Predictive Value of Exercise Renography for Presurgical Evaluation of Nephrogenic Hypertension

JOHN H. CLORIUS, JENS ALLENBERG, THOMAS HUPP, LUDWIG G. STRAUSS, PETER SCHMIDLIN, GISELA IRNGARTINGER, RICARDA WAGNER, AND CHANDRA MUKHOPADHYAY

SUMMARY Functional o-iodohippurate scintigrams were obtained in 18 hypertensive patients. Each patient was examined in the prone position and during exercise. An exercise-induced transient, bilateral, hippurate transport disturbance was sought as an expression of an exercise-mediated cortical perfusion abnormality. The study sought to test the hypothesis that patients who present evidence for an exercise-induced renal perfusion disturbance would have stabilized hypertension that was no longer surgically curable because of morphological changes of the peripheral vasculature. All 18 patients continued on to therapy: 13 proceeded to renovascular reconstructive surgery, 2 had a unilateral nephrectomy, and 3 were treated with percutaneous transluminal renal angioplasty. During preoperative exercise renography, evidence of bilateral renal dysfunction developed in 10 of 18 hypertensive patients during ergometric stress (abnormal exercise response). Following surgical therapy nine of these patients with abnormal exercise scintigrams continued to have hypertensive disease, while one patient was cured. The exercise renograms of eight hypertensive patients were not influenced by the exercise protocol, and operation cured seven of these eight patients. The results suggest that an accentuated vascular response to exercise occurs in the maintenance phase of renovascular hypertension, a disturbance not observed while the hypertension is curable by surgical therapy. (Hypertension 10: 280-286, 1987)

KEY WORDS • exercise renography • renovascular hypertension • hippurate kinetics

RENOGRAPHIC examinations have documented bilateral tissue retention of o-iodohippurate in 20% of all hypertensive patients examined while standing, a disturbance not demonstrated when patients were studied in the prone position.1 Radioactively labeled hippurate has renal kinetics comparable to p-aminohippurate.2,3 The known kinetics of this tracer indicates that the disturbed tracer transport in the upright position is the result of a transitory cortical perfusion abnormality. Many, but not all, of these patients had diabetes or compensated renal insufficiency. It thus appears probable that many hypertensive patients with a posture-dependent disturbance of cortical perfusion may have morphological alterations combined with a functional abnormality of peripheral renal vessels. Recently, exercise was shown to be a potent trigger of renal dysfunction in hypertension.4 Nearly 60% of all hypertensive subjects exhibited the transitory but prominent tracer transport disturbance during exercise, a response not seen in normotensive subjects. Normotensive subjects may respond with a slightly lengthened hippurate transit time because of the known physiological changes of renal blood flow in response to exercise.4,5 Although exercise can cause hippurate transit time alterations within narrow limits in normotensive subjects, the massive tracer transport abnormality observed in hypertension indicates that renal cortical blood flow is inappropriately disturbed by exercise in these patients.

To date it has not been possible to demonstrate an interdependence between the results of exercise renography and other common parameters used in the classification of hypertension. Exercise renography’s value...
remains unclear. The present study was performed to test the hypothesis that an exercise-induced change of hippurate handling identifies functional changes of the kidney that signify that renal hypertension is no longer curable by surgical therapy. Thus, patients with essential hypertension and intractable renal hypertension would show bilateral renal dysfunction during exercise and could not be differentiated renographically. Conversely, patients without evidence of exercise-induced renal dysfunction would be expected to profit from surgical intervention. To test this hypothesis we examined patients with renovascular stenosis before therapy.

Patients and Methods

We report the results of a blind clinical trial of 30 hypertensive patients who had angiographically documented unilateral or bilateral renovascular stenosis. All were potential candidates for surgical intervention of hypertension. All patients had at least a 75% vascular lumen reduction. All were referred to scintigraphy by vascular surgeons. Patients were included in this study when operation appeared probable because of the risk or presence of stenosis-induced renal functional impairment. Surgical therapy of renovascular hypertension is not common at this institution. The cure of hypertension was not the primary goal of the surgical intervention.

All 30 patients were referred to hippurate scintigraphy during the preoperative evaluation. Gamma camera renography with the patient in the prone position was performed to document the relative percentage of total function of each kidney. This examination also served as standard against which the exercise renogram was compared. Exercise renography followed, to test the stated hypothesis. Ten patients were excluded from final analysis because of incomplete or equivocal scintigraphic data. We failed to obtain a pulse response in one patient, so that exercise was considered inadequate. In two patients the exercise renogram was equivocal, and we chose to drop these patients from the comparison. The exercise renogram could not be evaluated due to a technical error in one patient. Four patients did not have the exercise study because of previous infarction in two patients and because of hypertensive blood pressure (BP) values that precluded the exercise protocol in two patients. Finally, two patients were physically incapacitated. One of these was wheelchair-bound, and one had undergone unrelated, recent abdominal surgery. Thus, 20 patients had a complete and unambiguous renal function examination that met the requirements for inclusion in the study. All renograms were evaluated by one investigator (J.H.C.), who did not have access to the patients' clinical data.

Six months after completion of the clinical trial, and following the surgical procedure, we began the clinical evaluation of the data. The following information was recorded from hospital records: antihypertensive medication required prior to operation, preoperative BP values, and the presence of bilateral or unilateral vascular lesions, as identified by angiography. The surgical procedure employed was recorded, as were the postoperative BP values and the antihypertensive drugs taken at time of discharge. Most patients were quickly lost to further follow-up. To learn about the late postoperative fate of each patient, we contacted the referring physician. Patients who had not returned to their referring physician were contacted directly. We then called their new physician or queried the patient about the BP values and the medication taken.

This follow-up resulted in knowledge of the BP status of each patient for an average of 18 months post operation; the shortest follow-up period was 6 months, the longest was 52 months. These clinical data were gathered by one associate (R.W.), who did not have access to the results of the preoperative scintigraphic examinations.

To assess the final development of the disease in hypertensive patients with normal and abnormal exercise scintigrams, we used slightly modified criteria established by the U.S. cooperative trial of surgical treatment of renovascular hypertension. Hypertension was considered cured if the diastolic BP was below 90 mm Hg in the absence of any antihypertensive medication. Operation was judged to have improved the disease when the diastolic BP was reduced by at least 15% with medication. Nonresponders were defined as those hypertensive patients who had a BP reduction of less than 15% or who required increasing doses of antihypertensive medication or a combination of three or more drugs.

The protocol required that each patient have two scintigrams preceding therapy. Each subject had renography in the prone position and in the upright (sitting) position during ergometric stress. Both examinations were obtained within 1 week, generally within 72 hours. To obtain adequate hydration, patients were asked to drink 400 ml of fluid during the 30 minutes before renography.

All patients received careful oral instructions about the examinations. The renogram in the prone position was begun within minutes after patient positioning. The exercise program was used to document the influence of exercise on hippurate kinetics. Patient comfort was emphasized during the test. The workload was considered adequate if it could be continued indefinitely and too heavy if it resulted in exhaustion. Patients sitting in front of the gamma camera on a bicycle ergometer were asked to sit straight-backed so that the kidney-to-camera distance was kept small. Pulse and BP were noted during the exercise and were monitored at 2- to 3-minute intervals. Ergometric resistance was set at 60 W for women and 80 W for men after 60 rotations/min was reached. After 1 to 2 minutes of exercise, the pulse rate change in response to exercise was noted. Renography was begun only after the pulse rate had increased at least 20 beats/min. Following radiotracer injection, the patients continued to exercise. Ergometric resistance was adjusted according to the wishes of the patients. In response to exercise,
intermittent claudication developed in five of the 18 patients included in the final analysis, making it necessary to reduce resistance. Two patients with a normal exercise study had to be examined at 35 and 40 W. Three patients with disturbed hippurate kinetics in response to exercise (abnormal exercise study) were examined at 20 W (two patients) and at 50 W (one patient).

Radionuclide renography was performed after intravenous injection of either 7 μCi [131I]o-iodohippurate or 6 μCi [125I]o-iodohippurate per kilogram of body weight. A 15-in. gamma camera equipped with a general-purpose medium-energy (360 keV) parallel-hole collimator was used for all studies, with a window setting at 25%, centered over the photopeak of the tracer. One-minute images were obtained, beginning with the injection, at 1 to 4, and 7, 9, 14, and 19 minutes. To identify the appearance of the tracer in the bladder, which was recognized on the sequential scans, we extended the uninterrupted 1-minute image sequence past the fourth minute when required. The examination was terminated after 20 minutes. Data were stored on magnetic tape and were analyzed by minicomputer. Regions of interest were placed over each kidney to determine single-kidney function. No attempt was made to exclude the renal pelvic system. Background regions of interest were placed automatically around each kidney using a 2-pixel width. 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 24 and 120 seconds. The third curve segment of the renogram was analyzed by inspection only. Results of prone and exercise renography and serial scintigrams were compared.

Results

The final postoperative clinical evaluation of our 30 patients showed that 22 had undergone reconstructive surgery, 2 had had a nephrectomy (Patients 1 and 7), and 3 had had percutaneous renal angioplasty (Patients 8, 13, and 17). Three scintigraphed patients did not proceed to therapy. When the scintigraphic and the clinical data were combined, we noted that 10 patients had been lost due to inadequate scintigraphic data and that three had not gone on to therapy. One patient was eliminated from both data sets; He was not operated on and was dropped because of inadequate scintigraphic data. The final evaluation thus includes a total of 18 hypertensive patients. Thirteen of these patients had a unilateral stenosis, 4 had bilateral stenosis, and 1 had a pyelonephritic small kidney (see Table 2). Thirteen had reconstructive surgery, 2 had a nephrectomy and 3 had percutaneous renal angioplasty.

Ten of 18 (56%) patients demonstrated a bilaterally disturbed transrenal hippurate transport during exercise (abnormal exercise renogram; Figure 1). The mean tracer appearance time in the bladder changed from 3.3 minutes in the prone position to 8.3 minutes during ergometric exercise (Table 1). Two of the patients with abnormal exercise renograms manifested a massive hippurate transport disturbance. In one (Patient 11), the tracer appeared in the bladder at 25 minutes, and in the other (Patient 14), 46 minutes after injection. For both of these patients we used a 20-minute value to calculate the mean tracer appearance time in the bladder to avoid having a few highly abnormal responses to exercise magnify the extent of the transport disturbance. Eight of 18 (44%) hypertensive patients failed to exhibit a bilateral exercise-mediated change of hippurate transport. Exercise resulted in a slight delay in the tracer excretion, so that this value changed from 3.2 minutes in the prone position to 3.7 minutes during exercise (see Table 1). Abnormal as well as normal exercise renograms were noted in patients with equal as well as dissimilar single-kidney function. Balanced renal function was defined as being between 45 and 55% for each kidney.

The mean systolic and diastolic BP values of patients with normal exercise renograms were lower than the values observed in patients with abnormal exercise renograms before therapy (see Table 1). Following renovascular surgery, the group with abnormal exercise renograms was clearly differentiated from the group with normal exercise renograms in terms of the final BP status (Table 2). Seven out of eight hypertensive patients with normal exercise renograms were considered cured of hypertension, while one was considered improved. In comparison, the abnormal exercise renogram population had only one patient whose hypertension was cured. This patient (Patient 13) had had a bilateral stenosis and a unilateral reduction of single-kidney function (left = 30%; right = 70%). During exercise he had a prominent disturbance of hippurate transport, so that the tracer appeared in the bladder at 4 minutes during prone-position scintigraphy and at 8 minutes during exercise. Six other patients had improved BP values, and three (Patients 16–18) were considered to be nonresponders to therapy.

Our patients were examined while taking antihypertensive medication (Table 3). On average, the patient with a normal exercise scintigarm required fewer antihypertensive drugs than did the patient who responded to exercise with a disturbed hippurate transport. The results of our study suggest that the antihypertensive medication used neither caused nor eliminated the cortical perfusion disturbance.

Discussion

Exercise renography demonstrates transient dysfunction of the kidney in many patients with hypertension and helps us to recognize a pathophysiological response that escaped previous detection. We believe that the described hippurate transport abnormality is indicative of a transient cortical perfusion disturbance. Fifty-six percent of the present population responded to exercise with prominent tracer retention in the tissue of both kidneys. However, even those patients considered to have normal exercise renograms demonstrated
a slight delay of tracer transport through both organs. This delay appears to be due to the known neurogenic influence of exercise, resulting in physiological renal vasoconstriction. This physiological response to exercise has been observed with exercise renography in normotensive subjects and should not be confused with the disturbance under investigation.

The present results support the hypothesis that an exercise-induced change of hippurate handling in the presence of nephrogenic hypertension indicates that

<p>| Table 1. Characteristics of Hypertensive Patients with Normal and Abnormal Exercise Renograms as Determined by Parenchymal Tracer Transports and Tracer Appearance in the Bladder |
|---------------------------------|-----------------|----------------|-----------------|-----------------|-----------------|</p>
<table>
<thead>
<tr>
<th>Exercise renogram</th>
<th>Disturbed hippurate transport</th>
<th>Bladder visualized (min)</th>
<th>Single kidney function</th>
<th>Preoperative</th>
<th>Postoperative</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal (n = 8)</td>
<td>Prone 0 0</td>
<td>Exercise 3.2 3.7</td>
<td>Age (yr) 51.6</td>
<td>BP 171/100 1.8</td>
<td>Late BP 142/82</td>
</tr>
<tr>
<td>Abnormal (n = 10)</td>
<td>Prone 0 10</td>
<td>Exercise 3.3 8.3</td>
<td>Age (yr) 52.7</td>
<td>BP 190/106 2.3</td>
<td>Late BP 156/87</td>
</tr>
</tbody>
</table>

Values for BP and no. of drugs are expressed as means.
the disease will not be cured by revascularization. This hypothesis was based in part on the observation that some patients diagnosed as having nephrogenic hypertension had an abnormal exercise renogram, an expression of a dysfunction observed in essential hypertension.

Efferent sympathetic stimulation is thought to be implicated in the pathogenesis of essential hypertension by increasing renal vascular resistance. Indeed, elevated renal vascular resistance has been one of the most consistent abnormalities documented in this disease. In his extensive review, Katholi suggests that renal nerves may not be important in maintaining established disease. This finding suggests that renal nerves may not be important in maintaining established disease. Thus, the increased vascular resistance seen in patients with essential hypertension may be either functional or structural, depending on the stage of the disease.

In nephrogenic hypertension, functional vascular changes may likewise be involved in the maintenance phase of the disease. It has long been recognized that the nonischemic kidney in renovascular hypertension can acquire the ability to sustain hypertension. During the maintenance phase, elevated BP values may be characterized as being nearly independent of other mechanisms, perhaps due to structural changes of the vasculature of the nonclipped kidney. Ploth, in his excellent review, points out that central and peripheral neurogenic mechanisms may be important for the maintenance of hypertension at this time. The hypertension may then be mediated through central neurogenic mechanisms influenced by afferent renal nerves. Afferent renal nerves would activate the sympathetic nervous system, to bring about renovascular responses comparable to those seen in essential hypertension. Katholi has summarized the present evidence for such a mechanism. Finally, we would not exclude the juxtaglomerular-afferent vascular axis from our consideration, since we believe that it may modify the functional vascular responses under consideration. It appears that adequate initial evidence has been accumulated to support our hypothesis that functional vascular responsiveness can be expected in both essential hypertension and in established nephrogenic hypertension.

Renovascular hypertension represents the most common cause of surgically curable hypertension, but the inability to reliably identify curable disease has been notable. Fouad et al., in a carefully documented study of 14 hypertensive patients, reported that two with a negative saralasin test, were cured by operation. Twelve responded to the saralasin test, but four had persistent hypertension after operation. Thus only eight of 14 patients demonstrated the BP response predicted by the test. The same study reported that neither plasma renin activity nor stimulated plasma renin activity permitted an acceptable differentiation between responders to operation and therapeutic failures. Picking et al. compared renin-sodium profiles with results achieved with angioplasty. Twenty patients with renovascular hypertension were studied. Sixteen had high renin-sodium profiles, two of whom failed to respond to angioplasty with normalized BP values, even though plasma renin activity returned to normal. Four patients had normal test results, and operation

<table>
<thead>
<tr>
<th>Patient no.</th>
<th>Stenosis</th>
<th>BP at discharge (mm Hg)</th>
<th>Final BP (mm Hg)</th>
<th>Months postop</th>
<th>No. of drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal renogram</td>
<td>1</td>
<td>U</td>
<td>180/100</td>
<td>130/75</td>
<td>100/60</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>U</td>
<td>160/85</td>
<td>130/80</td>
<td>160/80</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>U</td>
<td>200/120</td>
<td>130/90</td>
<td>140/90</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>U</td>
<td>170/110</td>
<td>150/80</td>
<td>150/95</td>
</tr>
<tr>
<td></td>
<td>5</td>
<td>U</td>
<td>170/100</td>
<td>150/100</td>
<td>135/70</td>
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<tr>
<td></td>
<td>6</td>
<td>U</td>
<td>160/80</td>
<td>130/85</td>
<td>160/90</td>
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<tr>
<td></td>
<td>7</td>
<td>PN</td>
<td>160/110</td>
<td>-</td>
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<tr>
<td></td>
<td>8</td>
<td>U</td>
<td>170/100</td>
<td>120/70</td>
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<table>
<thead>
<tr>
<th>Abnormal renogram</th>
<th>Stenosis</th>
<th>BP at discharge (mm Hg)</th>
<th>Final BP (mm Hg)</th>
<th>Months postop</th>
<th>No. of drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td>9</td>
<td>U</td>
<td>180/110</td>
<td>130/90</td>
<td>145/75</td>
<td>28</td>
</tr>
<tr>
<td>10</td>
<td>BI</td>
<td>240/140</td>
<td>160/80</td>
<td>160/80</td>
<td>7</td>
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<tr>
<td>11</td>
<td>U</td>
<td>200/120</td>
<td>140/80</td>
<td>130/80</td>
<td>25</td>
</tr>
<tr>
<td>12</td>
<td>U</td>
<td>240/100</td>
<td>140/70</td>
<td>100/90</td>
<td>10</td>
</tr>
<tr>
<td>13</td>
<td>BI</td>
<td>180/90</td>
<td>140/80</td>
<td>150/90</td>
<td>7</td>
</tr>
<tr>
<td>14</td>
<td>BI</td>
<td>200/110</td>
<td>160/70</td>
<td>170/90</td>
<td>6</td>
</tr>
<tr>
<td>15</td>
<td>BI</td>
<td>120/80</td>
<td>150/90</td>
<td>135/95</td>
<td>41</td>
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<tr>
<td>16</td>
<td>U</td>
<td>120/65</td>
<td>130/80</td>
<td>145/85</td>
<td>6</td>
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<tr>
<td>17</td>
<td>BI</td>
<td>220/120</td>
<td>160/100</td>
<td>140/80</td>
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<tr>
<td>18</td>
<td>U</td>
<td>200/130</td>
<td>200/100</td>
<td>190/100</td>
<td>52</td>
</tr>
</tbody>
</table>

BP data shown was obtained at rest at time of scintigraphy (Preop), at time of discharge, and at the late postoperative follow-up. U = unilateral stenosis; PN = pyelonephritis; NT = normotensive; BI = bilateral stenosis.
resulted in one failure, two improvements, and one cure. Finally, we refer to results presented by Delin et al. This group reported results with the basal renal vein renin ratio method. Twenty-six patients with renal vein renin determinations not indicative of renovascular hypertension were identified. Sixteen were successfully treated with operation. Of 38 patients with positive results, 16 were successfully treated and 22 were failures. Renin stimulation resulted in either false-positive or false-negative test results in 15 of 64 patients. These results suggest that new approaches warrant consideration. In all frankness, however, we would like to point out that it was not the goal of this study to seek a new procedure for the preoperative evaluation of patients with suspected renovascular hypertension. Rather, we wanted to test our hypothesis that a functional vascular response is involved in both essential and established nephrogenic hypertension. While we would be pleased if exercise renography could find a useful application, the present experience appears too limited to warrant such a recommendation.

We examined our patients while they were receiving antihypertensive medication. Pickering et al. reported his experience with renin determinations when patients received β-blockers or captopril. As expected, the renin determinations failed to have predictive value. To date we have not found any evidence that antihypertensive medication influences the results of the exercise renogram.

We were forced to examine some of our patients at exercise levels below those demanded by our protocol because of the presence of intermittent claudication. This change did not appear to reduce the value of the examination. We have been studying the exercise level required to elicit an abnormal exercise renogram. Exercise at a specific watt setting results in very different exercise levels for individual patients, as can be demonstrated with circulatory parameters. This difference may be due to differences in physical training or medication. To standardize exercise, we began to examine patients at the individual aerobic/anaerobic threshold, determined according to Pessenhofer et al. The method identifies the turning point from primarily aerobic to anaerobic energy production, with its subsequent increase in blood lactate levels. We have found at the aerobic/anaerobic threshold a pulse rate that is far lower than that achieved with the protocol used in this study. Nevertheless, the renal function response under investigation continues to be seen with a similar frequency. These observations raise questions about the level of exercise required to elicit the functional vascular response studied.
Exercise renography helped predict which patients could be cured of renovascular hypertension. We also realize that many patients with an abnormal exercise renogram profited from operation even though they were not cured of hypertension. We do not advocate exercise renography for routine patient evaluation, but we hope that continued investigation of the pathophysiological response elicited with this procedure will increase our understanding of hypertensive disease.

References
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