Clinical Evaluation of Patients with Hypertension and Exercise-Induced Renal Dysfunction

JOHN H. CLORIUS, JOHANNES MANN, PETER SCHMIDLIN, LUDWIG G. STRAUSS, THOMAS SAUR, AND GISELA IRNGARTINGER

SUMMARY An exercise-mediated renal o-iodohippurate transport abnormality was recently identified in patients with hypertension. The disturbance was not observed in normotensive controls. To learn more about this transient functional disturbance of the kidney, we obtained gamma camera hippurate renograms in 45 patients with hypertension. The final diagnoses indicated that 27 patients had essential hypertension, 15 had renal parenchymal or renovascular hypertension, 2 had malignant hypertension, and 1 had hypertension of pregnancy. We documented age, height, weight, global and unilateral renal function, blood pressure status, and antihypertensive medication used at time of scintigraphy. We also noted the serum catecholamine, sodium, and potassium levels. All patients were scintigraphed at rest and during exercise. The scintigraphic examination documented exercise-induced renal dysfunction in 28 (62%) patients (abnormal exercise renogram), while 17 (38%) had renograms not noticeably influenced by the exercise protocol (normal exercise renogram). When the results of scintigraphy were compared with the clinical data, a weak correlation was found between patient overweight and an abnormal response to exercise. There was no significant difference between groups with normal and abnormal exercise renograms with respect to the other parameters assessed. Exercise renography was not useful for differentiating renal and essential hypertension. Renography appears to demonstrate an exercise-mediated, transient, renal perfusion disturbance in certain patients with hypertension. The examination appears to assess a new parameter in hypertensive disease. Thus, the gamma camera renogram should be reevaluated in the patient with hypertension.

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KEY WORDS • exercise renography • hypertension • hippurate kinetics

A TRANSIENT, posture-mediated and exercise-mediated disturbance of renal o-iodohippurate handling was identified in patients with hypertension.1 Bilateral renal tissue retention of hippurate was noted during exercise in 57% of all hypertensive patients. Examinations of patients in the prone position failed to show this tracer transport disturbance. The known kinetics of radioactivity labeled o-iodohippurate indicated that the sequence of examinations had identified a transient cortical perfusion abnormality during exercise. The proximate cause, as well as the pathophysiological and clinical significance of the disturbance, remained unclear. More recently, the blood pressure (BP) response achieved following renovascular surgery was compared with results of the preoperative exercise renogram, and exercise renography was found to be useful in distinguishing responders from nonresponders to therapy.2 These results suggest that the functional disturbance observed with exercise renography merits further investigation. We believe that the exercise renogram helps to identify a previously undetected pathophysiological response and that the diagnostic information is not contained in other diagnostic tests. The present study thus sought to determine whether the results of exercise renography could be associated with a common clinical parameter or with the final classification of the disease.
Patients and Methods

We report on 69 patients referred to o-iodohippurate scintigraphy by nephrologists because of hypertension. All patients were to be examined in both the prone position and during ergometric exercise. Patients were included in the study even when normotensive at the time of scintigraphy. Exercise renography was not possible in 18 patients. Medical reasons precluded an exercise scintigram in seven patients with coronary artery disease, in one patient with a hypertensive crisis, and in one elderly physically debilitated hypertensive patient considered incapable of undergoing the procedure. The examination also could not be performed in a paraplegic patient and in two foreigners due to the language barrier. Lastly, six patients either refused to participate in the exercise study or simply failed to come to the appointment. Thus, 51 of the referred hypertensive patients had both examinations. Patients were given their appointment for scintigraphy at the beginning of their evaluation. Thus, the scintigraphic study and the laboratory tests were obtained concurrently. Two of the scintigraphed patients were excluded from this study because a drop in pulse occurred during the course of exercise. Four patients were dropped from the final evaluation because the exercise scintigram could not be classified securely as either abnormal or normal. Forty-five hypertensive patients were thus included in the final evaluation. The scintigraphic classification was performed by one investigator (J.H.C.) who had no knowledge of the clinical data or the final diagnosis.

The clinical data set was evaluated by a different investigator (T.S.) who had no access to the results of scintigraphy. He noted the final probable cause of hypertension. The final diagnosis was essential hypertension in nine patients and arterial hypertension in 18 patients. This second classification was used in patients with systolic BP of 160 mm Hg or greater, and normal creatinine concentration, urine status, and renal sonogram. Thus, hypertension of renal origin was considered unlikely in these patients. The morphological evaluation included a renal sonogram in all patients.

Twenty-three of the 45 hypertensive patients also had an angiogram. Angiograms existed for the five patients with renovascular disease and for the nine patients with the final diagnosis of essential hypertension. Angiograms also existed for nine other patients: two had malignant hypertension, four had arterial hypertension, and one each had the nephrotic syndrome, a pyelonephritic small kidney, and a small pelvic kidney. Scintigraphy was never used as basis for the final diagnosis.

The clinical records were screened to determine age, height, weight, and sex. We also noted the serum creatinine, serum catecholamine, serum potassium, and serum sodium levels. The funduscopic status was registered. Finally, to determine whether antihypertensive medication can provoke or eliminate the abnormal exercise renogram we ascertained the therapeutic regimen of each patient at the time of scintigraphy.

All evaluated patients underwent gamma camera renography in the prone position and during upright exercise, within 1 week. To obtain adequate hydration, patients were asked to drink 400 ml of fluid 30 minutes before each examination. All patients received careful oral instructions about the series of examinations. The goal of the study was explained. The renogram in prone position was begun within minutes after positioning of the patient. The exercise renogram was obtained while the patient sat in front of a gamma camera (Sigma 410; Ohio Nuclear, Solon, OH, USA) on a bicycle ergometer (Siemens, Holland). The patients were asked to sit straight-backed so that the kidney-to-camera distance would be small. Ergometric resistance was initially set at 60 W for women and 80 W for men after 60 rotations per minute was reached. We asked the patients to remain as comfortable as possible during the exercise examination. The work load was increased if the patient felt that it could be continued indefinitely, and it was reduced if it resulted in exhaustion. Thus, the patients themselves had final control over the work load used in the study. Renography was begun only after the pulse rate had increased at least 20 beats/min. Patients continued with exercise following radiotracer injection. Pulse and BP were monitored during an interruption of exercise at 10 minutes and again at the end of the study. We used pulse rate as an objective parameter to assess effectiveness of exercise and to identify potential overexertion. BP measurements were to identify potentially dangerous BP elevations in response to exercise.

Gamma camera renography was performed after intravenous injection of either [131I]o-iodohippurate, 7 μCi/kg body weight, or [123I]o-iodohippurate, 6 μCi/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 photo peak of the tracer. One-minute scintiscans were made from the 1st through the 4th minute and in the 7th, 9th, 14th, and 19th minutes. To identify the tracer’s appearance in the bladder, we extended the 1-minute images past the 4th minute as required. Examinations were terminated at 20 minutes. A minicomputer was used to place regions of interest over each kidney to determine single-kidney function. Background regions of interest were placed around each kidney. Single-kidney hippurate uptake, expressed as a percentage of the total uptake of both kidneys, was determined. Uptake was taken to be proportional to the gradient of the renogram between 24 and 120 seconds. The excretory segment of the renogram was qualitatively analyzed to judge parenchymal tracer excretion. Parenchymal isotope retention was judged on a four-step scale by an experienced observer (J.H.C.): 0 = regular tracer washout, 1 = slight tissue retention, 2 = prominent tissue retention, and 3 = massive retention. The prone scintigram served as the baseline study for the exercise scintigram. The results of the examination during exercise were compared to those obtained in prone position, to identify the exercise-induced hippurate transport disturbance.
To determine whether antihypertensive drugs, the clinical diagnosis, or funduscopic alterations could be linked to results obtained with exercise renography, we used a chi-square test. Wilcoxon tests were used to assess whether BP values, body weight, and serum creatinine, potassium, or sodium levels influenced results of exercise renography.

**Results**

The clinical and scintigraphic data of 45 hypertensive patients were included in the analysis. The prone-position renogram was always normal or failed to demonstrate a bilaterally disturbed hippurate transit. An exercise-induced bilateral transrenal hippurate transport disturbance was noted in 28 (62%) patients (abnormal exercise renogram). Parenchymal radiolabeled hippurate excretion was delayed, which resulted in an elevated third segment of the renogram and late tracer appearance in the bladder (Figure 1). The mean tracer transit to the bladder required 4.3 minutes in the prone position and 13.8 minutes during ergometric exercise (Table 1). The tracer failed to appear in the bladder during the 20-minute exercise examination in 11 patients. In order to calculate the mean appearance time of radioactivity in the bladder, we arbitrarily used the end of exercise (20 minutes) for these 11 hypertensive patients. The parenchymal tracer disturbance was also clearly recognized in the sequential scintigrams. Using the qualitative four-step scale for judging tissue isotope retention, we found five patients with Grade 1 (slight retention), two patients with Grade 2 (prominent retention), and 21 patients with Grade 3 (massive retention). The pulse rate observed during the prone examination and during exercise was similar for hypertensive patients with normal exercise and abnormal exercise renograms.

In 17 hypertensive patients the results of renography were not noticeably influenced by exercise. In these patients the mean appearance of radiolabeled tracer in the bladder remained nearly unchanged: 4.2 minutes at

![Figure 1](https://hyper.ahajournals.org/)

**Figure 1.** Renograms and sequential scintigrams of a 17-year-old hypertensive male patient, examined in prone position and during upright exercise. The sequence of examinations demonstrates the exercise-induced change in transrenal o-iodophippurate transport. The prone examination documents the timely hippurate excretion from the renal tissue. Note the pelvic activity during the 4th minute and the slight delay of tracer transit through the renal pelvis. Exercise initiated a massive disturbance of tracer kinetics; the transport abnormality is at the parenchymal level. The postexercise images demonstrate the initial outflow of radioactivity from the tissue to the pelvic system.
rest and 4.5 minutes during exercise (see Table 1). All patients were judged to have a regular isotope washout (Grade 0) from the kidney, using the four-step scale for judging tissue tracer retention.

Fourteen patients whose renograms failed to be influenced by exercise had balanced renal function in prone position, while two demonstrated a unilateral reduction. Single-kidney function could not be calculated for one patient. Fifteen hypertensive patients with an exercise-induced hippurate transport disturbance were found to have balanced renal function, while 12 had a unilateral disturbance. Again, single-kidney function could not be calculated for one of the patients. We considered renal function balanced when each kidney had between 45 and 55% of total function.

On the basis of the clinical evaluation 27 patients were considered to have essential hypertension, 10 had renal parenchymal disease, 5 suffered from renovascular disease, 2 had malignant hypertension, and 1 had hypertension of pregnancy (Table 2). We observed that exercise renography cannot differentiate essential from nephrogenic hypertension (Table 3).

Nine hypertensive patients with abnormal exercise renograms had a serum creatinine concentration between 1.3 and 3.3 mg/dl. Three patients had borderline values of 1.2 to 1.3 mg/dl; however, 11 patients with abnormal exercise renograms had normal values in the range between 0.7 and 1.1 mg/dl. The records of five patients did not contain these data. Mean values were clearly influenced in three patients with abnormal renograms whose creatinine concentration was 2.8, 3.1, and 3.3 mg/dl (see Table 2). The single most elevated creatinine concentration among the patients with normal exercise renograms was 1.5 mg/dl. The Wilcoxon test failed to distinguish patients with abnormal and normal exercise renograms on the basis of the serum creatinine level.

The serum catecholamine (n = 16), sodium (n = 36), and potassium (n = 36) values also were compared for both groups of hypertensive patients. The Wilcoxon test failed to demonstrate a relationship between the serum sodium and potassium values and an abnormal exercise renogram (see Table 3). The serum catecholamine data could not be analyzed statistically.
TABLE 3. Tests Used to Assess Various Parameters in Patients with Normal and Abnormal Renograms

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Test</th>
<th>Probability of difference between groups</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antihypertensive drugs</td>
<td>Chi-square</td>
<td>0.2-0.6</td>
</tr>
<tr>
<td>Serum sodium</td>
<td>Wilcoxon</td>
<td>0.8</td>
</tr>
<tr>
<td>Serum potassium</td>
<td>Wilcoxon</td>
<td>0.8</td>
</tr>
<tr>
<td>Creatinine</td>
<td>Wilcoxon</td>
<td>0.3</td>
</tr>
<tr>
<td>Body weight</td>
<td>Wilcoxon</td>
<td>0.94</td>
</tr>
<tr>
<td>Renal vs essential</td>
<td>Modified chi-square</td>
<td>0.32</td>
</tr>
<tr>
<td>hypertension</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blood pressure</td>
<td>Wilcoxon</td>
<td>0.32</td>
</tr>
<tr>
<td>Funduscopic changes</td>
<td>Chi-square</td>
<td>0.8</td>
</tr>
</tbody>
</table>

Tests were conducted to determine whether values of any parameter differed in the two populations. Overweight may be associated with an abnormal exercise renogram. The other parameters did not occur with an increased frequency in patients with either normal or abnormal exercise renograms.

Eight patients with normal exercise renograms had normal values, two had equivocal results. Four patients with abnormal exercise renograms had normal catecholamine values, and two had equivocal results.

The mean BP values for both hypertensive groups were similar (Figure 2). At the time of scintigraphy, 19 patients with an abnormal exercise scintigram had systolic values below or equal to 150 mm Hg, 7 had a systolic BP between 151 and 165 mm Hg, and 2 had systolic values in excess of 165 mm Hg. A similar distribution was noted in the normal exercise renogram population, which contained 11 patients with systolic BP values below 150 mm Hg, 5 with values between 151 and 170 mm Hg, and 1 with values in excess of 170 mm Hg. Diastolic BP values of 90 mm Hg or below were noted in six patients with an abnormal exercise response and in seven hypertensive patients with a normal exercise study. Hypertensive patients who responded to exercise with an abnormal renogram had a mean weight of 86.4 kg (height, 175 cm), while those who failed to exhibit an abnormal scintigram weighed 75.9 kg (height, 175 cm). The statistical analysis pointed to a possible direct relationship between patient overweight and an abnormal exercise renogram (see Table 3).

Antihypertensive drugs used at the time of scintigraphy are presented in Table 4. Hypertensive patients with an abnormal exercise response received more medication, on average, than did patients who failed to show the response. However, 9 of the 17 patients with normal exercise renograms and 11 of the 28 with abnormal exercise renograms were not taking medication at the time of the scintigraphic examination. The chi-square test was used to compare both groups with respect to the antihypertensive medication used (see Figure 1). It was not possible to demonstrate that antihypertensive medication influences the results of exercise renography.

Discussion

Exercise was recently shown to be a potent trigger of transient renal dysfunction in the hypertensive patient. Exercise may result in delayed tissue clearance of hippurate, which permits the renographic recognition of this abnormality. We believe that the exercise-mediated hippurate transport abnormality is an expression of a cortical vasomotor disturbance. The evidence is weighty and is based on the known renal kinetics of hippurate.

Our studies were performed with either [123I] or [131I] o-iodohippurate, a tracer with renal kinetics comparable to p-aminohippurate. Gamma camera renograms and sequential scintigrams permit evaluation of the transrenal tissue transport of the tracer, as well as assessment of single-kidney function. The prominent accumulation curves observed during exercise are the
result of a parenchymal hippurate deposition. Hippurate is actively pumped into proximal tubular cells, creating an interstitial concentration gradient that promotes its passive outflow across the cell membrane into the tubulus lumen. Cellular isotope accumulation occurs when luminal membrane injury disrupts the cellular exit of hippurate into the tubulus lumen. Tubular membrane injury has long been known to cause intracellular \( p \)-aminohippurate entrapment, but functional parenchymal hippurate accumulation also appears possible. Parenchymal tracer entrapment will occur when reduced glomerular filtration results in slowed washout of hippurate from the tubulus lumen, increasing the intraluminal hippurate concentration. This event disrupts the transit of hippurate from the cell into the lumen. Thus, both preglomerular and postglomerular pressure changes, which decrease the glomerular filtration rate, lower the cell-lumen concentration gradient and induce tracer entrapment. The observed hippurate transport abnormality is transient and can be observed in some hypertensive patients while they stand. The combination of upright posture and exercise has been shown to elicit the observed response in many hypertensive patients. This finding indicates that the disturbance is functional, rather than the result of membrane disruption. The observed hippurate transport disturbance thus appears to be due to an imbalance between tubular hippurate secretion and the glomerular filtration rate.

The most probable explanation for the observed hippurate transport disturbance is a vascular constriction of preglomerular vessels. Afferent arteriolar constriction would decrease glomerular filtration by reducing both glomerular blood flow and glomerular filtration pressure. Although efferent arteriolar constriction could cause glomerular filtration to fall, because of a rise in the colloid osmotic pressure, it would also reduce blood flow to, and isotope uptake by, the tubulus cells. This does not appear to be the case. Generally, tracer uptake appears to be maintained. The observed renal handling of radiolabeled hippurate suggests the presence of a vas afferens contraction, as does the kidney's regulatory mechanism, which likewise points to a functional disturbance of preglomerular vessels.

An initial exercise-induced rise in BP would cause a reflex contraction of smooth muscles at the vas afferens, to maintain the glomerular filtration rate. Activation of the juxtaglomerular apparatus could also induce a vas afferens contraction. While a disturbance of the regulatory mechanisms that control the juxtaglomerular-afferent vascular axis may be involved, we would stress the importance of sympathetic activity, and this influenced our selection of the exercise protocol. Efferent sympathetic fibers can influence the juxtaglomerular apparatus, the proximal renal tubule, and the ascending portion of the cortical loop of Henle. Efferent renal sympathetic nerves are known to have a particularly powerful effect on the constriction of efferent arterioles. Thus, effenter sympathetic nerves affect the control of the renal vasculature. Hollenberg and colleagues have presented evidence that sympathetic nerves modify a functional vascular disturbance that results in an elevated vascular resistance. Although considerable evidence implicates a vas afferens contraction as the cause of the observed hippurate transport disturbance, we have no evidence that exercise can induce the perfusion disturbance in the nonhypertensive, hydrated subject. In hypertensive persons exercise appears to trigger afferent vascular response that is inappropriate for the exercise stimulus. All hypertensive patients referred to scintigraphy were included in the present study. Twenty-two of our patients had normal systolic BP values at the scintigraphy. Sixty-two percent of our patients had an exercise renogram. The present data suggest that the results of exercise scintigraphy are independent of the BP at the time of scintigraphy. The present study showed that hypertensive BP values are not in themselves the cause of the cortical perfusion abnormality, since many of the examined hypertensive patients had normotensive BP values at scintigraphy. Thus, an abnormal result in an exercise study should not be interpreted as identifying a protective mechanism of the kidney against an acute hemodynamic rise of systemic BP.

The frequency of renal dysfunction in hypertension...
suggests that the cortical perfusion abnormality must also occur in patients with primary hypertension. Our theoretical model led us to expect that both patients with established nephrogenic hypertension and many patients with essential hypertension would have an abnormal exercise renogram. Indeed, this expectation was confirmed. Fifteen of the 28 patients with an abnormal exercise response were considered to have essential hypertension. Furthermore, patients with renovascular and with renoparenchymal hypertension frequently had an abnormal exercise response. The frequency of nephrogenic hypertension doubtless resulted because patients were referred by the nephrology unit. However, some patients with primary as well as nephrogenic hypertension also had normal exercise renograms. Thus, it was possible to demonstrate that the exercise renogram could not differentiate nephrogenic and essential hypertension.

We considered it important to demonstrate that the cortical perfusion abnormality was not the result of antihypertensive medication. The presented data suggest that the perfusion abnormality was not caused by antihypertensive drugs or drug combinations. Eleven of our patients with an abnormal exercise renogram had not been placed on antihypertensive medication at the time of scintigraphy, and seven hypertensive patients receiving antihypertensive drugs failed to exhibit evidence of a cortical perfusion abnormality. Furthermore, the medication taken by our patients also failed to eliminate the exercise-induced nippurate transport disturbance. Hypertensive patients with an abnormal exercise renogram tended to receive more medication than did those with normal exercise renograms. We postulate that hypertensive patients with an abnormal exercise response have a more therapy-resistant form of hypertension.

The possible association between an abnormal exercise renogram and patient overweight was probably due to the known relationship between obesity and primary hypertension. We also noted that diabetes was common among the patients with abnormal exercise renograms. Again, primary hypertension and diabetes are known to occur together. These results appear to support our contention that exercise-induced hippurate transport disturbance occurs commonly in patients classified as having essential hypertension.

The present data suggest that those diseases that result in an elevated systemic BP can, but need not, be associated with a renal cortical perfusion abnormality. We were unable to identify a single parameter that was specific for patients with exercise-induced renal dysfunction. The renogram thus appears to offer the research-oriented physician a simple, noninvasive technique to study a functional vascular response of the kidney that escaped earlier detection, which appears to be independent of other commonly used data obtained for the classification of the patient with hypertension. We believe that the exercise renogram will be a useful new tool for the investigation of hypertension.

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References
Clinical evaluation of patients with hypertension and exercise-induced renal dysfunction.

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