# Renovascular Hypertension: A Perfusion Disturbance That Escaped Recognition

John H. Clorius, Fritz Reinbold, Thomas Hupp, Alexander Mandelbaum, Peter Schmidlin and Gerhard van Kaick

*Department of Oncologic Diagnosis and Therapy, German Cancer Research Center; Division of Vascular Surgery, and Department of Nephrology, University of Heidelberg, Germany*

A bilateral, exercise-mediated, hippurate transport disturbance was previously described when patients with fixed renovascular hypertension were imaged with o-iodo-hippurate. This study sought to test the hypothesis that patients with an abnormal exercise scintigram have a perfusion abnormality characterized by dysregulation of renal blood flow. We imaged 23 patients with hypertension and angiographically documented renovascular disease in the supine position, as well as during upright exercise. Seven normotensive volunteers served as controls. We measured the resting glomerular filtration rate (GFR) and the effective renal plasma flow (ERPF) with a single compartment radiotracer infusion clearance. The clearance examination also included a measurement period with 25 watt ergometric exercise. Nine hypertensive patients had normal exercise renograms. These patients had age-appropriate clearance values at rest and during exercise, as well as age-appropriate best-organ (generally without stenosis) GFR and ERPF values. The filtration fraction (FF) was 0.21 at rest and 0.22 during exercise. Fourteen hypertensive patients had a bilateral, exercise-induced disturbance of hippurate transport. In these patients, the global resting GFRs and ERPFs were decreased 40% from age-appropriate predicted values. The FF remained at 0.20. Light exercise caused a pronounced contraction of GFR and a less severe reduction in the ERPF. During exercise the mean filtration fraction was only 0.12. The exercise-induced reduction in the clearance values was bilateral, which indicated that the perfusion of nonstenosed organs was compromised as well. We suggest that the described perfusion abnormality occupies a relevant position during the maintenance phase of fixed renovascular hypertension.

**J Nucl Med 1993; 34:48–56**

Exercise is known to induce a transitory, bilateral, renal hippurate transport disturbance in nearly 60% of all patients with hypertensive disease (*1*). The hippurate transport abnormality is readily documented, and easily recognized with serial scintigrams, since radiolabeled hippurate is trapped in the tissue of both kidneys. The entrapment also results in delayed hippurate excretion into the bladder, and causes renograms to have an elevated third-curve segment. The exercise-mediated hippurate transport abnormality is not associated with a particular form of hypertension, but is seen in renovascular and renoparenchymal hypertension, malignant hypertension and in primary hypertension (*2*). Earlier investigations indicated that beta blockers, sympatholytic drugs, vasodilators or diuretics did not cause or eliminate the disturbance (*2*). The exercise-mediated abnormality of hippurate kinetics was seen in patients receiving various combinations of these drugs, but was also observed in hypertensive patients who received no medication at all. It was recently shown that hypertensive patients with renovascular disease and abnormal exercise renograms continue to be hypertensive following successful revascularization (*3,4*). Conversely, the same clinical entity, renovascular stenosis and hypertension, was associated with curable hypertension when exercise failed to elicit the pathologic exercise response. We are excited about this protocol's ability to predict curability of hypertension in these patients, and we are intrigued by the mechanisms responsible for hippurate transport disturbance during exercise. It is important to recognize that relevant renal hippurate transport disturbance is invariably bilateral, even in the presence of angiographically demonstrated unilateral disease. We previously hypothesized an exercise-mediated, afferent arteriolar contraction as the most probable cause for parenchymal tracer entrapment (*2,4*). The present study sought to test the hypothesis that a perfusion disturbance causes abnormal exercise scintigrams. We therefore measured glomerular filtration rate (GFR) and effective renal plasma flow (ERPF) at rest and during exercise in patients with normal and abnormal exercise scintigrams and renovascular hypertension.

## METHOD

Twenty-three patients, referred for evaluation of renovascular hypertension, and 7 normotensive controls were studied. The control group included only healthy normotensive physicians. The hypertensives had unilateral or bilateral renal artery stenosis with 75% or greater lumen reduction of one vessel, verified at

Received May 4, 1992; revision accepted Jul. 31, 1992.

For correspondence or reprints contact: John H. Clorius, MD, Department of Oncologic Diagnosis and Therapy, German Cancer Research Center, Im Neuenheimer Feld 280, D-6900 Heidelberg, Germany.

**TABLE 1**
Main Associated Diseases and Antihypertensive Medication of Nine Patients with Probable Renovascular Hypertension and Normal Exercise Scintigrams

| Patient no. | Stenosis | Associated disease | Drugs at scintigraphy |
|---|---|---|---|
| 1 | U | Arteriosclerosis | 1,2 |
| 2 | U | Arteriosclerosis | None |
| 3 | U | Arteriosclerosis | 3 |
| 4 | U | Fibromuscular dysplasia | 1,2,3 |
| 5 | U | Fibromuscular dysplasia | None |
| 6 | U | Renal insufficiency coronary heart disease | 2,4,5 |
| 7 | U | Arteriosclerosis | 1,2,5 |
| 8 | Bi | Arteriosclerosis | 2,4 |
| 9 | U | Arteriosclerosis | 2,3 |

1 = diuretics; 2 = calcium antagonists; 3 = beta blockers; 4 = sympatholytic drugs; 5 = ACE inhibitors; U = unilateral stenosis; Bi = bilateral stenosis.

angiography. The population was highly selective since the hypertensives were not considered suitable candidates for percutaneous transluminal angioplasty (PCTA), resulting in their referral to vascular surgeons. Surgical revascularization was considered in order to preserve organ function. Eighteen hypertensive patients were considered to have concurrent arteriosclerosis. Sixteen were referred with this diagnosis, while two additional patients with compensated renal insufficiency and co-occurring hypercholesterinaemia (Nos. 6, 15) are included in this population. Three hypertensive patients had vascular lesions due to fibromuscular dysplasia (Nos. 4, 5, 23). The antihypertensive medication taken by each patient at the time of scintigraphy was noted (Table 1, 2).

The patients received a supine-position resting $^{131}$I-hippurate sequential renal scintigram and a scintigraphic examination while sitting upright during ergometric exercise not exceeding 80 watts. Using a single compartment dual-tracer infusion clearance and the tracers $^{131}$I-hippurate and $^{111}$In-DTPA (diethylentriamine pentaacetic acid), we measured both GFR and ERPF in the supine position at rest and during 25 watt ergometric exercise in both the control group and the hypertensive patients.

Twenty patients were referred for a renal function study by vascular surgeons, three by nephrologists. All patients received careful oral instructions about the series of examinations, in which the goal of the examination was explained. The examination invariably involved the following sequence: gamma camera renography in the supine position; clearance examination at rest 30–40 min after completion of the supine gamma camera renogram; determining GFR and ERPF during exercise without repositioning the patient. Upright exercise scintigrams were generally obtained on the following day, but always within three days of the initial examination.

Gamma camera renography was carried out after intravenous injection of 7 $\mu$Ci $^{131}$I-o-iodo-hippurate per kg body weight. We used a 15-in. camera equipped with a general-purpose, medium-energy, parallel-hole collimator. The window was opened 25% and was centered over the photopeak of the tracer. One-minute scintiscans were made from the 1st through the 4th min, and from the 7th, 9th, 14th and 19th min thereafter. Examinations were terminated at 20 min. A minicomputer was used to place regions of interest over each kidney to determine single-kidney function. Background regions of interest were placed below and

**TABLE 2**
Main Associated Diseases and the Antihypertensive Medication of 14 Patients with Probable Renovascular Hypertension and Abnormal Exercise Scintigrams

| Patient no. | Stenosis | Associated disease | Drugs at scintigraphy |
|---|---|---|---|
| 10 | U | — | 5 |
| 11 | Bi | Arterioslcerosis, renal insufficiency, coronary heart disease | 1,2,3,5 |
| 12 | U | — | None |
| 13 | Bi | Arteriosclerosis, renal insufficiency | 1,2,3 |
| 14 | U | Arteriosclerosis | 1 |
| 15 | Bi | Renal insufficiency | 1,3,4 |
| 16 | U | Arteriosclerosis | 1,5 |
| 17 | U | Arteriosclerosis, renal insufficiency | 1,2,3,4 |
| 18 | Bi | Arteriosclerosis | 1,2,3,5 |
| 19 | U | Arteriosclerosis, renal insufficiency | 1,4,5 |
| 20 | U | Arteriosclerosis, renal insufficiency | 1,2,3,4 |
| 21 | U | Arteriosclerosis | 1 |
| 22 | U | Arteriosclerosis | 2 |
| 23 | U | Fibromusuclar dysplasia | 2 |

1 = diuretics; 2 = calcium antagonists; 3 = beta blockers; 4 = sympatholytic drugs; 5 = ACE inhibitors; U = unilateral stenosis; Bi = bilateral stenosis.

along the lateral border of each kidney. Single-kidney hippurate uptake, expressed as a percentage of total uptake of both kidneys, was determined. Uptake was taken to be proportional to the gradient of the renogram between the 24th and 120th sec. The excretory segment of the renogram was qualitatively analyzed to judge parenchymal tracer excretion. The supine scintigram served as the base study against which the exercise scintigram was compared to identify the exercise-induced hippurate transport disturbance.

The exercise scintigram was obtained while the patient sat in front of a gamma camera on a bicycle ergometer. Patients were asked to sit straight-backed and lean against the camera to reduce movement and minimize the kidney-to-camera distance. Ergometric resistance was initially set at 60 watt for women and 80 watt for men after 60 rotations per min were reached. We asked patients to remain comfortable during exercise. The workload was reduced upon request to avoid exhaustion. Thus, the patients themselves had final control over the workload used. Renography was begun after the pulse rate had increased at least 20 bpm. Patients continued with exercise following radiotracer injection. Pulse and blood pressure were monitored at irregular intervals during exercise. We used the pulse rate as an objective parameter to assess effectiveness of exercise and to identify potential overexertion. Blood pressure measurements identified potentially dangerous elevations in response to exercise.

The clearance examination began 50–70 min after simultaneous intravenous injection of 7 $\mu$Ci $^{131}$I-hippurate and 3.5 $\mu$Ci $^{111}$In-DTPA per kg body weight. The hippurate was injected for sequential scintigraphy, and $^{111}$In-DTPA was given concurrently. The time lapse between tracer injection and infusion clearance served to fill the extravascular compartments. A butterfly placed into a superficial vein of the right arm was used for a continuous drip infusion. During the clearance examination, the elimination of the tracers was monitored by two scintillation probes placed over the right and left shoulder of each patient. Each detector monitored one of the two radioisotopes by means of energy discrimination. The collected signals were used to activate an infusion pump system via feedback control. The pump system had two separate pumps, which contained either $^{131}$I-hippurate or $^{111}$In-DTPA. A separate step motor was used to drive each pump so that steady-state conditions were reached. The first 10 min of the clearance examination were required to equilibrate the feedback control system. The infusion rate needed to sustain a constant plasma activity level, respectively a constant external count rate over the shoulder, was then maintained with the feedback control system for 30 min. At the end of the resting clearance period, we drew 10 ml of blood from the cubital vein of the left arm to obtain a plasma sample. A probe from the infused saline containing the tracer served as standard for each isotope. A microcomputer was used to register the motor step rates, to document the serum activity level of each isotope in the probe's field of view, and to carry out the clearance calculations after the activity concentration of the standard and the serum sample were registered. By using these data, the clearance was calculated with the equation:

$$Cl = \frac{I \times A_{st}}{A_{pl}}, \qquad \text{Eq. 1}$$

where Cl = clearance (ml/min); I = number of motor steps per time ($min^{-1}$); $A_{st}$ = activity pumped per motor step ($\mu$Ci); and $A_{pl}$ = specific activity of plasma ($\mu$Ci/ml).

Immediately after completion of the resting clearance measurement period, and without repositioning the patients, we began the exercise protocol with 25 watts. The ergometer was firmly attached to the frame of the patient support used for the clearance examination. The pulse was monitored to ensure that the pulse rate rose and remained at 20 beats above resting values or higher. The average clearance period during exercise was 15 min.

An age-appropriate, normal GFR and ERPF was calculated for each person using the equations:

$$Cl_{In} = 157 - (1.16 \times age) \qquad \text{Eq. 2}$$

$$Cl_{PAH} = 820 - (6.75 \times age), \qquad \text{Eq. 3}$$

where $Cl_{In}$ = the inulin clearance and $Cl_{PAH}$ = clearance of para-aminohippurate (*5*). Iodine-131-hippurate has greater serum binding than PAH (*6*), so that the radiolabeled tracer has a slightly smaller clearance than PAH (*7,8*). Iodine-131-hippurate clearance results were therefore multiplied by a factor of 1.2 to obtain a PAH equivalent value. Since DTPA and inulin have comparable renal kinetics, the GFR may be calculated directly with both substances (*9*). All measured clearance values were normalized and expressed in ml/min × 1.73 $m^2$.

Data are presented as mean values ± s.d. The small number of patients studied made it impossible to verify that a normally distributed population was studied. To avoid multiple statistical tests on this population, we restricted statistical analysis to the best-organ and compared the GFR of patients with normal and abnormal exercise scintigrams during exercise, for which analysis of variance was used.

## RESULTS

Twenty-three patients considered to have renovascular hypertension had a supine sequential scintigram as well as upright exercise scintigraphy. Fourteen developed a bilateral, transitory hippurate transport disturbance in response to upright exercise (Fig. 1). During scintigraphy in the supine position, the radiolabeled tracer appeared, on average, 3.4 min after intravenous injection in the urinary bladder. Exercise caused a delay in tracer appearance in the bladder, the first activity being seen 10.9 min after injecting the radioactivity (Table 3). These patients also demonstrated exercise-induced parenchymal tracer retention, which was documented in sequential scintigrams and in an elevated third curve segment of the renogram. In comparison, nine patients had scintigrams little influenced by exercise. The mean tracer appearance time in the bladder occurred after 3.3 min during the examination at rest and after 4.1 min during exercise (Table 3).

GFR and ERPF were determined in seven normotensive controls (Figs. 2 and 3). The mean age of the male volunteers was 39 yr. Accordingly, the mean predicted global GFR was 112 ml. The actual measured mean resting GFR was 102 ml. Twenty-five watt ergometric exercise caused the filtration rate (FF) to fall to 93 ml/min × 1.73 $m^2$. These control subjects had a predicted ERPF of 557 ml. The measured mean resting plasma flow was 543 ml, while exercise caused it to fall 13% to 477 ml. The FF was 0.19 at rest and 0.20 during exercise (Table 4).

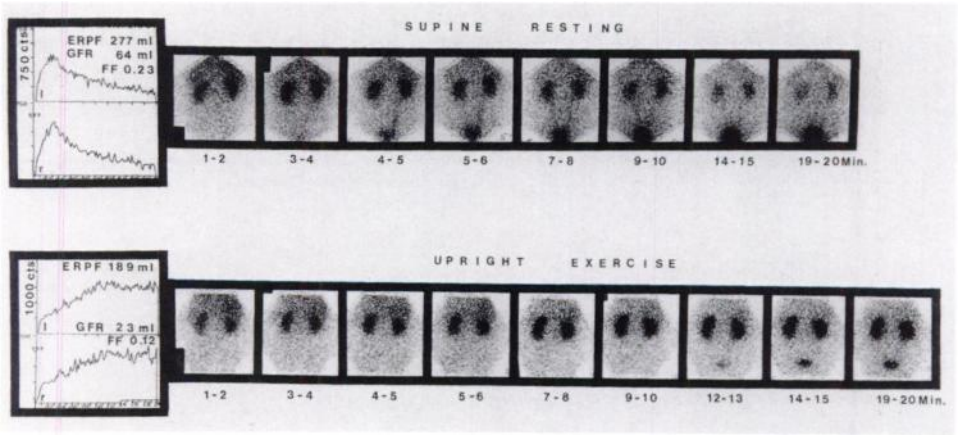


**FIGURE 1.** Renogram and sequential scintigrams of a 45-yr-old hypertensive male patient (no. 12) with angiographically documented unilateral vascular stenosis, examined in supine position and during upright exercise. The sequence of examinations demonstrate the exercise induced changein transrenal o-iodohippurate transport. The supine examination documents timely hippurate excretion from renal tissue, as evidenced by time-activity curves, tracer excretion into the bladder during the 4th minute and hippurate washout from the tissue of both kidneys towards the end of the examination. Exercise initiated a massive disturbance of tracer kinetics: the transport abnormality is at the parenchymal level. Note the clearance data, obtained during 25 watt ergometric exercise, which demonstrate that the hippurate transport disturbance is associated with a reduced ERPF and GFR, as well as a reduced FF.

All hypertensive patients had a clearance examination in the supine position, at rest, and during 25 watt ergometric exercise. The nine patients with normal exercise scintigrams had a mean, predicted, age-dependent GFR of 98 ml. The mean resting GFR of these hypertensives was reduced about 15%. Exercise caused the GFR to fall slightly to about 80% of the predicted value (Table 4). We noted a similar relationship between predicted and measured ERPF values. The mean, predicted, age-dependent ERPF was 478 ml for this group of patients. The resting ERPF was 394 ml/min (FF 0.21). As in normotensive controls, exercise caused a slight reduction of the ERPF to 357 ml (FF 0.22). Note that the FF remained quite stable. The data show that normal patients and those patients with a normal exercise scintigram responded to exercise in a similar manner, with a slight reduction in both GFR and ERPF. In comparison, patients with an abnormal exercise scintigram had a different clearance pattern. Both the predicted GFR and ERPF were lower since this patient population was older (Table 3). Thus, while the mean, predicted GFR was 87 ml, the measured value was nearly 40% reduced, being only 54 ml/min. During exercise, we documented a sharp fall in GFR to only 23 ml (Table 4), which was only 26% of the predicted value. The predicted ERPF of these patients was 415 ml/min. The mean measured value at rest was clearly compromised at 272 ml, which was 65% of the expected value. During exercise, the ERPF dropped to 45% of the mean predicted value and was 185 ml (FF 0.12).

The FF was calculated for every examination at rest and during exercise. The FF of hypertensives with normal exercise scintigrams was 0.21 at rest and 0.22 during exercise (Table 4). Individual values varied from 0.17 to 0.24 during the examination at rest and from 0.16 to 0.27 during exercise. While the spread of the values was higher during exercise, it should be noted that only one patient had a clearly reduced FF of 0.16. All other values were 0.18 or higher. The control population with a similar

**TABLE 3**
Twenty-three Patients with Renovascular Hypertension Grouped According to the Response to Exercise Scintigraphy

| Exercise renography | Age (yr) | Bilateral disturbance of parenchymal transport: Supine resting | Bilateral disturbance of parenchymal transport: Upright exercise | Bladder visualized (min): Supine | Bladder visualized (min): Exercise | Pulse: Resting | Pulse: Exercise | Blood pressure mean: Resting | Blood pressure mean: Exercise | Mean blood pressure pulse measurements per study | Watt (range) |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Controls (n=7) | 39 | 0 | 0 | 2.7 | 3.0 | 67 | 107 | 123/83 | 139/80 | 5.1 | 80–80 |
| Normal (n=9) | 51 | 0 | 0 | 3.3 | 4.1 | 74 | 110 | 162/96 | 189/98 | 3.4 | 65–68 |
| Abnormal (n=14) | 60 | 0 | 14 | 3.4 | 10.9 | 70 | 106 | 156/96 | 188/100 | 3.5 | 58–70 |

The two subgroups were compared with respect to age, parenchymal tracer transport, tracer appearance in the bladder, pulse rate, blood pressure and ergometric work load (watt). Data are presented as mean values.

**TABLE 4**
Twenty-three Patients with Renovascular Hypertension Grouped According to the Scintigraphic Exercise Results

| | Normotensives (7 controls) | Normal exercise scintigram (9 patients) | Abnormal exercise scintigram (14 patients) |
|---|---|---|---|
| Mean predicted resting GFR | 112 ± 12 ml | 98 ± 21 ml | 87 ± 12 ml |
| Mean measured resting GFR | 102 ± 18 ml | 83 ± 20 ml | 54 ± 17 ml |
| Mean GFR during exercise | 93 ± 20 ml | 77 ± 21 ml | 23 ± 16 ml |
| Mean predicted resting ERPF | 557 ± 81 ml | 478 ± 119 ml | 415 ± 70 ml |
| Mean measured resting ERPF | 543 ± 129 ml | 394 ± 99 ml | 272 ± 86 ml |
| Mean ERPF during exercise | 477 ± 117 ml | 357 ± 117 ml | 185 ± 80 ml |
| Predicted FF | 0.20 | 0.21 | 0.21 |
| FF at rest | 0.19 | 0.21 | 0.20 |
| FF during exercise | 0.20 | 0.22 | 0.12 |

The mean predicted resting, GFR, ERPF and the filtration fraction (FF) are shown, along with the measured clearance values at rest and during exercise.

spread of individual values had a FF of 0.19 at rest and 0.20 during exercise.

The FF of hypertensives with an abnormal exercise scintigram differed considerably from both comparison groups, particularly during the exercise period. Thus, the FF at rest was generally in the physiologic range with only three values noticeably reduced: one at 0.13 and two at 0.16. Light exercise, however, induced gross reduction in the FF of this group. The mean value dropped to only 0.12, reaching values of zero in two individuals when the glomerular filtration ceased, or dropped into an unmeasurable range. Indeed, all but three hypertensive patients had values below 0.15.

Pronounced stenosis will compromise both GFR and ERPF in the poststenotic kidney and modify global clearance values. When stenosis-induced and exercise-mediated perfusion compromise coexist, global clearance values will not permit the recognition and separate evaluation of the abnormality due to exercise. We therefore determined both GFR and ERPF of the best organ for each patient. This approach demonstrated that all patients with a normal exercise scintigram had at least one kidney with normal clearance values at rest. Indeed, the approach indicated that the best kidney of patients with normal exercise scintigrams may experience hyperperfusion during periods of rest, since both GFR and ERPF were slightly elevated (Table 5, Figs. 4, 5). The approach also showed that only 4 of 14 patients with a pathologic exercise scintigram had reduced resting clearnace values in the kidney with best function. Predicted and measured clearance values were very similar in this population.

GFR and ERPF of the best kidney was also assessed during exercise since the abnormal exercise scintigram is associated with a bilateral hippurate transport disturbance.

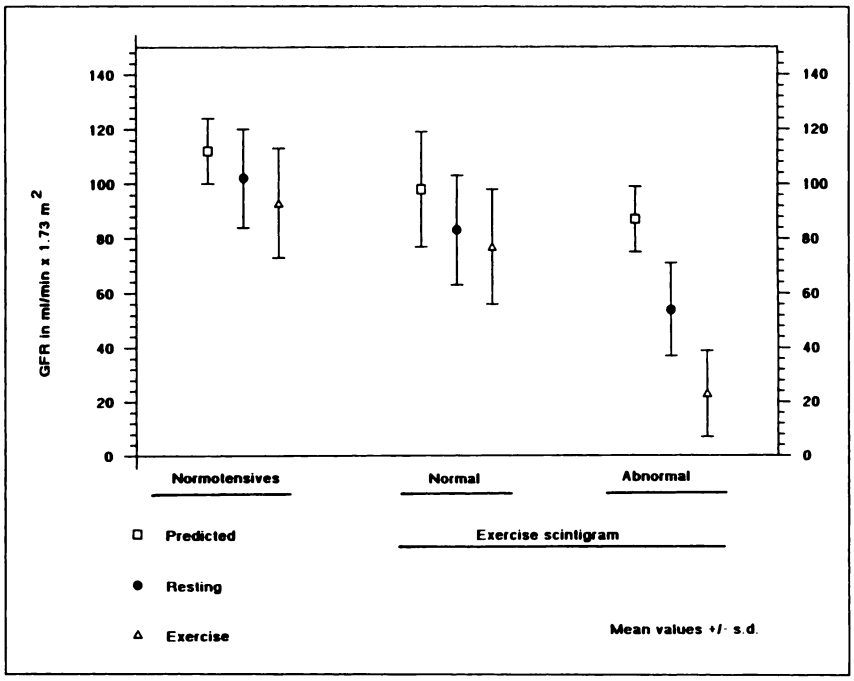


**FIGURE 2.** GFRs of 23 hypertensives and 7 controls. The hypertensives are grouped with respect to the results of exercise scintigraphy. The predicted and measured values, at rest and during exercise are demonstrated. Note: the GFR of hypertensives with normal and abnormal exercise scintigrams differ during exercise.

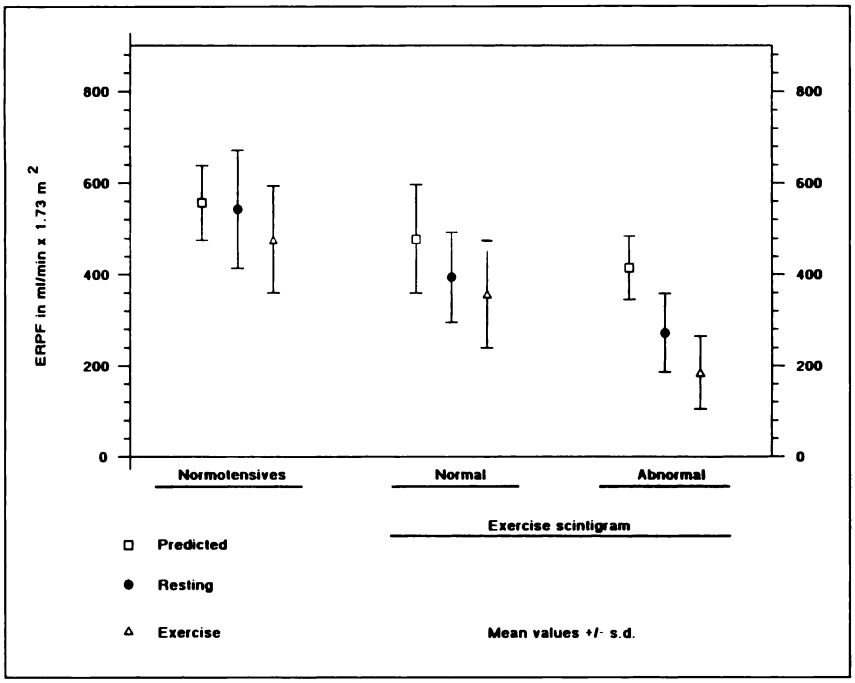


**FIGURE 3.** The global ERPF of 23 patients with renovascular hypertension, and 7 controls, is shown. The hypertensives are grouped with respect to the results of exercise scintigraphy. The predicted and measured values, both at rest and during exercise are demonstrated.

The best kidney of patients with abnormal exercise scintigrams experienced a notable reduction of GFR and ERPF values: mean best-organ GFR fell from 40 ml at rest to 17 ml during 25 watt ergometric exercise (Table 5). This result found statistical support when the GFR of the best kidney of patients with normal, and abnormal exercise scintigrams was compared. Analysis of variance indicates with 99% probability that both populations of hypertensive patients have a different GFR during such periods of light work.

We tried to evaluate the investigated, exercise-mediated response with a standardized workload. Since exercise at a specific watt setting results in very different exercise levels for individual patients, we used the pulse rate response to monitor the exercise. The pulse rate response to exercise was similar for patients with normal and abnormal exercise scintigrams (Table 3), as was the mean watt range used in the examinations (Table 3).

Many patients responded to exercise with a rise in blood pressure. Five of nine (55%) hypertensive patients with a normal exercise scintigram had a 10% or greater rise in systolic blood pressure during exercise. Eight of 14 (57%) hypertensive patients with an abnormal exercise scintigram had a similarly pronounced rise in systolic blood pressure during ergometric stimulation. However, four exercise negatives and six patients with abnormal exercise scintigrams failed to develop a significant rise in blood pressure during exercise. Similarly, there was no observable difference in the resting diastolic blood pressure between both groups of patients. Also, exercise did not cause diastolic values to regularly rise or fall in patients with normal or abnormal exercise scintigrams.

## DISCUSSION

Our studies were performed with $^{131}$I-o-iodohippurate, a tracer with renal kinetics comparable to para-aminohippurate (*8,10*). Gamma camera renograms and sequential scintigrams permit evaluation of the transrenal tissue transport of the tracer, as well as assessment of single kidney function (*11,12*). The prominent accumulation curves observed during exercise are the result of parenchymal hippurate deposition. Hippurate is actively pumped

**TABLE 5**
Twenty-three Patients with Renovascular Hypertension Grouped According to Exercise Renogram Results

| Best kidney | Normal execise scintigraphy (n = 9) | Abnormal exercise scintigraphy (n = 14) |
|---|---|---|
| Predicted one-kidney resting GFR | 49 ± 10 ml | 44 ± 6 ml |
| Measured best-kidney GFR at rest | 61 ± 21 ml | 40 ± 12 ml |
| Best-kidney GFR during exercise | 54 ± 12 ml | 17 ± 14 ml |
| Predicted one-kidney resting ERPF | 238 ± 60 ml | 207 ± 34 ml |
| Best kidney measured ERPF at rest | 290 ± 95 ml | 202 ± 67 ml |
| Best kidney ERPF during exercise | 256 ± 90 ml | 137 ± 65 ml |

The mean predicted best kidney resting GFR and ERPF are shown with the mean measured clearance values at rest and during exercise.

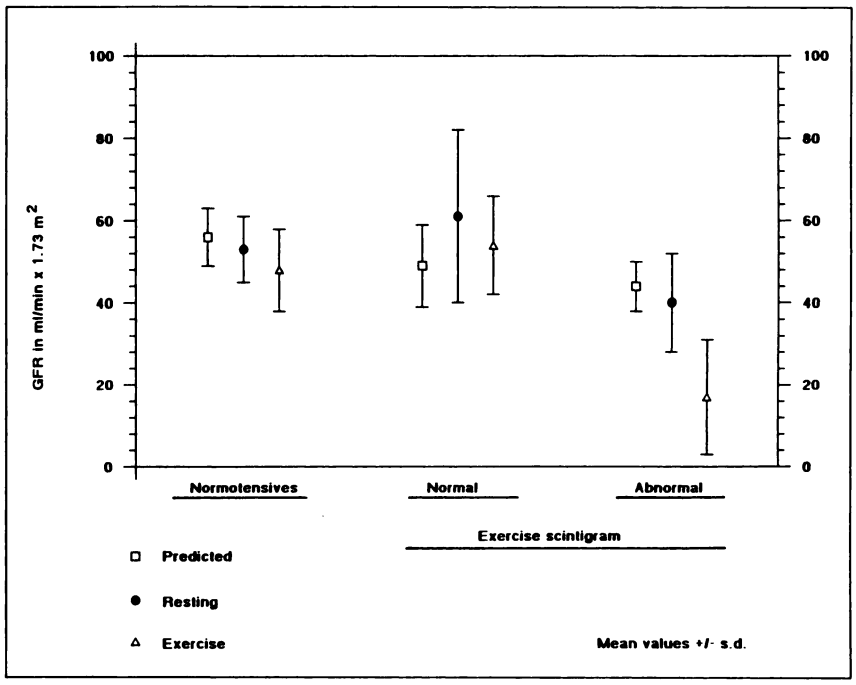


**FIGURE 4.** Single kidney GFRs are demonstrated for the organ with best function of 23 patients with renovascular hypertension and for 7 controls. Predicted single kidney GFR is half the age-predicted global value. Best-organ GFR was estimated from the measured global clearance values multiplied by the single kidney function calculated from the renogram. Note the wide divergence in the GFR during exercise in patients with normal and abnormal exercise scintigrams.

into proximal tubular cells, creating an interstitial concentration gradient that promotes its passive outflow across the cell membrane into the tubulus lumen (*13,14*). We were able to demonstrate that functional parenchymal hippurate accumulation is possible (*1,15*). This functional tracer entrapment will occur when reduced glomerular filtration results in slowed washout of hippurate from the tubulus lumen, increasing the intraluminal hippurate concentration. The event disrupts the transit of hippurate from the cell into the lumen. Thus, both preglomerular and postglomerular pressure changes, which decrease GFR, lower the cell-lumen concentration gradient and induce tracer entrapment. Thus, the scintigraphic images suggest the existence of an exercise-mediated disturbance of intrarenal flow.

We sought to determine whether the hippurate transport disturbance of abnormal exercise scintigrams is indeed due to an imbalance between tubular hippurate secretion and GFR (*2,4*). The clearance data indicate that hypertensive patients with abnormal exercise scintigrams have a notable reduction of GFR and a less pronounced fall in ERPF during exercise. This results in an exercise-mediated highly

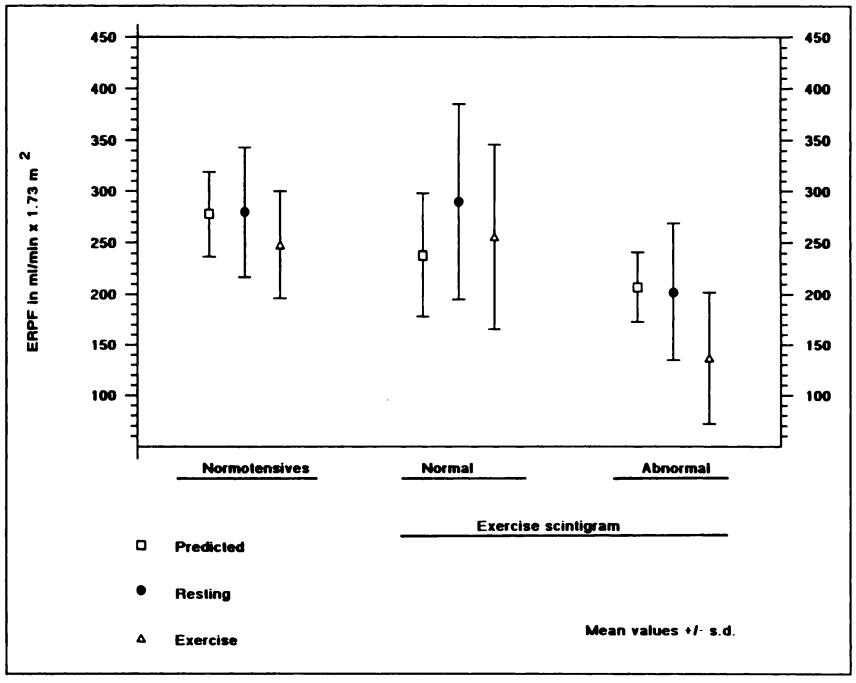


**FIGURE 5.** Single kidney ERPF rates are demonstrated for the organ with best function in 23 patients with renovascular hypertension and for 7 controls. Predicted single kidney ERPF is half the age-predicted global value. Best organ ERPF was estimated from the measured global ERPF values multiplied by the single kidney function calculated from the renogram.

abnormal FF suggestive of resistance-vessel dysfunction. The most probable explanation for the low FF seen in patients with an abnormal exercise scintigram is the existence of exercise-mediated vascular dysfunction of pre- or post-glomerular vessels.

The signal characteristic of an abnormal exercise renogram in renovascular hypertension due to unilateral stenosis is bilateral hippurate transport disturbance. This suggests that the better kidney warrants particular attention. This organ of both exercise positives and negatives was compared. Patients with renovascular hypertension and a normal exercise scintigram appeared to have elevated GFR and ERPF values at rest, suggesting the possibility of hyperperfusion of this organ. The data are not conclusive, due to a wide overlap with the predicted range. This result, however, differed from that seen in patients with abnormal exercise scintigrams, who appeared to have reset both GFR and ERPF into a lower range. While resting values were normal, exercise caused both GFR and ERPF to contract. This was the single most important result of this study, since it supported the interpretation of the scintigrams that abnormal exercise scans result from a perfusion disturbance in the apparently noninvolved, nonstenosed organ of patients with renovascular hypertension.

The perfusion abnormality of the best kidney of patients with abnormal exercise scintigrams is masked. It could not be identified without the exercise protocol (Table 6). To identify the value of the exercise procedure, we placed all 23 hypertensive patients into a single population and recalculated both predicted and resting clearance data for the combined population. The calculated mean, age-dependent, normal GFR and ERPF of the whole population was divided by two to obtain the normal one-kidney GFR and ERPF for our group of hypertensive patients. We then recalculated the actual measured clearance data to obtain the mean, best-kidney GFR and ERPF at rest for the total population. The predicted GFR was 46 ml; the expected ERPF was 219 ml. The mean measured GFR of the best organ was 48 ml, while the ERPF was 236 ml. Without the use of exercise scintigraphy, the best kidney would have been judged to have a normal perfusion. This may explain why the perfusion disturbance was not recognized earlier.

**TABLE 6**
Predicted and Resting Clearance Data for the Combined Patient Population

| | GFR | ERPF |
|---|---|---|
| Predicted | 46 | 219 |
| Measured at rest | 48 | 236 |

The mean, best-organ resting GFR and ERPF are shown and compared to the mean predicted clearance values for the population. Note that the described perfusion disturbance fails to be identified when the data obtained with the exercise protocol fails not to be used.

A transitory perfusion abnormality may have little relevance for maintenance of renovascular hypertension since the function disturbance can be compensated for during periods of normal perfusion. However, considerable evidence has been accumulated that indicates that the perfusion abnormality is easily and quickly activated and that its intensity is variable. When nonselected hypertensives were examined in the standing position, 20% developed a disturbed transrenal hippurate transport (*1,15*). When light exercise was used, we documented abnormal hippurate transport in nearly 60% of the examined population. This suggests that increased stimulation increases the frequency with which the disturbance is observed. Similarly, we previously attempted to standardize the exercise protocol by obtaining scintigrams at the threshold at which exercise results in anaerobic energy production. The turning point from aerobic to anaerobic energy production was identified by an increase in blood lactate levels. These studies showed that the abnormal exercise scintigram is regularly seen at the aerobic/anaerobic threshold, which required less exercise than the pulse rate levels achieved in our studies (*3*). The range of FFs calculated from the clearance data also suggests that the perfusion abnormality is variable in its severity. Finally, we strongly suspect that emotional stress induces the perfusion disturbance as well. Obviously, we do not know how sensitive hippurate transport is for recognition of discreet abnormality. We therefore hypothesize that hypertensives with an abnormal exercise scintigram have a variously severe renal perfusion disturbance throughout much of the day: while standing, walking, working and probably during periods of emotional stress. Unilateral or bilateral stenosis may therefore be complicated by bilateral ischemia due to resistance vessel dysfunction. Thus, in established renovascular hypertension, renal sodium handling can be expected to have unrecognized relevance in the maintenance of elevated systemic blood pressure (*16, 17*).

It should be recognized that perfusion of the poststenotic kidney is determined in part by peripheral vascular resistance. Thus, the functional significance of a vascular stenosis will change as vascular resistance varies. Peripheral vascular resistance is presently neglected in the evaluation of vascular stenosis. The demonstration of a functional abnormality of the kidney's resistance vessels suggests that many hypertensives with renal artery disease may have a dual disturbance of perfusion: one resulting from stenosis, and one eminating from the kidney's resistance vessels. More importantly, unilateral vascular stenosis can be expected to be associated with either hypertension of the two kidney one clip type, or with bilateral ischaemia due to resistance vessel dysfunction.

A decade has passed since the posture and exercise-mediated hippurate transport disturbance was identified in hypertensive disease (*1,15*). The well known renal kinetics of hippurate and the functional pattern of tracer

excretion implicated resistance vessels and renal perfusion in the disturbance. We consider the investigation of resistant vessel perfusion compromise to be as relevant to the understanding of hypertension as perfusion disturbances of prerenal origin. The perfusion abnormality under investigation, easily recognized with the exercise scintigram, appears to merit extensive research.

## REFERENCES


1. Clorius JH, Schmidlin P. The exercise renogram. A new approach documents renal involvement in systemic hypertension. *J Nucl Med* 1983;24: 104–109.
2. Clorius JH, Mann J, Schmidlin P, Strauss LG, Saur T, Irngartinger G. Clinical evaluation of patients with hypertension and exercise-induced renal dysfunction. *Hypertension* 1987;10:287–293.
3. Clorius JH, Allenberg JR, Hupp T, et al. Predictive value of exercise renography for presurgical evaluation of nephrogenic hypertension. *Hypertension* 1987;10:280–286.
4. Hupp T, Clorius JH, Allenberg JR. Renovascular hypertension. Predicting surgical cure using exercise renography. *J Vasc Surg* 1991;14:200–207.
5. Diem K, Lentner C, eds. *Wissenschaftliche Tabellen. Documenta Geigy,* 7th edition. Stuttgart: Georg Thieme Verlag; 1975;527.
6. Maher FT, Strong CG, Elveback LR. Renal extraction ratios and plasma binding studies of radioiodinated orthoiodohippurate and iodopyracet and of p-aminohippurate in man. *Mayo Clin Proc* 1971;46:189–192.
7. Mackay A, Eadie A, Cumming AMM, Graham AG, Adams FG, Horton PW. Assessment of total and divided renal plasma flow by $^{123}$I-hippuran renography. *Kidney International* 1981;19:49–57.
8. Stadalnik RC, Vogel JM, Jansholt A-L, et al. Renal clearance and extraction parameters of ortho-iodohippurate (I-123) compared with OIH (I-131) and PAH. *J Nucl Med* 1980;21:168–170.
9. Cohen ML. Radionuclide clearance techniques. *Semin Nucl Med* 1974;4: 23–38.
10. Blaufox MD, Potchen EJ, Merrill JP. Measurement of effective renal plasma flow in man by external counting methods. *J Nucl Med* 1967;8: 77–85.
11. Britton KE, Chir B, Brown NJG. The clinical use of CABBS renography: investigation of the "non-functioning kidney" and renal artery stenosis by use of $^{131}$I-hippuran renography modified by computer assisted blood background subtraction (CABBS). *Br J Radiol* 1968;41:570–579.
12. Zielinski FW, Holly FE, Robinson GD, Bennett LR. Total and individual kidney function assessment with iodine-123 orthoiodohippurate. *Radiology* 1977;125:753–759.
13. De Grazia JA, Scheibe PO, Jackson PE, et al. Clinical applications of kinetic model of hippurate distribution and renal clearance. *J Nucl Med* 1974;15:102–114.
14. Foulkes EC. Kinetics of p-aminohippurate secretion in the rabbit. *Am J Physiol* 1963;205:1019–1024.
15. Clorius JH, Schmidlin P, Raptou E, Huber W, Georgi P. Hypertension associated with massive, bilateral, posture-dependent renal dysfunction. *Radiology* 1981;140:231–235.
16. Di Bona GF. Sympathetic nervous system influences on the kidney. *AJH* 1989;2:119 S–124 S.
17. Bruun NE, Rehling M, Skott P, Giese J. Enhanced fractional sodium reabsorption in the ischaemic kidney revisited with lithium as a probe. *Scand J Clin Lab Invest* 1990;50:579–585.