The Exercise Renogram and Its Interpretation

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The exercise renogram is a rarely used diagnostic procedure, but it may visualize an exercise-induced change in renal function related to the pathophysiology of essential hypertension, which could greatly increase interest in this examination. The aim of this study was to demonstrate the interpretative approach and the terminology which is used to describe results of exercise renography, using a population of hypertensives with renovascular disease. **Methods:** We reviewed the examinations of 70 hypertensives who had supine renography as well as exercise renography with a 60–80 W work load. Forty-eight patients were examined with ^{99m}Tc-MAG3 and 22 with ^{131}I hippurate. The renographic and angiography results were recorded as well as the antihypertensive drugs used and the site of vascular lesions. **Results:** Thirty-three hypertensives developed a bilateral-abnormal exercise renogram, which appears to be associated with primary hypertension. Eight individuals responded to exercise with a unilateral-abnormal exercise renogram, in a kidney behind a stenosis. Only 19 patients had a normal exercise renogram, and 10 had only one functioning kidney. Pathology recognized but unrelated to the intervention included nonfunctioning and small kidneys and pelvic retention. **Conclusion:** Exercise renography's only indication is for recognition of pathology unique to hypertension, since other function disturbances were recognized in resting renograms.

Key Words: renography; technetium-99m-MAG3; hypertension; indium-111-DTPA; exercise

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Posture-dependent renal retention of hippurate was identified in hypertensive disease more than a decade ago when patients were examined while standing (*1*). Specifically, in some hypertensives the washout of hippurate from the renal tissue of both kidneys was greatly delayed while standing, causing late bladder visualization and a bilateral elevation of the third segment of the renogram. The prolongation of tracer transit from the tissue of both kidneys was not observed when the hypertensives were lying down. The disturbance was only seen in individuals with hypertensive disease. Intervention with exercise was tried in the hope of activating the disturbance through sympathetic nervous system (SNS) stimulation. During exercise, nearly 60% of all hypertensives developed the disturbance (*2*), which was later called a bilateral-abnormal exercise renogram. The frequency with which exercise induced the change made it highly probable that it was associated with essential hypertension. Clinical studies which followed sought to determine whether exercise-mediated dysfunction is related to the pathophysiology of essential hypertension. Since essential hypertension causes 90% of all hypertension, it was expected that this disease must often co-occur with the less frequent forms. Accordingly, bilateral-abnormal exercise-renograms were seen not only in essential hypertension but also in hypertensives with renovascular and renoparenchymal disease and in malignant hypertension (*3*).

We used hypertension associated with renovascular disease as the model to evaluate the disturbance. It was shown that those hypertensives with a bilateral-abnormal exercise renogram had incurable hypertension (*4,5*). Our results leave unanswered whether exercise mediated dysfunction may also occur in fixed renovascular hypertension, which we have always suspected. This caused us to prefer the use of the term non-Goldblatt hypertension to describe those hypertensives with incurable disease (*6*). The prognostic information was very accurate for hypertensives with unilateral renovascular disease. It was recently shown that the investigated bilateral, exercise-mediated change in renal function recurs over long time intervals, and is uninfluenced by changed antihypertensive drug regimens, or by revascularizations (*7*). This was expected for a disturbance with a possible role in maintaining essential hypertension. Exercise-mediated renal dysfunction was also evaluated in patients with essential hypertension to verify the model and show that observations made in hypertensives with renovascular disease hold true for essential hypertension (*3,8–10*).

No other procedure is presently available for eliciting and evaluating the investigated disturbance and learn how it relates to primary hypertension. Recognition of exercise mediated renal dysfunction should therefore be the primary reason for using exercise renography in hypertensives, whether clinically or in a research setting. This study seeks to demonstrate results obtained when ergometric exercise is combined with the renogram. The presented results and their discussion should clarify interpretation, terminology and the indication for this intervention.

MATERIALS AND METHODS

Seventy hypertensive patients with renovascular disease had resting and exercise renography. All patients had renovascular disease, demonstrated by angiography. Patients were examined during a 1.5-year interval beginning in 1991. To limit the population, we only included patients who also had a clearance examination glomerular filtration rate (GFR), and effective renal plasma flow (ERPF) were determined with a single-compartmental, dual-tracer infusion clearance using the tracers ^{131}I-hippurate and ^{111}In-DTPA. The procedure was recently described in detail (*8*); 120 μCi of both radiotracers were injected intravenously 40–60 min before beginning with the clearance examination to fill the extravascular compartments. Each tracer was monitored by a scintillation detector placed over the shoulder of the patient. Collected signals activated an infusion pump by feedback control to sustain the constant plasma activity level for each isotope. The infused activity was registered. A serum sample was taken at the end of the resting clearance study. Without repositioning the patients, both GFR and ERPF were measured during 25 W ergometric exercise. The minimum clearance period during exercise was 10 min. Clearance was calculated with the equation $Cl = I \times A_{st}/A_{pl}$ where Cl = clearance (ml/min); I = number of motor steps per time (min^{-1}); A_{st} = activity pumped per motor step (μCi); and A_{pl} = specific activity of plasma (μCi/ml). Hippurate clearance results were multiplied by a factor of 1.2 to obtain a PAH equivalent value. We only used the clearance results for the demonstration of clinical findings, since these data were reported previously (*8,11*) and would not help to clarify the interpretative

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TABLE 1

Exercise Renography was Used to Identify Exercise-Mediated Renal Dysfunction in Seventy Hypertensives with Renovascular Disease*

Exercise renogram	Lesion location			Vascular pathology			
	Age	Unilateral	Bilateral	Artheriosc.	FMD	Other	No. of drugs
Normal (n = 19)	51 ± 16	16	3	9	9	1	1.9 ± 1.2
Unilateral-abnormal (n = 8)	49 ± 14	6	2	5	3	0	1.9 ± 1.2
Bilateral-abnormal (n = 33)	57 ± 13	24	9	25	3	5	2.3 ± 1.3
Silent kidney (n = 10)	54 ± 13	7	3	9	1	0	2.6 ± 1.2

*Location and cause of vascular lesions, the mean number of antihypertensive drugs used and the age at scintigraphy are shown.

approach. Forty-eight patients had atherosclerosis, 16 fibromuscular dysplasia, three abdominal aneurysms, which involved a renal vessel, and in three the cause of the vascular lesion was not defined. Additionally, seven hypertensives had diabetes, six were overweight and 11 had compensated renal insufficiency. The mean age at scintigraphy was 54.3 yr. The antihypertensive medication was continued at scintigraphy and recorded (Table 1).

Each patient had a resting gamma camera renogram in the supine position, and one while sitting upright on a bicycle ergometer leaning against the gamma camera. Both examinations were generally obtained within 2 days and were never more than 1 wk apart. Patients were asked to drink 400 ml fluid before renography to assure adequate hydration.

Careful instruction about the sequence of studies preceded each examination. Supine-position renography was started after the patient was positioned for the examination. During the exercise protocol, the patients sat on a bicycle ergometer in front of a gamma camera. Pulse and blood pressure were monitored throughout the period of exercise, which began with 60 W for women and 80 W for men. Ergometric resistance was decreased when requested so that the patients had final control over the resistance level used. We tried to exercise at 60 rotations per minute and sought to increase the pulse rate by at least 20 beats per min. Patients were exercised 1–3 min before renography to verify that the level of exercise would cause the pulse rate to increase. After radiotracer injection the patients continued to exercise.

Radionuclide renography was started after intravenous injection of 7 μCi ^{131}I ortho-iodohippurate, or 6 μCi ^{99m}Tc-MAG3 per kilogram body weight. Both examinations were obtained with the same tracer in each patient. A 15-in. gamma camera equipped with a general-purpose, high-energy (360 keV), parallel-hole collimator was used for all studies with hippurate and a low-energy, parallel-hole, general-purpose collimator for ^{99m}Tc. A window setting at 20%, centered over the photopeak of the tracer, was used for all studies. We used 12 sec per frame during data acquisition, and 1-min images were obtained from the first through the fourth minute, and at 7, 9, 14 and 19 min after tracer injection. The examination lasted 20 min.

Data was stored on magnetic tape and analyzed with the computer workstation of the camera. Single-kidney function was determined with the region of interest (ROI) technique. The renal pelvic system was not excluded from the ROI. Background ROIs were placed around each kidney. Single-kidney tracer uptake, expressed as a percentage of total uptake for both kidneys, was calculated. The uptake was taken to be proportional to the gradient of the renogram between 24 and 120 sec. The third curve segment was analyzed by inspection.

Supine and exercise gamma camera serial scintiscans were compared to recognize extent of exercise mediated tissue retention of the tracer in one or both kidneys. Scintiphotos and renograms, together with the calculated single-kidney function, were used for recognition of abnormality in the resting and exercise studies.

RESULTS

We examined 70 hypertensives with renovascular disease with the exercise renogram as well as with supine position gamma camera renography. The patients were grouped according to the exercise mediated renal response. The examination with exercise identified hypertension specific dysfunction, as well as pathology unrelated to exercise.

Thirty-three hypertensives developed a bilateral-abnormal exercise renogram (Fig. 1). Five of these were diabetics, and nine had compensated renal insufficiency. These patients had bilateral, exercise-induced tissue retention of the tracer during exercise. The renograms had an elevated excretory segment, and the images showed delayed tracer transport into the bladder. Mean tracer excretion into the bladder was delayed during exercise and was seen after 4.2 ± 0.9 min while resting and 11.1 ± 4.9 min during exercise (Table 2). Seven of these

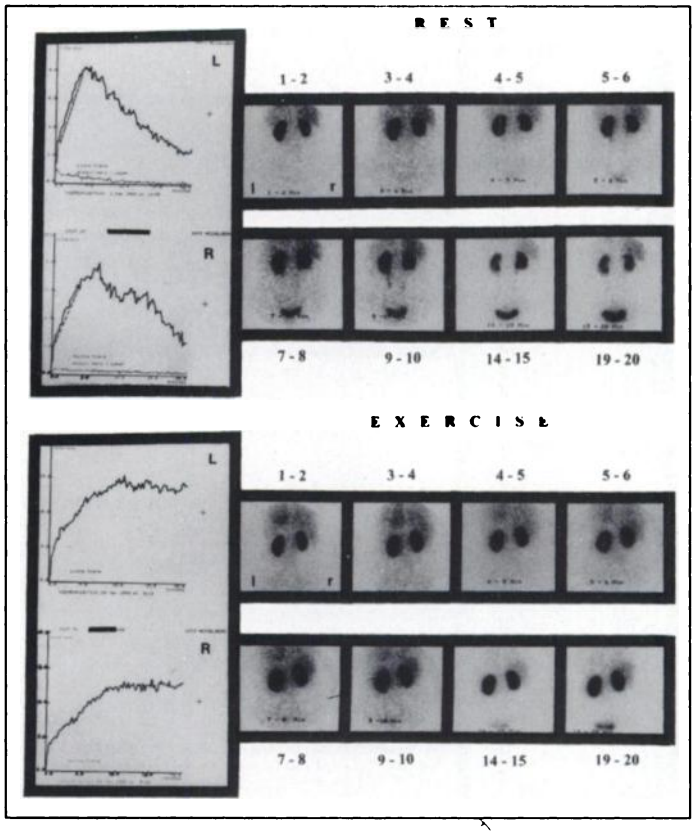

FIGURE 1. Renogram of a 50-yr-old hypertensive patient with right side renal artery stenosis. Function: 44% right side. Required medication: ACE inhibitor, alpha receptor antagonist and β-blocker. Bladder visualized in the 6 min image (clearance in ml/min × 1,73 m^2; GFR 80 ml; ERPF 347 ml; FF 0.23). Exercise provoked the typical bilateral-abnormal exercise renogram with tissue retention of the tracer in both kidneys, delayed excretion and elevated excretory segments of the renogram (clearance in ml/min × 1,73 m^2; GFR 26 ml; ERPF 182 ml; FF 0.14).

TABLE 2
Typical Hypertension-Associated Changes of Tracer Kinetics with Exercise

Exercise renogram	Pats	Tracer transport disturbed			Bladder seen	
		Rest	Exercise			
		Unilateral	Unilateral	Bilateral	Rest	Exercise
Normal	19	0	0	0	4.2 ± 1.2	4.4 ± 1.2
Unilateral-abnormal	8	1	8	0	4.0 ± 0.6	5.4 ± 1.2
Bilateral-abnormal	33	7	0	33	4.2 ± 0.9	11.1 ± 4.9
Silent kidney	10	0	7	./.	4.7 ± 0.8	10.4 ± 7.3

*Seventy hypertensives had exercise renography and were grouped according to the response to this intervention. The frequency of tracer transit disturbances through tissue are shown together with the mean time of tracer excretion into the bladder, at rest and during exercise.

hypertensives had scintigraphic evidence of renovascular disease in supine-position renograms, with unilaterally disturbed tracer washout from the kidney behind the stenosis. The angiograms demonstrated a vascular lumen reduction equal to, or exceeding 90% (Fig. 2).

Eight hypertensives developed a unilateral-abnormal exercise renogram (Table 2). This exercise-mediated retention of the tracer in the cortex was only seen in the kidney behind a vascular stenosis (Fig. 3). Tracer excretion into the bladder was timely due to noninvolvement of the contralateral kidney. One of these hypertensives also had a tracer transport disturbance in the stenosed kidney while resting, and exercise slowed tracer washout from the tissue even more (Fig. 3).

Nineteen of the 70 hypertensives had a normal exercise renogram. Two of these were diabetic and two had elevated serum creatinine values. It is not suggested that exercise failed to influence results of renography in these individuals. Mean renal tracer excretion was slightly delayed during exercise (Table 2). Exercise also caused the third curve segment of the renogram to descend less rapidly and slowed tracer washout from the tissue during the 20-min examination (Fig. 4). Pathology unrelated to exercise was seen in resting renograms. Single-kidney function compromise was identified in exercise

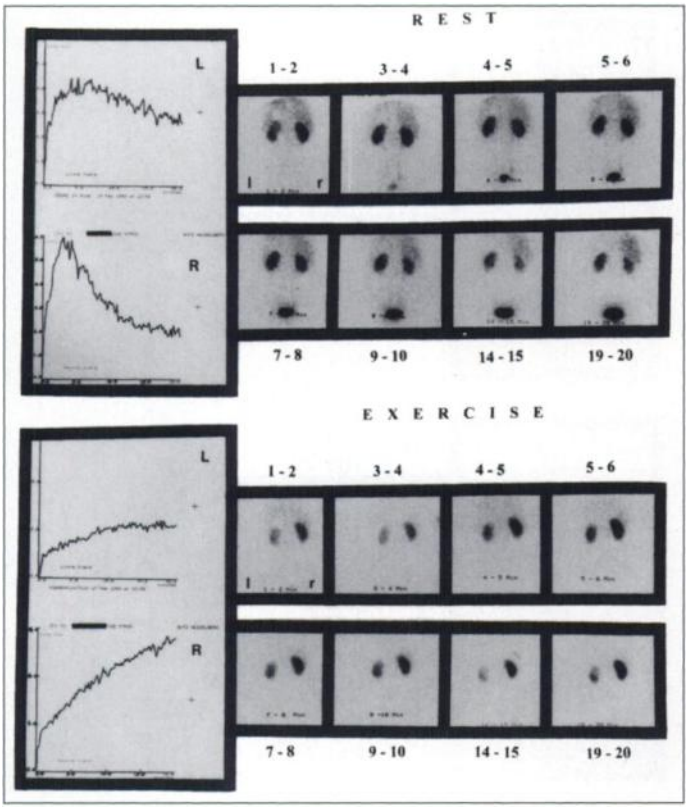

FIGURE 2. A 45-yr-old hypertensive man had a four drug regimen including a calcium antagonist, β-blocker, sympatholytic and diuretic drug at scintigraphy (BP = 170/120 mm Hg). Angiography = unilateral renal artery stenosis left. Note: reduced tracer uptake in the left kidney. Function left 36% (GFR 53 ml; ERPF 248 ml; FF 0.22). Exercise renography demonstrates bilateral tissue retention of the tracer, delayed excretion into the bladder and an accumulation renogram (GFR 16 ml; ERPF 171 ml; FF 0.09). It was concluded that both renovascular and essential hypertension were present.

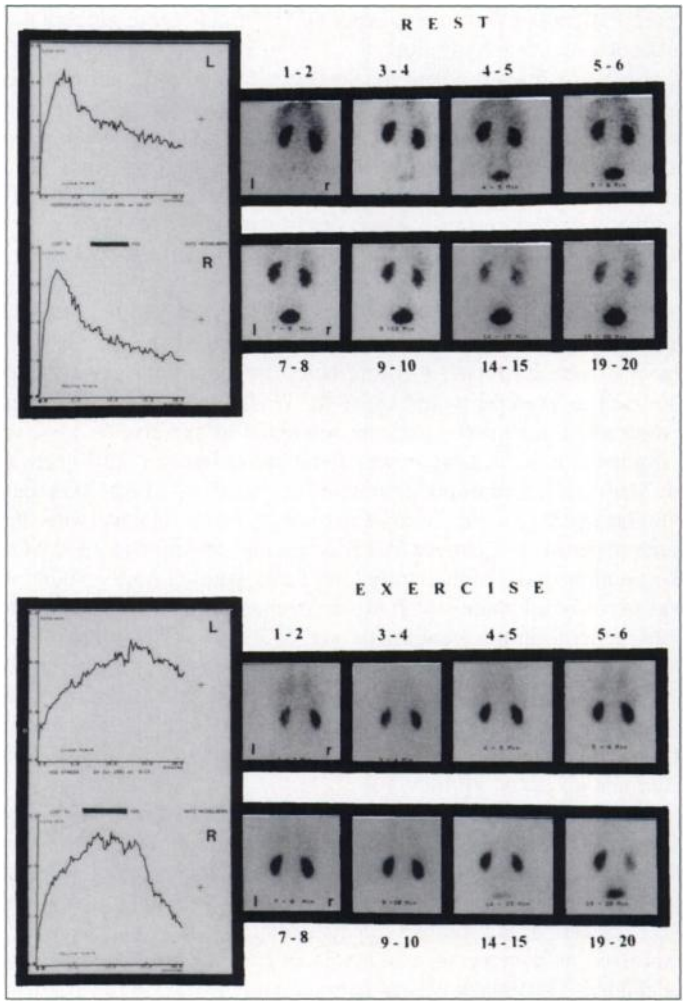

FIGURE 3. A 68-yr-old hypertensive man examined to determine BP response to revascularization of the stenosed left renal artery. Renography demonstrated slight function compromise (left 43%) (clearance in ml/min × 1,73 m^2; GFR 105 ml; ERPF 502 ml; FF 0.21). The patient developed a unilateral-abnormal exercise renogram during exercise with prominent tracer retention in the left kidney's tissue. Intermittent excretion disturbance with collection system activity is seen on the right side (clearance in ml/min × 1,73 m^2; GFR 125 ml; ERPF 492 ml; FF 0.25).

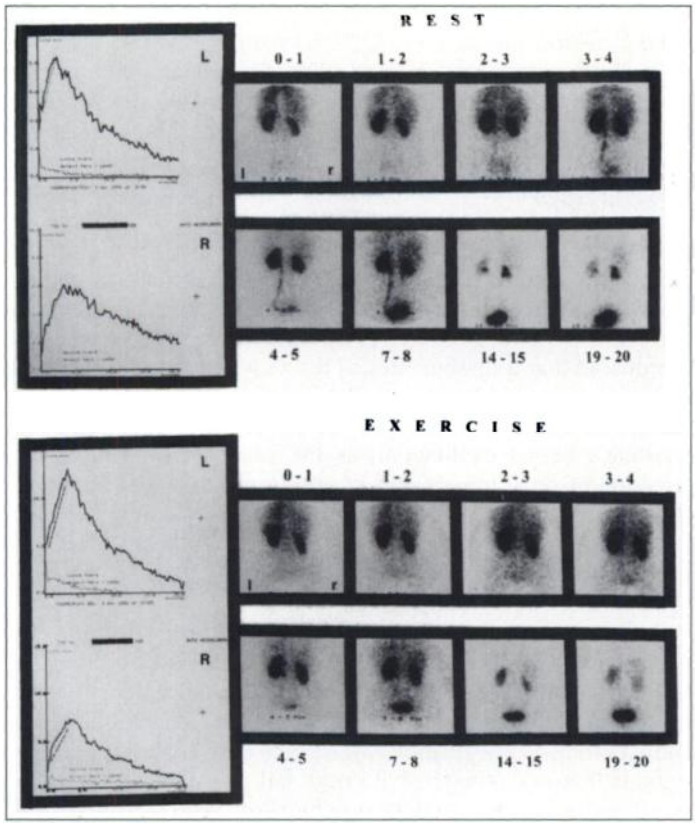

FIGURE 4. A 43-yr-old hypertensive woman with RAS of the right kidney. Single kidney function: left 62%, right 38%. Renal tracer transit was timely (clearance in ml/min × 1,73 m^2; GFR 110 ml; ERPF 514 ml; FF 0.21). The normal exercise renogram shows that exercise fails to significantly influence tracer transport. Note the 1 min excretion delay (clearance in ml/min × 1,73 m^2; GFR 110 ml; ERPF 537 ml; FF 0.21).

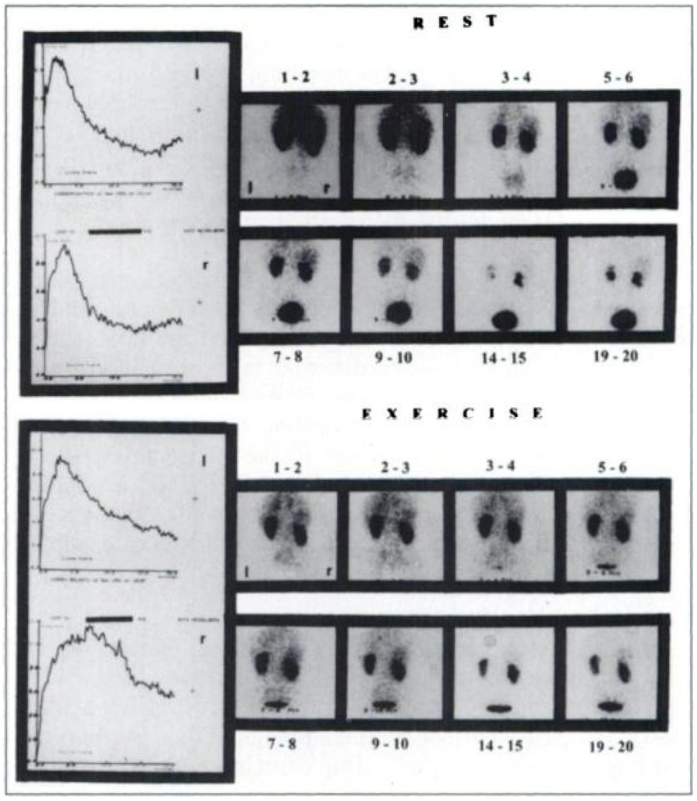

FIGURE 5. Renograms of a 54-yr-old patient with bilateral renovascular disease. BP 280/150. Calculated single kidney function: left 52%, right 48%. Normal clearance values (clearance in ml/min × 1,73 m^2; GFR 84 ml; ERPF 456 ml; FF 0.18). A normal exercise renogram with excretion delay from the right kidney. The pelvic activity caused renogram deformation. Late images demonstrate the tracer in the collecting system (clearance in ml/min × 1,73 m^2; GFR 101 ml; ERPF 504 ml; FF 0.20).

and resting gamma camera examinations. Furthermore, normal exercise renograms were diagnosed in six hypertensives who had unilateral pelvic retention during exercise, a result also seen in two in the resting study (Fig. 5). Bilateral pelvic retention was seen once at rest and during exercise. Finally, four hypertensives with a normal exercise renogram had a small kidney, recognized in both examinations.

The upright and supine position examinations gave similar results in 59 patients, with single-kidney function differing less than 5% between examinations. We noted a 6%–8% difference four times, while a 9% or greater difference in renal function was calculated for seven patients. The mean calculated single-kidney function difference between exercise renography and supine renography was only 3.5% when the comparison included all examinations. Thus, the paired Student's t-test failed to identify a difference between supine and upright single-kidney function calculated for the left kidney, as well as for the better functioning kidney, at all levels of significance, for patients classified as having a normal, unilateral-abnormal and bilateral-abnormal exercise renogram.

Ten hypertensives had only one functioning kidney. Exercise caused a tracer-transport disturbance in this organ in seven patients, while tracer transit remained timely in three (Table 2).

Hypertensives with a normal- and a unilateral-abnormal exercise renogram used similar numbers of antihypertensive drugs at the time of scintigraphy, namely 1.9 ± 1.2 on average (Table 1). Those with a bilateral-abnormal exercise renogram required an average of 2.3 ± 1.3 antihypertensive drugs. Numerous drugs were used at the time of scintigraphy, including diuretics, calcium antagonists, beta-blockers, sympatholytic drugs and angiotensin-converting enzyme inhibitors.

DISCUSSION

It is becoming ever more probable that the bilateral-abnormal exercise renogram visualizes a function disturbance directly related to the pathophysiology of essential hypertension (*8–10*), which may result in wide-ranging investigative and clinical applications for this approach.

Bilateral Abnormal Exercise Renogram

The term bilateral-abnormal exercise renogram describes abnormal retention of renal tracers in the tissue of both kidneys during exercise. Exercise induced tracer deposition in the tissue is recognized with ease in the great majority of patients. This transport disturbance is invariably associated with an elevated excretory segment of the renogram and generally with delayed tracer excretion. When tracer excretion is not delayed, appearing 4–5 min after injection, the bladder contains little activity at the end of the study. Clearance determinations previously demonstrated that a bilateral-abnormal exercise renogram is associated with a severely reduced GFR and a lesser decrease in the ERPF during exercise (*8,11*). Parenchymal retention and delayed tracer excretion into the bladder thus appear to result from slow transit through the tubular lumen. This has always suggested to us that the disturbance results from resistance vessel dysfunction, causing glomerular filtration to fall (*3*). The disturbance varies in intensity among individuals.

Unilateral Abnormal Exercise Renogram

The unilateral-abnormal exercise renogram appears to be specific for renovascular disease, and our observations indicate that it is corrected by successful revascularization. The unilateral disturbance has relevance not because it recognizes renovascular disease, but because it may mimic the bilateral

abnormality. This occurs when hypertensives with bilateral renovascular disease develop a unilateral-abnormal exercise renogram in each kidney. The resulting exercise renogram is indistinguishable from the disturbance seen in essential hypertension co-occurring with renovascular disease. Bilateral revascularization cures hypertension. Its relevance to the differential diagnosis is recognized by noting the greater accuracy achieved when prognosticating the BP response in unilateral renovascular disease (*5*).

A nonfunctioning kidney can result in diagnostic error, since two organs are needed to differentiate the unilateral- and the bilateral-abnormal exercise renogram. When the nonfunctioning kidney is distal to stenosis, and the nonstenosed organ develops the tracer transport disturbance during exercise, essential hypertension remains probable. Conversely, a normal exercise renogram is diagnosed if the nonstenosed kidney continues to have normal tracer transport. When a nonfunctional organ is seen in bilateral renovascular disease, the unilateral and bilateral tracer transport disturbances cannot be differentiated.

Normal Exercise Renogram

Normal exercise renogram does not imply that resting and exercise renograms are identical, or that the study lacks pathology. Since exercise is used to provoke tracer retention in the tissue, the term "normal exercise renogram" simply indicates that tracer transit is normal during exercise. However, exercise generally slows MAG3 washout from the tissue, causing slight retention of the tracer. T_{max} is generally delayed, together with a mean 1–2 min shift in tracer excretion, due to an exercise-mediated physiologic change in renal blood flow (*12,13*). Clearly-defined scintigraphic cutoff values have not been established to separate normal from pathologic tracer transport in response to exercise. When tracer transit through tissue is normal, we refer to a normal exercise renogram, even if other abnormalities are visible. Abnormal results unrelated to exercise are described as separate findings.

Functional disturbances not relevant to the unique questions answered by the protocol are regularly observed. A unilateral reduction of renal function was frequent in this population, since all patients had vascular disease. Pelvic retention, unrelated to posture and exercise was identified in resting and exercise examinations. When pelvic retention was only seen during exercise it appeared to be without clinical relevance. These secondary results were described subordinate to the main finding, e.g., normal exercise renogram, with pelvic retention during exercise. Pelvic retention can occasionally mimic tissue retention and cause the primary classification to be incorrect.

Vascular Dysregulation During Exercise

Most investigators of hypertensive disease have serious reservations about exercise renography as an investigative tool. This appears based on renography's well-documented limitations for recognizing flow compromise, as is known from investigations of renovascular disease (*14–16*). Indirect evidence for this failing was the interest in and rapid acceptance of captopril scintigraphy (*17–19*) and clearance procedures (*20,21*). Neither approach would have found the acceptance it has today if renography were sensitive for recognizing reductions in renal blood flow. Thus, renography fails to identify individuals using antihypertensive drugs, including those which influence renal hemodynamics. Similarly, a bilateral and equal reduction of blood flow will often fail to be identified. In comparison, dysregulation is readily recognized, and this is used for evaluation of renovascular disease with the captopril renogram. In renovascular hypertension, the angiotensin converting enzyme inhibitor causes efferent vessel dilation in the kidney behind the stenosis (*22*); its diameter is too wide for maintaining filtration pressure. The functional unity of the resistance vessels is disturbed, causing glomerular filtration and the filtration fraction (FF) to fall. This pharmacological disruption of glomerular filtration is readily recognized with radioisotope procedures. This is possible because the PAH analogs continue to be deposited in the tubular lumen, while reduced glomerular filtration slows its washout. Since disruption of glomerular filtration causes trapping of PAH analogs, it was always considered probable that the bilateral-abnormal exercise renogram is the result of dysregulation of flow (*3*). We consider it probable that a dissociation of the vascular tonus of afferent and efferent vessels causes the bilateral-abnormal exercise renogram. If this is shown to be correct, it would implicate resistance vessel dysfunction as the cause of bilateral tissue retention of renal tracers during exercise in essential hypertension. It remains to be determined how these results and their interpretation can be integrated into the well-documented data which support the work of Hollenberg et al. (*23*) and the hypothesis of Sealy et al. (*24*).

Patients continued on antihypertensive therapy during the two renographic examinations. Although antihypertensive drugs can influence renal blood flow (*25*), all evidence, suggests that the disturbance is neither caused nor eliminated by antihypertensive medication (*8*). Results of exercise renography suggest that antihypertensive drugs fail to influence the functional unity of pre- and postglomerular vessels, since drug therapy fails to correct the disturbance during exercise. The renographic studies also suggest that these drugs do not initiate the disturbance, since tissue retention of tracer is not seen during resting examinations in patients receiving antihypertensive therapy.

CONCLUSION

Bilateral, exercise-mediated renal dysfunction appears to be hypertension specific and is probably unique to essential hypertension. Accumulating evidence suggests that the renal disturbance may be the expression of a primary renal mechanism of hypertension. Exercise renography identified this renal disturbance in 50%–60% of all hypertensive subjects. This suggests that a pathophysiological disturbance associated human essential hypertension can be readily evaluated with exercise renography. To encourage the clinical investigation of essential hypertension, the interpretative approach of this rarely used scintigraphic procedure was demonstrated in a population of hypertensives.

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Scintigraphic Evidence of Pulmonary Vascular Occlusion in Sickle Cell Disease

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The acute chest syndrome of sickle cell disease is believed to be primarily a microvascular event. It will rarely involve the larger pulmonary vasculature. We present a case of sickle cell disease where segmental pulmonary arteries were temporarily occluded during the episode of sickling.

Key Words: sickle cell; chest syndrome; lung perfusion

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The acute chest syndrome of sickle cell anemia is characterized by chest pain, fever and prostration from vascular occlusion due to sickling. We recently documented such a vascular occlusive process by pulmonary scintigraphy.

CASE REPORT

A 27-yr-old man with known sickle cell disease presented to the emergency department of our institution with right upper quadrant pain of 2 wk duration radiating to the chest and back. The pain was pleuritic in nature and unrelated to bony structures. It had accentuated in the last 3 days, being associated with a dry cough, night sweats and a low grade temperature of 37.7°C. On physical examination, breath sounds were normal except for dullness at the right base. While abdominal ultrasound was unremarkable, chest radiography documented a pleural effusion in the right lung (Fig. 1). The arterial PO_2 was normal. A perfusion lung scan (Fig. 2A), requested to identify vascular occlusion, demonstrated numerous moderate and large peripheral wedge-shaped defects of perfusion primarily in the right lung but also on the left, with a normal ventilation scan except for hypoventilation at the site of effusion (Fig. 2B). Since Doppler venous studies of the lower limbs were normal, and other factors predisposing to pulmonary embolisation were absent, a diagnosis of an acute chest syndrome of sickle cell disease was made. Supportive therapy consisting of analgesics, oxygen and intravenous hydration was then instituted immediately. The patient promptly improved and was discharged 2 days later.

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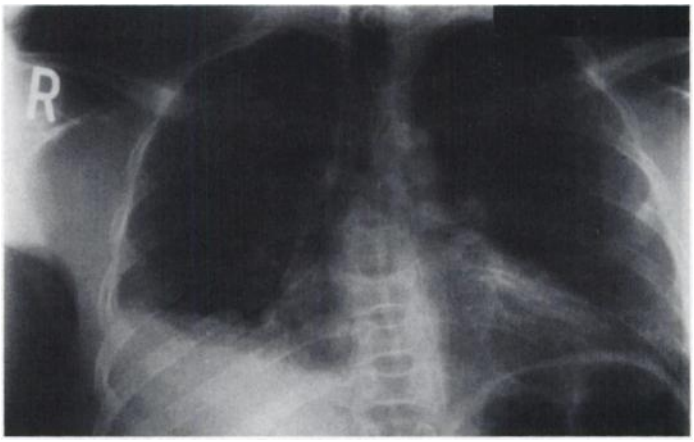

FIGURE 1. Chest radiograph shows the presence of a right-sided effusion.

Repeat pulmonary scintigraphy 1 wk later documented the resolution of many of the perfusion abnormalities, although some minor residual evidence of the vascular occlusive process persisted (Fig. 3). Additionally, at no time in the clinical follow-up of the patient was there any indication of a smoldering DVT.

DISCUSSION

The acute chest syndrome (ACS) of sickle cell anemia generally occurs in patients with homozygous sickle cell disease, hemoglobin sickle cell (sulfur chloride) disease and S-beta thalassemia (*1,2*). It is a complex of chest pain, fever and prostration usually accompanied by various levels of hypoxia as well as pulmonary opacities on chest radiography (*3–5*). It is potentially life threatening, accounting for up to 25% of hospital admissions and deaths in patients with sickle cell disease when severe hypoxia develops precipitously with depressed oxygen tension triggering adherence of the sickled red cells to the endothelium of the pulmonary microvasculature (*5*). Other potential mechanisms for the acute vascular damage of ACS include thrombosis of small- to medium-size arteries and bone marrow embolism from areas of ischemic bone necrosis (*2–5*).