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

R enographic 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

From the German Cancer Research Center and the University of Heidelberg, Heidelberg, West Germany.

Address for reprints: John H. Clorius, M.D., Institute of Nuclear Medicine, German Cancer Research Center, P.O. Box 10 1949, D-6900 Heidelberg, West Germany.

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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 essen-
tial hypertension and intractable renal hypertension
would show bilateral renal dysfunction during exercise
and could not be differentiated renographically. Con-
versely, patients without evidence of exercise-induced
renal dysfunction would be expected to profit from
surgical intervention. To test this hypothesis we ex-
amined 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 docu-
mented unilateral or bilateral renovascular stenosis.
All were potential candidates for surgical intervention
of hypertension. All patients had at least a 75% vascu-
lar 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-
al impairment. Surgical therapy of renovascular hyper-
tension 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 scintig-
raphy during the preoperative evaluation. Gamma
camera renography with the patient in the prone posi-
tion was performed to document the relative percent-
age of total function of each kidney. This examination
also served as standard against which the exercise
renogram was compared. Exercise renography fol-
lowed, 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 be-
cause of hypertensive blood pressure (BP) values that
precluded the exercise protocol in two patients. Final-
ly, 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 ex-
amination that met the requirements for inclusion in
the study. All renograms were evaluated by one inves-
tigator (J.H.C.), who did not have access to the pa-
tients’ 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 medica-
tion required prior to operation, preoperative BP
values, and the presence of bilateral or unilateral vas-
cular lesions, as identified by angiography. The surgical
procedure employed was recorded, as were the postop-
erative 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 op-
eration; the shortest follow-up period was 6 months,
the longest was 52 months. These clinical data were gath-
ered by one associate (R.W.), who did not have access
to the results of the preoperative scintigraphic exami-
nations.

To assess the final development of the disease in
hypertensive patients with normal and abnormal exer-
cise scintigrams, we used slightly modified criteria
established by the U.S. cooperative trial of surgical
treatment of renovascular hypertension.6 Hypertension
was considered cured if the diastolic BP was below 90
mm Hg in the absence of any antihypertensive medica-
tion. Operation was judged to have improved the dis-
ease 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 antihy-
pertensive medication or a combination of three or
more drugs.

The protocol required that each patient have two
scintigrams preceding therapy. Each subject had re-
nography in the prone position and in the upright (sit-
ting) position during ergometric stress. Both examina-
tions 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 influ-
ence of exercise on hippurate kinetics. Patient comfort
was emphasized during the test. The workload was
considered inadequate if it could be continued indefi-
nitely and too heavy if it resulted in exhaustion. Pa-
tients 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
radionuclide injection, the patients continued to exer-
cise. 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 pelvonephritic 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 scintgram 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
FIGURE 1. Renograms and sequential scintigrams in a 15-year-old hypertensive patient (Patient 11) with unilateral stenosis of the right renal artery. The sequence of examinations demonstrates the exercise-induced change of hippurate kinetics. The prone examination showed that the right kidney had 30% of total function. Parenchymal tracer transport through both kidneys was regular when examined at rest. Exercise caused a massive bilateral abnormality of tracer kinetics. Note the parenchymal tissue retention and the lack of activity excretion into the bladder during the 20-minute examination. Five minutes after cessation of exercise, we documented a rapid washout of activity from the tissue of both kidneys.

Figures a and b show the effect of exercise on the right kidney. The sequence of examinations demonstrates the exercise-induced change of hippurate kinetics. The prone examination showed that the right kidney had 30% of total function. Parenchymal tracer transport through both kidneys was regular when examined at rest. Exercise caused a massive bilateral abnormality of tracer kinetics. Note the parenchymal tissue retention and the lack of activity excretion into the bladder during the 20-minute examination. Five minutes after cessation of exercise, we documented a rapid washout of activity from the tissue of both kidneys.

Table 1. Characteristics of Hypertensive Patients with Normal and Abnormal Exercise Renograms as Determined by Parenchymal Tracer Transport and Tracer Appearance in the Bladder

<table>
<thead>
<tr>
<th>Exercise renogram</th>
<th>Disturbed hippurate transport</th>
<th>Bladder visualized (min)</th>
<th>Single kidney function</th>
<th>Preoperative BP (mm Hg)</th>
<th>No. of drugs</th>
<th>Postoperative BP (mm Hg)</th>
<th>No. of drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal (n = 8)</td>
<td>0</td>
<td>3.2</td>
<td>Equal 5</td>
<td>171/100</td>
<td>1.8</td>
<td>142/82</td>
<td>1 patient: 3 All others: none</td>
</tr>
<tr>
<td>Abnormal (n = 10)</td>
<td>0</td>
<td>3.3</td>
<td>Equal 3</td>
<td>190/106</td>
<td>2.3</td>
<td>156/87</td>
<td>1 patient: none All others: 2 (x)</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 points out that in essential hypertension of recent onset, increased vascular resistance represents a functional abnormality. Furthermore, Katholi notes that animal studies showed that renal denervation did not change arterial pressure or sodium excretion in 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 hyper tension 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 responses 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 and associates, in a comprehensive review of the subject, have discussed the indications for surgical treatment of renovascular hypertension. The indications for surgical treatment are: (1) renovascular hypertension with contralateral renal failure; (2) renovascular hypertension with evidence of renovascular disease in the uninvolved kidney; (3) renovascular hypertension with a positive saralasin test; and (4) renovascular hypertension that has not responded to medical treatment.

TABLE 2. Comparison of BP Status of Hypertensive Patients with Normal and Abnormal Exercise Renograms

<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></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>U</td>
<td>180/100</td>
<td>130/75</td>
<td>31</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>U</td>
<td>160/85</td>
<td>130/80</td>
<td>13</td>
<td>0</td>
</tr>
<tr>
<td>3</td>
<td>U</td>
<td>200/120</td>
<td>130/90</td>
<td>39</td>
<td>3</td>
</tr>
<tr>
<td>4</td>
<td>U</td>
<td>170/110</td>
<td>150/80</td>
<td>6</td>
<td>0</td>
</tr>
<tr>
<td>5</td>
<td>U</td>
<td>170/100</td>
<td>150/100</td>
<td>8</td>
<td>0</td>
</tr>
<tr>
<td>6</td>
<td>U</td>
<td>160/80</td>
<td>130/85</td>
<td>6</td>
<td>0</td>
</tr>
<tr>
<td>7</td>
<td>PN</td>
<td>160/110</td>
<td>—</td>
<td>33</td>
<td>0</td>
</tr>
<tr>
<td>8</td>
<td>U</td>
<td>170/100</td>
<td>120/70</td>
<td>7</td>
<td>0</td>
</tr>
<tr>
<td>Abnormal renogram</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>U</td>
<td>180/110</td>
<td>130/90</td>
<td>28</td>
<td>3</td>
</tr>
<tr>
<td>10</td>
<td>BI</td>
<td>240/140</td>
<td>160/80</td>
<td>7</td>
<td>1</td>
</tr>
<tr>
<td>11</td>
<td>U</td>
<td>200/120</td>
<td>140/80</td>
<td>25</td>
<td>2</td>
</tr>
<tr>
<td>12</td>
<td>U</td>
<td>240/100</td>
<td>140/70</td>
<td>10</td>
<td>1</td>
</tr>
<tr>
<td>13</td>
<td>BI</td>
<td>180/90</td>
<td>140/80</td>
<td>7</td>
<td>0</td>
</tr>
<tr>
<td>14</td>
<td>BI</td>
<td>200/110</td>
<td>160/70</td>
<td>6</td>
<td>3</td>
</tr>
<tr>
<td>15</td>
<td>BI</td>
<td>120/80</td>
<td>150/90</td>
<td>41</td>
<td>1</td>
</tr>
<tr>
<td>16</td>
<td>U</td>
<td>120/65</td>
<td>130/80</td>
<td>6</td>
<td>3</td>
</tr>
<tr>
<td>17</td>
<td>BI</td>
<td>220/120</td>
<td>160/100</td>
<td>7</td>
<td>2</td>
</tr>
<tr>
<td>18</td>
<td>U</td>
<td>200/130</td>
<td>200/100</td>
<td>52</td>
<td>3</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.11 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.17 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.18 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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