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Exercise Activates Renal Dysfunction in Hypertension

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A bilateral, exercise-mediated renal functional abnormality was first described more than a decade ago. The disturbance is specific for hypertension, is seen in different forms of hypertension, and has been studied most extensively in hypertensives with renovascular disease. The bilateral-abnormal exercise renogram identifies the disturbance. Hypertensives with unilateral renovascular disease were studied in the continuing evaluation of the bilateral function disturbance.

We examined 31 hypertensives with documented unilateral renovascular disease, all of whom had renography at rest and during 60 to 80 W ergometric exercise. An additional seven normotensives and 17 essential hypertensives served as controls, and had the same sequence of studies. All patients reported upon continued on to an infusion clearance with ^{131}I-hippurate and ^{111}In-diethylenetriamine pentaacetic acid to determine glomerular filtration rate (GFR) and effective renal plasma flow (ERPF) at rest, and during 25 W ergometric exercise.

Eighteen of 31 hypertensives with unilateral renovascular disease were found to have a bilateral-abnormal exercise renogram. Clearance examinations in these identified a prominent reduction of the GFR and a lesser decrease in the ERPF during exercise. Hypertensives with normal exercise renograms did not have the exercise mediated abnormal clearance pattern. Similar results were observed in the control population of essential hypertensives, 65% of whom developed the functional disturbance. The seven normotensives controls did not exhibit the exercise mediated function changes.

We conclude that an exercise-mediated bilaterally occuring functional disturbance exists in certain hypertensives, who then have a bilateral-abnormal exercise renogram. Associated with this is a distinctly abnormal clearance during exercise which is characterized by a low filtration fraction. Am J Hypertens 1996;9:653–661

KEY WORDS: **Hypertension, kidney, renal dysfunction, radioisotopes, exercise, renography.**

An exercise mediated tissue transport disturbance of the radiolabeled para-aminohippurate (PAH) analog hippurate was reported a decade ago in a population of unselected hypertensives.[1] The examined population had a normal transrenal ^{131}I-hippurate transport when examined at rest. Repeat examinations during ergometric exercise caused bilateral tissue entrapment of the labeled hippurate. Slow tracer washout from the tissue resulted in delayed excretion of hippurate into

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the bladder, and thereby caused an elevation of the excretory segment of the renogram. The renographic pattern had not been described. The known kinetics of hippurate however, suggested that the exercise mediated change in tracer transport might well be an expression of an exercise-induced disturbance of perfusion. Evidence to date indicate that the disturbance is specific for hypertension[1,2] and that it can not be recognized with the commonly used clinical tests employed in the evaluation of hypertension.[3] The disturbance was seen in nearly 60% of unselected hypertensives.[1] It was shown that bilateral-abnormal exercise renograms occur in patients classified as having essential hypertension, malignant and renoparenchymal hypertension, as well as in hypertension associated with renovascular disease.[3] This last group has been used as a model to evaluate the disturbance.

This study continues to use hypertensives with renovascular disease to investigate exercise-mediated renal dysfunction. An earlier study had assessed global and unilateral glomerular filtration rate (GFR) and effective renal plasma flow (ERPF) in hypertensives with bilateral-abnormal exercise renograms.[4] It was based on a much smaller patient population, which did not permit the selective study of those with unilateral renovascular disease, since one third of the patients had bilateral renovascular lesions. Consequently, we estimated GFR and ERPF for the "better" kidney. This study estimates global and nonstenosed single kidney clearance values for a homogenous population of hypertensives with unilateral renovascular lesions. The potential influence of large-vessel disease on GFR and ERPF was thus eliminated, for the nonstenosed kidney.

It was the goal of this study to define the investigated disturbance relative to clearance parameters and show that the disturbance, while studied in hypertensives with renovascular disease, is not specific to this population or caused by the vascular lesion.

METHODS

Thirty-one patients, 19 male and 12 female, are included in the present evaluation. All hypertensives with angiographically documented unilateral renal artery stenosis, examined at this center with exercise renography and a clearance examination, are included in the study. Patients with bilateral vascular disease were excluded from evaluation. Stenosis was defined as a 50% or greater lumen reduction. The caliber of the stenosis was estimated from single projection angiography. The average age of the patient population was 55.6 years. The vascular stenosis was 16 times on the left side and 15 times on the right side. Twenty hypertensive patients had atherosclerosis, three with diabetes, four with hypercholesteremia, two with renal artery aneurisms on the side of the stenosis, four with abdominal aneurysms, and one with compensated renal insufficiency. Five hypertensives had vascular lesions due to fibromuscular dysplasia and in six patients the angiograms failed to define the cause of vessel disease. The antihypertensive medication taken by each patient at the time of scintigraphy was documented (Table 1, Table 2). The control populations consisted of 17 patients with essential hypertension, and seven normotensive volunteers.

The diagnosis of essential hypertension was formulated when secondary causes of hypertension were considered highly improbable. A normal urinalysis and ultrasound study, combined with normal serum creatinine and serum urea values made hypertension of renal orgin unlikely. Both angiograms and captopril renal scintigrams were used only when the initial screening procedure suggested the need for these additional studies. Serum potassium was determined to exclude primary aldosteronism. All patients were checked for evidence of thyroid disease.

All hypertensives had a supine-position resting sequential renal scintigram with either ^{131}I-hippurate or ^{99m}Tc-mercaptoacetyl-triglycine (MAG_3), as well as a scintigraphic examination while sitting upright during ergometric exercise not exceeding 80 W.

All patients received oral instructions about the series of examinations, in which the goal of the procedure was explained. When ^{131}I-hippurate was used, the examinations occurred in the following sequence: γ-camera renography in the supine position, clearance examination at rest 30 to 40 min after completion of the supine position γ-camera renogram, determination of GFR and ERPF during exercise without repositioning the patient. Upright exercise renograms were generally obtained on the following day. Hypertensives examined with ^{99m}Tc-MAG_3 were examined on 3 separate days. An attempt was made to complete all examinations within a 4 day period.

γ-Camera renography was carried out after intravenous injection of either 7 μCi ^{131}I-*O*-iodo-hippurate, or 6 μCi ^{99m}Tc-MAG_3/kg body weight. We used a large field of view (50 cm) γ-camera equipped with a general-purpose, medium-energy, parallel-hole collimator for imaging ^{131}I, and fitted the camera with a low-energy, all-purpose parallel-hole collimator for examinations with ^{99m}Tc. The window was opened 25% and was centered over the photopeak of each tracer. Data acquisition for the renogram generation was 12 sec per frame. One-minute scintiscans were made from the 1st through the 4th minute, and from the 7th, 9th, 14th and 19th min thereafter. Examinations were terminated at 20 min. A computer workstation was used to place regions of interest over each kidney to determine single kidney function. Background regions of interest were placed below and 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 gra-

TABLE 1. HYPERTENSION-ASSOCIATED DISEASES AND ANTIHYPERTENSIVE MEDICATION OF 13 PATIENTS WITH UNILATERAL RENAL ARTERY STENOSIS AND A NORMAL EXERCISE RENOGRAM

Patient	Vascular Stenosis (%)	Associated Disease	Drugs at Scintigraphy
1	85	Athero, diabetes Type II	1, 3, 5, B
2	90	Athero, renal stones, hyperchol (273 mg/dL)	5
3	>50	Athero	2, 3, 5
4	60	Fibromuscular dysplasia	2
5	75	Fibromuscular dysplasia, renal infarct	4
6	>75	Athero	1, 2
7	70	Athero	none
8	>75	Athero, renal artery aneurysm	3
9	>75	Fibromuscular dysplasia	none
10	70	Renal insufficiency, hyperchol (255 mg/dL)	2, 4, 5
11	>75	Athero	1, 2, 5
12	100	Athero, diabetes	2, 4, A
13	>75	Athero	2, 3

Column 4: 1, diuretics; 2, calcium antagonists; 3, β-blockers; 4, sympatholytic drugs; 5, angiotensin converting enzyme inhibitors; A, diabetes mellitus managed with dietary measures only; B, diabetes mellitus managed with oral medication (glibenclamid).

Column 3: hyperchol, hypercholesterolemia (norm: 220 mg/dL); athero, atherosclerosis.

dient of the renogram between the 24th and 120th sec. The supine scintigram served as the base study against which the exercise renogram was compared in order to identify the exercise-induced tissue tracer transport disturbance. To evaluate this exercise mediated change in tracer transit through the tissue of the kidney we visually compared resting and exercise sequential scintigrams. This identified the degree of parenchymal tracer trapping effectively, albeit qualitatively. We also compared the two studies with respect to the tracer's appearance in the bladder and the elevation of the excretory segment of the renogram, both of which also documented the exercise induced delay in renal tracer transit.

The exercise scintigram was obtained while the patient sat in front of a γ-camera on a bicycle ergometer. Patients were asked to sit straight-backed and press against the camera to reduce movement and minimize the kidney-to-camera distance. Ergometric resistance was initially set at 60 W for women and 80 W for men after 40 to 60 rotations/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

TABLE 2. HYPERTENSION-ASSOCIATED DISEASES AND ANTIHYPERTENSIVE MEDICATION OF 18 PATIENTS WITH UNILATERAL RENAL ARTERY STENOSIS, AND A BILATERAL-ABNORMAL EXERCISE RENOGRAM

Patient	Vascular Stenosis (%)	Associated Disease	Drugs at Scintigraphy
14	70	Pyelonephritis, hyperchol (265 mg/dL)	3, 4, 5
15	>50	Fibromuscular dysplasia	1, 2, 3
16	90	Adiposity	3
17	70	Abdominal aneurism, diabetes, hyperchol (294 mg/dL)	3, A
18	50	Athero	1, 2
19	>50	Athero, abdominal aneurism, hyperlipemia (252 mg/dL)	2, 3
20	50	Athero	1, 2
21	90	Fibromuscular dysplasia	2
22	90	Athero, adiposity, hyperchol (198 mg/dL)	1, 2, 3, 4
23	70	Athero	1, 2, 3, 4
24	70	Athero, fibromuscular dysplasia	2, 3, 4, 5
25	>75	None	5
26	>75	None	none
27	>75	Athero, coronary heart disease	1
28	70	Athero	1, 5
29	90	Athero, comp. renal insuf.	1, 4, 5
30	100	Athero, abdominal aneurism, silent kidney	1
31	50	Athero, abdominal aneurism, renal artery aneurysm	2

over the workload used. Renography was begun after the pulse rate had increased at least 20 beats/min. Patients continued with exercise following radiotracer injection. Pulse and blood pressure were monitored at irregular intervals during exercise (Table 3). 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.

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 W ergometric exercise. The clearance examination of hypertensives examined with hippurate began 50 to 70 min after simultaneous intravenous injection of 7 μCi ^{131}I-hippurate and 3.5 μCi ^{111}In-DTPA/kg body weight. Hippurate was injected for sequential scintigraphy, and the ^{111}In-DTPA was given concurrently. The time lapse between tracer injection and infusion clearance served to fill the extravascular compartments. Hypertensives scintigraphed with ^{99m}Tc-MAG$_3$ had the clearance examination on a separate day. They received 120 μCi ^{131}I-hippurate and 120 μCi ^{111}In-DTPA intravenously 30 min before commencing with the infusion clearance.

A butterfly needle placed into a superficial vein of the right arm was used for a continuous infusion clearance. During the 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 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 a 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:

$$Cl = \frac{I \times A_{st}}{A_{pl}}$$

where Cl = clearance (milliliters/minute); I = number of motor steps per time (reciprocal minutes); A_{st} = activity pumped per motor step (microcuries); and A_{pl} = specific activity of plasma (microcuries/milliliter).

Immediately after completion of the resting clearance measurement period, and without repositioning the patients, we began the exercise protocol with 25 W. 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 10 min.

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

$$Cl_{In} = 157 - (1.16 \times age)$$

$$Cl_{PAH} = 820 - (6.75 \times age),$$

where Cl_{In} = the inulin clearance and Cl_{PAH} = clearance of paraaminohippurate.[5] ^{131}I-Hippurate has greater serum binding than PAH,[6] so that the radiolabeled tracer has a slightly smaller clearance than PAH.[7,8] ^{131}I-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 was calculated directly.[9] All measured clearance values were normalized and expressed in milliliters/minute × 1.73 meters squared. To arrive at the age-appropriate single organ GFR and ERPF we halved the predicted global values. We calculated the clearance values of organs not situated behind a vascular stenosis from the measured global GFR and ERPF and multiplied by the percentage of renal function of the nonstenosed kidney as determined from the renogram.

Data are presented as mean values ± standard deviation. The clearance data of normotensives and hypertensives with a normal as well as a bilateral-abnormal exercise renogram were analyzed with the paired *t* test, to

TABLE 3. HYPERTENSIVE PATIENTS WITH NORMAL AND BILATERAL-ABNORMAL EXERCISE RENOGRAMS ARE COMPARED WITH RESPECT TO PULSE RATE AND BP WHILE SITTING AND DURING UPRIGHT EXERCISE. MULTIPLE PULSE AND BP MEASUREMENTS WERE OBTAINED DURING EXERCISE AND WERE AVERAGED

Exercise Renogram	Pulse Rate (beats/min)		Blood Pressure (mm Hg)	
	Sitting	Exercise	Sitting	Exercise
Normal (N = 13)	77 ± 13	110 ± 14	169/98	196/97
Abnormal (N = 18)	71 ± 8	114 ± 15	156/100	182/98

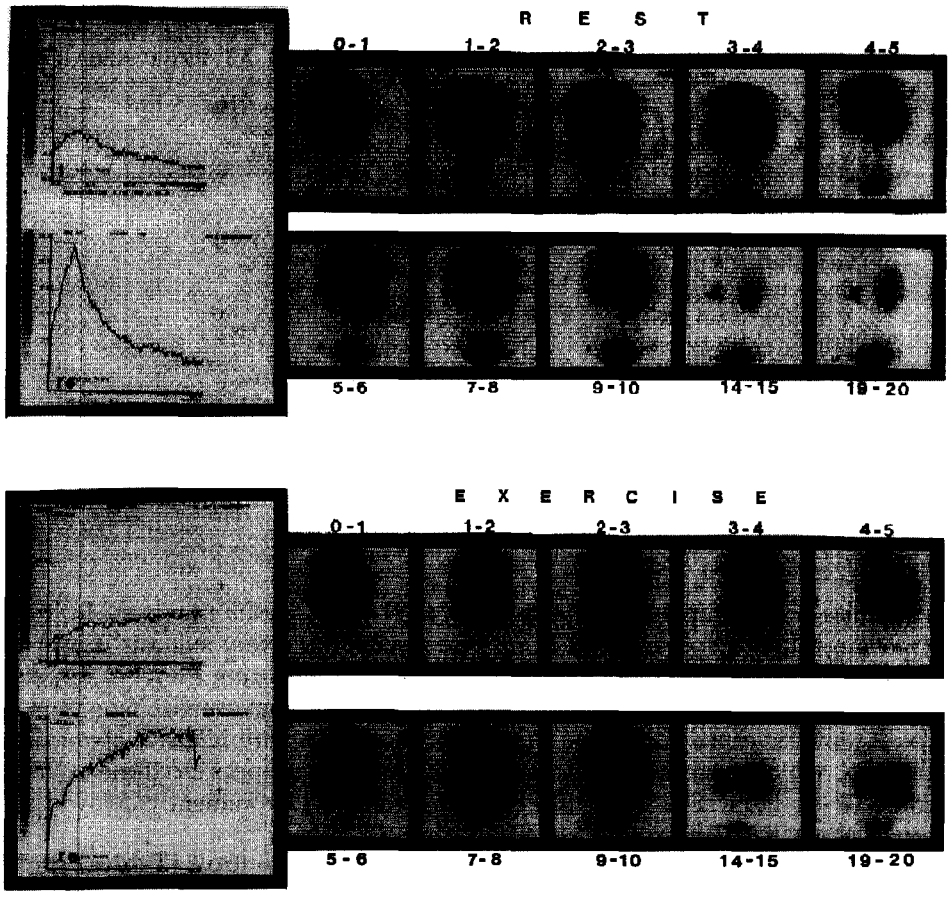

FIGURE 1. *A 39 year old hypertensive female patient was scintigraphed after angiography identified a renal artery stenosis on the left side. Hypertensive disease was identified 16 years previously. γ-Camera renography was used to estimate single kidney function: left 28%, right 72%. Transrenal tracer transport was timely. Tracer appeared in the bladder during the 4th min. Ergometic exercise activated the function disturbance which resulted in a bilateral-abnormal exercise renogram. Note the bilateral tissue retention in the kidneys, and delayed excretion of tracer into the bladder. The excretory segment of the renogram was elevated due to retention of the tracer in the tissue. The demonstrated results are relatively typical for a bilateral-abnormal exercise renogram. In seven of the 18 hypertensives the disturbance was less pronounced, eight others had a transit abnormality during exercise comparable to that shown here, while two had an even more pronounced tracer transit disturbance.*

determine whether GFR, ERPF, and filtration fraction (FF) change during exercise. A one-sided test was used. The boundary level of significance was $P = .001$.

RESULTS

Thirty-one hypertensives with angiographically documented unilateral renovascular stenosis had both renography and clearance examinations at rest and during ergometric exercise, to determine whether evidence of bilateral renal dysfunction occurred during exercise. Eighteen hypertensives developed bilateral-abnormal exercise renograms (Figure 1); in 13 the exercise renogram was normal. Patients with a bilateral-abnormal exercise renogram had a normal transrenal tracer transit while resting, and developed a transport disturbance during exercise. This was able to be recognized using serial scintigrams, since the radiolabeled renal tracers were trapped in the tissue of both kidneys. This also caused a delayed excretion of the tracer into the bladder, and an elevated excretory segment of the renogram.

Global Clearance Values (Table 4) Global clearance values of hypertensives with renovascular lesions and a normal exercise renogram were compared to those with a bilateral-abnormal exercise renogram. Due to the 2.3 year mean-age difference between the populations, the age-appropriate predicted GFR and ERPF was 3% less in patients with bilateral-abnormal exercise renograms. Hypertensives with a normal exercise renogram had mean global resting GFR of 84 mL and an ERPF of 410 mL, which was 11% below predicted results. Exercise caused an additional 7% reduction of the GFR (P = NS) and a 14% reduction in the ERPF (P = NS). The FF was 0.204 during the resting measurement, and 0.221 during exercise (P = NS). The 18 hypertensives with a bilateral-abnormal exercise renogram had a mean 24% reduction in the global resting GFR and ERPF, relative to the predicted GFR and ERPF of 91 mL and 436 mL, respectively. The mean resting FF of 0.208 was comparable to that of hypertensives with normal exercise renograms. Five of these 18 hypertensives did not respond to exercise with a fall in FF, while 13 hypertensives reacted to exercise with a prominent reduction in the FF value. Even though five failed to respond to the 25 W level of exercise, the mean measured GFR values of this population of 18 fell by 60% from 69 mL to 27 mL ($P < .001$), while the ERPF fell by 32% from 333 mL to 228 mL ($P < .001$), resulting in a fall of FF to 0.119 ($P < .001$).

Nonstenosed Kidney Clearance (Table 5) The clearance data of the kidney without stenosis-induced flow

TABLE 4. 31 HYPERTENSIVES WITH UNILATERAL RENAL ARTERY STENOSIS WERE GROUPED ACCORDING TO RESULTS OF EXERCISE RENOGRAPHY. THE MEAN PREDICTED GFR, ERPF AND FILTRATION FRACTION (FF) ARE SHOWN AT REST AND DURING EXERCISE

	Normal Exercise Renogram (N = 13)		Bilateral-Abnormal Exercise Renogram (N = 18)	
Predicted global GFR	94 ± 17		91 ± 13	
Measured total GFR	84 ± 20	NS	69 ± 14	S
GFR during exercise	78 ± 32		27 ± 25	
Predicted global ERPF	452 ± 101		436 ± 76	
Measured total ERPF	410 ± 113	NS	333 ± 75	S
ERPF during exercise	352 ± 130		228 ± 84	
FF at rest	0.204 ± .02	NS	0.208 ± .04	S
FF during exercise	0.221 ± .06		0.119 ± .09	

Data are mean values ± SD.

NS, not significant; S, significant at $P < .001$.

GFR and ERPF in milliliters/minute × 1.73 meters squared.

compromise was estimated to judge how GFR and ERPF change during exercise. In the presence of a bilateral-abnormal exercise renogram, the mean resting GFR and ERPF were in the expected midnormal range. The 25 W ergometric exercise resulted in a 60% reduction of the GFR, which decreased from 44 to 18 mL/min on average ($P < .001$). The mean ERPF contracted less severely when it fell from 211 to 149 mL/min ($P < .001$). The exercise mediated change caused the FF to fall to 0.12 ($P < .001$). These results differ noticeably from those observed in hypertensives with a normal exercise renogram, in whom GFR and ERPF in the nonstenosed kidney were slightly elevated relative to predicted values. Thus while the mean predicted GFR was 47 mL/min, the mean measured value was 55 mL/min (P = NS). Light exercise caused both GFR and ERPF to retreat into the midnormal range (P = NS). The FF of these hypertensives was similar at rest and during exercise, being 0.21 and 0.22, respectively (P = NS).

The bladder appearance time of the tracer reflects tissue transport. In hypertensives with unilateral renal artery stenosis it was 4.3 min and 4.8 min at rest and during exercise, respectively, when patients with normal exercise renograms were studied. In hypertensives with bilateral-abnormal exercise renograms, the tracer appearance time in the bladder was 3.9 min at rest, and prominently delayed to 11.2 min during exercise.

Controls (Tables 6 and 7) Controls with essential hypertension demonstrated a comparable renographic and clearance pattern as those with unilateral renovascular disease. Eleven of 17 had a bilateral-abnormal exercise renogram. These 11 controls had a FF reduction from 0.19 at rest to 0.06 during 25 W exercise ($P < .001$). The six with a normal exercise renogram had a mean resting FF of 0.22, which went to 0.24 during exercise (P = NS). All patients with essential hypertension had resting clearance values within the age-appropriate normal range. Furthermore, calculated single kidney function determined from the supine position

TABLE 5. 31 HYPERTENSIVES WITH UNILATERAL RENAL ARTERY STENOSIS WERE GROUPED ACCORDING TO RESULTS OF EXERCISE RENOGRAPHY. THE MEAN ONE-KIDNEY PREDICTED GFR AND ERPF ARE SHOWN ALONG WITH THE NONSTENOSED ORGAN'S CLEARANCE VALUES AT REST AND DURING EXERCISE

	Normal Exercise Renogram (N = 13)		Bilateral-Abnormal Exercise Renogram (N = 18)	
Predicted one-kidney GFR	47 ± 9		46 ± 7	
Measured GFR at rest	55 ± 17	NS	44 ± 10	S
GFR during exercise	51 ± 18		18 ± 17	
Predicted one-kidney ERPF	226 ± 51		218 ± 38	
Measured ERPF resting	268 ± 80	NS	211 ± 47	S
ERPF during exercise	228 ± 72		149 ± 58	

Data are means ± SD.

NS, not significant; S, significant at $P < .001$.

All data in milliliters/minute.

TABLE 6. 17 PATIENTS WITH ESSENTIAL HYPERTENSION WERE GROUPED ACCORDING TO THE RESULTS OF EXERCISE RENOGRAPHY. THE MEAN MEASURED GFR AND ERPF AND THE FILTRATION FRACTION (FF) ARE SHOWN AT REST AND DURING EXERCISE

	Normal Exercise Renogram (N = 6)		Bilateral-Abnormal Exercise Renogram (N = 11)	
Measured total GFR	106 ± 19	NS	87 ± 16	S
GFR during exercise	99 ± 15		22 ± 22	
Measured total ERPF	524 ± 145	NS	468 ± 74	S
ERPF during exercise	440 ± 148		287 ± 100	
FF at rest	0.22 ± 0.02	NS	0.19 ± 0.02	S
FF during exercise	0.24 ± 0.05		0.06 ± 0.06	

Data are means ± SD.

NS, not significant; S, significant at $P < .001$.

GFR and ERPF in milliliters/minute.

renogram failed to identify single kidney function compromise (50% ± 5%).

The normotensive controls failed to respond to exercise with a bilateral-abnormal exercise renogram. Both GFR and ERPF fell about 10% during exercise (P = NS). The mean FF was 0.19 while resting, and 0.20 during exercise (P = NS).

DISCUSSION

This research began as a search for renal function disturbances in hypertensive disease. Initially the evaluated disturbance was identified while studying hypertensives in prone and standing positions.[10,11] Renography was then paired with exercise to assess renal function during physiologic sympathetic nervous system (SNS) stimulation, since Hollenberg[12] and Essler[13] implicated the renal SNS in primary hypertension. It was hoped that exercise would increase intensity and frequency of the disturbance. During exercise nearly 60% of all hypertensives developed an exercise-mediated bilateral disturbance of transrenal hippurate transit.[1,3] No attempt has been made to determine whether the SNS is really involved in the investigated renal response. Our work has focused on demonstrating the existance of the function disturbance, and finding the evidence to relate it to hypertensive disease. No attempt has been made to identify the site of the disturbance, largely because the whole organ approach of the tracer procedures does not permit the disturbance to be localized.

We believe that our data are most readily explained if a renal perfusion disturbance, characterized by dysregulation, is assumed to cause the tracer transit disturbance during exercise. We would like to present the reasons that suggested a dysregulative disturbance to us even while recognizing that another cause may eventually be identified. Hippurate is secreted by proximal tubular cells into the tubular lumen.[14,15] Radiolabeled hippurate excretion would be delayed by a reduced glomerular filtration, since it slows the washout of the tracer from the tubulus lumen. Both preglomerular and postglomerular changes of vascular resistance can lead to a reduced filtration pressure, and induce deposition of the tracer in the tissue as observed in sequential scintigrams. This ability to visualize a change in filtration pressure is regularly used when renal artery stenosis are evaluated with baseline and captopril renal scintigrams.[16,17] The literature on renography and sequential renal scintigraphy also indicate that a flattened second-curve segment, delayed curve maximum (T_{max}), and an elevated excretory curve segment due to tracer trapped in tissue occur when flow is compromised[18–21] (Figure 1). These renographic findings are also characteristic for the bilateral-abnormal exercise renogram.

The present study, and most of those preceding it, were guided by the hypothesis that intermittent, bilateral, posture, and exercise mediated renal dysfunction occurs in hypertension, is specific for hypertension, and is capable of initiating or maintaining hypertensive disease. This working hypothesis included numerous investigative questions, each in need of independent study. Thus different aspects of this hypothesis have been studied; the present investigation is simply one in this series. The present study, combined with the results of the earlier investigations of hypertensives with renovascular disease,[21,23,24] is making it ever more probable that the bilateral-abnormal exercise renogram occurs in essential hypertension and perhaps in fixed renovascular hypertension. The very frequent occurrence of primary hypertension suggests that essential hypertension will often appear together with secondary forms. Thus any population of hypertensives can be expected to have individuals who have the exercise mediated renal function disturbance, even if it were unique to primary hypertension.

Hypertension associated with unilateral renovascular disease was used as a model to study the exercise-mediated renal disturbance. It should be noted that bilateral renogram deformation was provoked by ex-

TABLE 7. NORMOTENSIVE CONTROLS HAD A NORMAL EXERCISE RENOGRAM. THE MEAN MEASURED GFR AND ERPF AND THE FILTRATION FRACTION (FF) ARE SHOWN AT REST AND DURING EXERCISE

	GFR	ERPF	FF
Resting	102 ± 18	543 ± 129	0.19
Exercise	93 ± 20	477 ± 117	0.20

Resting v exercise: all data nonsignificant.
GFR and ERPF in milliliters/minute.

ercise in unilateral vascular disease. The clearance data document the disturbance with a second modality. To define the dysfunction with clearance parameters we estimated the GFR and ERPF of the nonstenosed organ separately. This was done to permit the clearance pattern to be demonstrated while excluding the influence of stenosis. We believe that the GFR and ERPF data for the nonstenosed kidney show that the disturbance is independent of large vessel disease. The data from patients with essential hypertension, as well as data from Fine et al[2] who also studied patients with primary hypertension, show clearly that renal artery stenosis should not be considered the cause of the bilateral disturbance.

Both hypertensives with renovascular disease, and the controls with primary hypertension continued with their antihypertensive drug regimens during the sequence of examinations. We recognize that antihypertensive drugs may influence renal blood flow. Since a hemodynamic abnormality is considered a possible explanation for the investigated disturbance, the continuation of drug therapy requires comment. Considerable data indicate that the exercise-mediated disturbance is not caused by a specific antihypertensive drug, or drug combination. The antihypertensive medication was regularly documented in our patients,[3,4,22–24] and failed to identify a relationship between the results of exercise renography and drug therapy. We noted, however, that patients with bilateral-abnormal exercise renograms require more medication, on average, than those with a normal exercise renogram. An earlier study also included 20 hypertensives who had not been placed on antihypertensive medication.[3] Nine of these had normal exercise renograms and 11 bilateral-abnormal exercise renograms. Thus the frequency of the disturbance was comparable to that observed in hypertensives taking medication. Recently, Fine examined 15 patients with primary hypertension, and four normotensive controls, with the exercise renogram, using a rigorous protocol which included the discontinuation of antihypertensive drugs.[2] Seven of these hypertensives developed a bilateral-abnormal exercise renogram. A separate study from our laboratory showed that a change in antihypertensive medication failed to influence results of exercise renography.[24] Also, exercise renograms obtained during drug therapy were sensitive for predicting the blood pressure response to revascularization.[22,23] We suggest that this predictive value could not exist if the exercise-mediated disturbance were the result of, or directly influenced by, the drug regimens used. We would also like to point out that renography is insensitive for recognizing the use of antihypertensive drug therapy. Finally, if drug therapy were the direct cause of the bilateral-abnormal exercise renogram, we would expect the disturbance to be seen in resting examinations as well. Thus all data to date suggest that the bilateral-abnormal exercise renogram is not caused or eliminated by antihypertensive medication.

The presented data suggests that a very frequent hypertension-associated renal function disturbance escaped recognition. This may be due to the fact that the abnormality is functional, intermittent, and discrete. When the resting clearance data of all hypertensives included in this report are brought together it becomes impossible to identify the disturbance in the nonstenosed kidney (Table 8). The measured and the predicted age-appropriate resting GFR and ERPF values are nearly identical. The disturbance is only recognized when the results obtained during exercise are considered as well. Thus renal investigations using other methods may fail to recognize this abnormality if they are carried out on inactive or restrained subjects.

The statistical analysis of the data deserves comment since the selected boundary level of significance was placed at $P = .001$, and therefore failed to identify relationships at a lower level of significance. Both normotensives and hypertensives with a normal exercise renogram experienced a small reduction in the GFR during exercise. This exercise-mediated reduction in the GFR lacked significance for each subpopulation at every cutoff level selected. In comparison, the change in the ERPF noted during exercise would have achieved significance if a lower boundary level had been used. This was true for the normotensive controls ($P = .05$) and for the hypertensives (essential hypertensives, $P = .05$; renovascular hypertensives, $P = .01$). We mention this because it shows that the

TABLE 8. MEAN PREDICTED AND MEASURED CLEARANCE VALUES OF THE NONSTENOSED KIDNEYS OF THE WHOLE POPULATION

	GFR (N = 31)	ERPF (N = 31)
Predicted	46	221
Measured, resting	48	235

The disturbance is obscured when data from the exercise protocols is excluded. All data in milliliters/minute.

reduction in the ERPF noted during exercise was statistically significant at a lower level of confidence, but was not hypertension specific. This compares to the exercise-mediated reduction of GFR and ERPF, in those hypertensives with a bilateral-abnormal exercise renogram. Here both GFR and ERPF changes were very highly significant ($P < .0001$) and unique to hypertension.

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