levels from both renal veins. Top, Tc-99m glucoheptonate images show decreased perfusion of upper part of right kidney at 18 sec (left upper) and decreased concentration at 5 min (right upper) and 1 hr (left lower). Image 40 min after [^{131}I] Hippuran (right lower) shows abnormal parenchymal retention, worse on left side. Bottom, aortogram. Double renal arteries bilaterally. Upper artery on right is very small. Decreased nephrogram upper part of right kidney. Fine renal arterial branches are irregular bilaterally. Atherosclerosis of aorta.

TABLE 3. RESPONSE TO SARALASIN

Lowering BP	in angiotensinogenic hypertension
	renovascular disease
	bilateral fine vessel disease
	bilateral parenchymal disease
	malignant hypertension
	estrogen-progestin contraceptives
	Cushing's disease
Rare	bilateral cystic disease
	obstructive uropathy
	renin-secreting tumors
Raising BP	low renin hypertension

tensive patients in whom the saralasin test is positive. As judged by this small series, scintigraphic abnormalities are observed in two-thirds of patients with a positive infusion test. By imaging, unilateral renovascular lesions can usually be differentiated from bilateral renal disease, and the side of unilateral involvement or segmental ischemic lesions can be identified. Eighty-eight percent of renal-artery stenoses are detected by scintigraphy with Tc-99m glucoheptonate. Bilateral renal disease associated with angiotensinogenic hypertension is detected by scintigraphy in 89% (16 of 18 patients). It is best identified by delayed bilateral parenchymal retention of [^{131}I] Hippuran, 30 min or later after injection.

Renal scintigraphy appears useful also in hypertensive patients with negative or doubtful saralasin tests in whom the results of other tests (including renin assays) are discordant, or in whom the clinical suspicion of renovascular disease is high. Under these circumstances, however, the diagnostic yield of detection of unilateral renovascular disease by scintigraphy is low (5% in this series). In this group of patients, there is a higher incidence of unilateral renal lesions, particularly chronic pyelonephritis and obstructive uropathy. Unfortunately, imaging alone often fails to distinguish between unilateral renovascular lesions and unilateral renal lesions. The latter, however, can usually be identified by intravenous urography. The frequency of these "incidental" renal lesions in hypertension without abnormalities of the renin-angiotension system is greater than that of renovascular disease, and may be as high as 18% (*6*).

We did not perform renal scintigraphy in hypertensive patients in whom either renovascular disease was not suspected clinically, or the saralasin response was negative, or other tests were not discordant. In all likelihood, the diagnostic detection rate of renovascular lesions by scintigraphy in such patients would be very low and economically unjustifiable.

In our experience, Tc-99m glucoheptonate is superior to [^{131}I] Hippuran for the detection of unilateral vascular lesions, especially when focal or segmental. Perhaps this superiority is entirely due to the physical characteristics of Tc-99m, which are optimal for imaging with the scintillation camera. All three parts of the imaging procedure performed with the Tc-99m agent are useful in the detection of renal vascular disease. With delayed images alone, many unilateral renovascular lesions would be missed. Frequently this disease is detected by differences in perfusion or tubular function in the absence of renal atrophy. The detection rate by intravenous urography, on the other hand, is low unless atrophy is present (*2*).

The rapid-film scintigraphic demonstration of a unilateral decrease in renal perfusion is not specific for renal-artery stenosis, the common causes for which are listed in Table 4. Renal ptosis or anterior displacement due to hematoma following renal biopsy may cause an apparent decrease in perfusion due merely to differences in the depth and orientation of the two kidneys. In this situation, additional views in the anterior and lateral projections are helpful.

The current techniques of renal imaging with gamma cameras have numerous shortcomings for the assessment of hypertensive patients. When imaging and intravenous urography both show nonfunction of one kidney, it is not possible to rule out angiotensinogenic hypertension. In two patients with severe hydronephrosis of one kidney and positive infusion tests, high renal vein renin levels were detected from the seemingly functionless kidneys. Bilateral asymmetrical renal artery stenosis is often misdiagnosed by radiotracer imaging as only unilateral vascular disease. More accurate methods of measuring the renal function of the opposite "normal" kidney are needed in patients with renal artery stenosis, because a minor reduction in function

TABLE 4. DIFFERENTIAL DIAGNOSIS OF UNILATERAL DECREASE IN RENAL PERFUSION

Renal causes	Renal artery stenosis
	Renal vein thrombosis
	"Chronic" pyelonephritis
	Ureteral obstruction
	Masses compressing hilar vessels
Renal tamponade	Perirenal abscess
	Perirenal hematoma
Apparent decrease	Ptosis
	Perirenal abscess
	Perirenal hematoma

is often not detected by current gamma-imaging methods.

In conclusion, this study suggests that the saralasin infusion test should be considered the primary screening procedure for the detection of angiotensinogenic hypertension because of its specificity and relatively infrequent false negatives. Consequently, there is now less need to consider radiotracer methods for routine screening of hypertensives, and indeed this has seldom been carried out in the past. Scintigraphy, however, is valuable in those patients with positive infusion tests, in those with discordant laboratory results, and in those with a high clinical suspicion of renovascular disease. Intravenous urography can probably be limited to those patients with positive scintigraphic studies to differentiate renovascular disease from lesions with pelvocalyceal abnormalities such as chronic pyelonephritis.

ACKNOWLEDGMENT

Supported in part by a grant from the National Institute of General Sciences USPHS GM-18248.

FOOTNOTES

* Saralasin (P-113), an angiotensin II antagonist, is 1-sar-8-ala-angiotensin II: Eaton Laboratories, Norwich, N.Y.

† Searle Radiographic HP or Ohio-Nuclear Series 100 camera.

‡ Model 430, Analytical Development Association Corp., Sunnyvale, Calif.

REFERENCES

1. MAXWELL MH, BLEIFER KH, FRANKLIN SS, et al.: Cooperative study of renovascular hypertension. Demographic analysis of the study. *JAMA* 220: 1195–1204, 1972

2. BOOKSTEIN JJ, ABRAMS HL, BUENGER RE, et al.: Radiological aspects of renovascular hypertension. I. Aims and methods of radiology study group. *JAMA* 220: 1218–1224, 1972. Part 2. The role of urography in unilateral renovascular disease. *JAMA* 220: 1225–1230, 1972

3. MCNEIL BJ, VÁRADY PD, BURROW BA, et al.: Measures of clinical efficacy. Cost-effectiveness calculations in the diagnosis and treatment of hypertensive renovascular disease. *N Engl J Med* 293: 216–221, 1975

4. FARMELANT MH, SACHS C, BURROWS BA: Prognostic value of radioisotopic renal function studies for selecting patients with renal arterial stenosis for surgery. *J Nucl Med* 11: 743–748, 1970

5. STEWART BH, DUSTAN HP, KISER WS, et al.: Correlation of angiography and natural history in evaluation of patients with renovascular hypertension. *J Urol* 104: 231–238, 1970

6. FAIRMAN MJ, HARPUR JE, HAMILTON M: Value of routine intravenous pyelography in the investigation of hypertension. *Postgrad Med J* 50: 508–510, 1974

7. BRUNNER HR, GAVRAS H, LARAGH JH, et al.: Angiotensin-II blockade in man by sar^1-ala^8-angiotensin II for understanding and treatment of high blood pressure. *Lancet* 2: 1045–1048, 1973

8. STREETEN DHP, ANDERSON GH, FREIBERG JM, et al.: Use of an angiotensin II antagonist (saralasin) in the recognition of "angiotensinogenic" hypertension. *N Engl J Med* 292: 657–662, 1975

9. STREETEN DHP, FREIBERG JM, ANDERSON GH, et al.: Identification of angiotensinogenic hypertension in man using 1-sar-8-ala-angiotension II (saralasin, P-113). *Circ Res Suppl I* 36: 1–125; 37: 1–132, 1975

10. LARAGH JH: The classification and treatment of essential hypertension using the renin-sodium index for vasoconstriction-volume analysis. *Johns Hopkins Med* 137: 184–194, 1975

11. VAUGHAN ED JR, BUHLER FR, LARAGH JH, et al.: Hypertension and unilateral parenchymal renal disease: evidence for abnormal vasoconstriction-volume interaction. *JAMA* 233: 1177–1183, 1975