Renovascular Hypertension Identified by Captopril-Induced Changes in the Renogram

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SUMMARY Radioisotope renography was performed in 21 patients with hypertension and unilateral renal artery stenosis with and without premedication with 25 mg of captopril, and the results were compared with the effect of percutaneous transluminal angioplasty on the blood pressure, assessed 6 weeks after angioplasty. Angioplasty caused a considerable decrease in blood pressure in 15 of the 21 patients. In 12 of these 15 patients, captopril induced changes in the time-activity curves of the affected kidney only, suggesting deterioration of the excretory function of that kidney, while the function of the contralateral kidney remained normal. After angioplasty the asymmetry in the time-activity curves diminished despite identical pretreatment with captopril. Such captopril-induced unilateral impairment of the renal function was not seen in the six patients with unilateral renal artery stenosis whose blood pressure did not change after percutaneous transluminal angioplasty or in 13 patients with hypertension and normal renal arteries. The functional impairment of the affected kidneys was characterized by a decrease of Tc-diethylenetriamine pentaacetic acid uptake and a delay of I131-hippurate excretion, while the I131-hippurate uptake remained unaffected. These data are in agreement with a reduced glomerular filtration rate and diuresis during preservation of the renal blood flow, changes that can be expected after converting enzyme inhibition in a kidney with low perfusion and an active, renin-mediated autoregulation of the glomerular filtration rate. These data suggest that functional captopril-induced unilateral changes, shown by split renal function studies with noninvasive gamma camera scintigraphy, can be used as a diagnostic test for renovascular hypertension caused by unilateral renal artery stenosis. With the criteria used, a sensitivity of 80% and a specificity of 100% were obtained. (Hypertension 9:451-458, 1987)

KEY WORDS • unilateral renal artery stenosis • hippurate renogram • diethylenetriamine pentaacetic acid renogram • captopril • converting enzyme inhibition • renal function • renovascular hypertension • percutaneous transluminal angioplasty

RECENTLY, it has been shown that a kidney with renal artery stenosis may exhibit impaired excretory function during converting enzyme inhibition (CEI). This effect is thought to be due mainly to interruption of the autoregulation of the glomerular filtration rate (GFR), which becomes dependent on the stimulated intrarenal angiotensin II when the perfusion pressure is low. This impairment of renal function only comes to the attention of clinicians in patients without a normal kidney (i.e., either with a single kidney with renal artery stenosis or with bilateral renal artery stenosis). These patients demonstrate an oliguria and a rise of serum creatinine or urea concentration. However, if renal insufficiency occurs in a kidney with stenosis of its renal artery when a normal contralateral kidney is present, this unilateral renal insufficiency remains undetected because the healthy kidney maintains the overall GFR and diuresis.

The present study was performed prospectively to investigate whether in patients with renovascular hypertension caused by unilateral renal artery stenosis, a unilateral change in renal function induced by CEI can be unmasked by radioisotope renography. We also tried to ascertain whether such unilateral change in these radioisotopic studies after CEI is seen specifically in patients with functioning renal artery stenosis, as judged by a good antihypertensive effect of percutaneous transluminal angioplasty (PTA), and not in patients with nonfunctioning renal artery stenosis or without renal artery stenosis. Criteria by which these
changes can be quantified were selected retrospectively. Furthermore, in patients who underwent PTA, renography during CEI was repeated after PTA. When unilateral renal insufficiency occurs before PTA, renal insufficiency should not occur after successful dilatation of the artery stenosis. Confirmation of this assumption indicates that renography during CEI could be a useful test in patients with hypertension and unilateral renal artery stenosis to determine whether that stenosis contributes to the elevated blood pressure. This technique has been applied in preliminary studies with a single patient and a small group.

Patients and Methods

Thirty-four patients with known or suspected renal artery stenosis in whom arteriography and PTA were planned were selected for this study. The suspicion of renovascular hypertension was based on a moderate to severe hypertension with insufficient response to antihypertensive medication or on the asymmetry of a $^{131}$I-hippurate renogram performed during the workup of these patients.

Unilateral renal artery stenosis was demonstrated on arteriograms in 21 of the 34 patients. PTA was performed on these patients, and the stenosis was dilated sufficiently in 19 patients, as shown by arteriography performed immediately after the procedure. In the other two patients, nephrectomy of a small kidney with a severe entrance stenosis was performed. Characteristics of these patients are given in Table 1. The remaining 13 patients had essential hypertension because arteriography showed normal renal arteries. Assessment of the blood pressure response and a control renogram were performed at the clinic 6 weeks after PTA (or nephrectomy). In 15 of the 21 patients with renal artery stenosis, the hypertension was cured or improved after PTA or nephrectomy. In six patients PTA had no noticeable effect on the blood pressure. Criteria for cure, improvement, or no result are derived from the American cooperative study. Based on these data the 34 hypertensive patients were divided into three groups: 1) renovascular hypertension (i.e., functional renal artery stenosis; 15 patients); 2) nonfunctional renal artery stenosis (6 patients); and 3) normal renal arteries (13 patients).

Gamma camera renograms with and without captopril pretreatment were done on 2 different days before PTA and repeated with captopril pretreatment 6 weeks after PTA. To avoid residual retention of radionuclides the two studies before PTA were made at least 3 days apart. All antihypertensive therapy was withdrawn on the day of the renogram. Diuretics were not taken during the 48 hours before each examination. For patients taking a converting enzyme inhibitor, this medication was discontinued at least 3 weeks before the first investigation.

During each examination the patients were fasting but consumed a water load of 0.5 L in the hours before the i.v. administration of the radionuclide. Captopril was administered orally in a 25-mg dose 1 hour before the examination. As shown by Ferguson et al., this dose is followed by almost complete CEI from 15 to 120 minutes after ingestion.

Renography with 35 MBq $^{99m}$Tc-diethylenetriamine pentaacetic acid (DTPA) and 18 MBq $^{131}$Iorthoiodohippurate was performed successively with a large-field-of-view gamma camera (Siemens LFOV, Erlangen, West Germany) with high energy parallel-hole collimator and computer data acquisition. Data were stored in eighty 15-second frames of a $64 \times 64$ cell matrix during 20 minutes. Kidney regions of interest were generated automatically on the composed image in the first 5 minutes by determination of the distinctive intensity of the image. The time-activity curve based on measurement between the kidneys was used for the correction of blood background activity.

Calculations of the following variables were performed from the $^{131}$I-hippurate renogram: 1) the percentage uptake in the second minute by the affected/affected + contralateral kidney; 2) the time to peak of the affected minus the contralateral kidney in minutes; and 3) the relative activity of hippurate at 15 minutes, that is, the activity of the affected/contralateral kidney during the 15th minute X the activity of the contralateral/affected kidney during the second minute. The percentage uptake of the affected/affected + contralateral kidney was calculated from the $^{99m}$Tc-DTPA renogram. Because of high background activity in the beginning of the curve, this value was calculated for the third minute. In addition, the uptake of the $^{131}$I-hippurate and $^{99m}$Tc-DTPA in each kidney in the second and third minute, respectively, was expressed as a fraction of the injected dose, measured using the gamma camera, and presented in arbitrary units. This single kidney uptake capacity was measured when the patient was in a standardized position in relation to the collimator, thus allowing comparison between successive examinations. Because the decision to include this single kidney uptake capacity was made later in the study, it was not done in all patients. During renography, blood pressures were recorded by trained staff using Korotkoff phase V for diastolic blood pressure.

Results

Typical results for one patient (Patient 14 in Table 1) are given in Figure 1. This patient's hypertension was cured after PTA of a stenosis of the left renal artery. Before PTA, pretreatment with captopril slowed down the excretion of $^{131}$I-hippurate and strongly reduced the uptake of $^{99m}$Tc-DTPA in the left kidney, while the curves for the right kidney remained unchanged. Six weeks after PTA, notwithstanding the same pretreatment with captopril as before PTA, the uptake and excretion of the radioisotopes by the two kidneys became synchronized, although the left kidney remained smaller.

All individual data of the selected variables from the time-activity curves in the three groups of patients are shown in Figures 2 through 4. The magnitude and the direction of the changes in these variables caused by
Captopril or PTA can be read off the lines that connect the data for each patient.

In the upper part of Figure 2, which shows the relative 131I-hippurate uptake in the second minute of the affected kidney as a percentage of the total uptake, the percentages before PTA and without captopril show a wide variation from our normal value of 45 to 55% in all three patient groups. In the first group (renal artery stenosis, cured + improved), 13 patients had an uptake in the affected kidney of less than 50% of total while the two other patients had small contralateral kidneys but an intact renal artery. Half of the patients with normal arteries also showed an abnormal asymmetrical hippurate uptake (the kidney with the lowest uptake less than 45% of total uptake). As explained in the Methods, these patients were frequently selected because they showed an asymmetrical hippurate uptake. In all three patient groups captopril changed neither the contribution of the affected kidneys in relation to the total uptake nor the single kidney uptake capacity in relation to the dose injected, not even in the affected kidneys of the group with functional renal artery stenosis. After PTA, notwithstanding the same captopril pretreatment, the affected kidneys of all but one patient...
with a functional artery stenosis showed an increase of their relative hippurate uptake to a percentage above the pre-PTA value with and without captopril. This pattern was not seen in four patients with nonfunctioning renal artery stenosis; their relative hippurate uptake in the affected kidney did not change after PTA.

During a later phase of the renographic curves captopril only changed the variables representing the handling of hippurate in the functional renal artery stenosis group (see Figure 3). The difference in time to peak, already prolonged 1 minute or more on the affected side in 13 of the 15 patients in the first group, was increased after captopril by at least 1 additional minute, and frequently by much more. Two patients with the longest difference in time to peak in renography without captopril demonstrated an exceptional decrease of this variable after captopril, although their differences in time to peak remained strongly abnormal. The third exception with a modest decrease did have a segmental renal artery stenosis. After PTA, the difference in time to peak decreased to the normal value of less than 1 minute in all patients. The relative activity at 15 minutes increased markedly in seven of the 15 patients in Group 1, whereas no remarkable changes were seen in the two other patient groups.

Figure 4 shows the results of the DTPA uptake in the third minute. Captopril clearly induced a decrease of the DTPA uptake in the affected kidney relative to the total uptake in all patients of the group with functional renal artery stenosis. The single kidney DTPA uptake relative to the dose injected shows that the decrease of the affected to total ratio was caused mainly by a decreased uptake of the affected kidney. Only in two patients was an increase of the DTPA uptake in the affected kidney recorded. However, in these patients the affected/affected + contralateral uptake ratio was decreased by captopril. After PTA, despite captopril pretreatment, the DTPA uptake of the affected kidneys increased, as did the affected/affected + contralateral uptake ratio. No consistent changes were seen in the relative uptake of DTPA in the contralateral kidney. In the two other patient groups, both without renovascular hypertension, the DTPA uptake did not show consistent changes after captopril nor did it change after PTA.

Figures 2 through 4 show that captopril-induced alterations of the DTPA and hippurate renograms in the group of patients with functional renal artery stenosis...
FIGURE 2. $^{131}$I-hippurate renal uptake in hypertensive patients divided into three groups: functioning and nonfunctioning unilateral renal artery stenosis, as determined retrospectively by the result of percutaneous transluminal angioplasty (PTA) on the blood pressure, and a third group with normal renal arteries. In each group values are shown before (pre) and after (post) treatment with captopril. In patients who had PTA, an additional post-PTA value, also with captopril pretreatment, is shown. The lines connect individual values. The upper plate represents the uptake of hippurate in the affected kidney in relation to the total renal uptake (normal values, 50 ± 5%; in the patients with normal renal arteries the kidney with the lowest uptake is used as the numerator). The lower plates show the uptake of the kidney as a fraction of the dose injected (arbitrary units). No consistent captopril-induced changes could be detected.

generally were not seen in the group of patients without functional renal artery stenosis. To determine the sensitivity and specificity of these captopril-induced changes the following analysis of the data was done. First, three variables were selected that showed the captopril-induced changes: 1) the DTPA uptake, affected/affected + contralateral; 2) the difference in time to peak between the affected and the contralateral kidney in the hippurate curves; and 3) the relative activity at 15 minutes of the hippurate curve. Second, limits were imposed on each of these three groups of data to obtain reasonable differentiation between the group of 15 patients with and the group of 19 patients without renovascular hypertension. The following limits were selected to decide whether there was a captopril-induced change: 1) a decrease of the DTPA uptake of 4% or more; 2) an increase by 1 minute or longer in the difference in time to peak on the hippurate curve; 3) an increase on the hippurate curve of 1.0 or more of the relative activity at 15 minutes.

The percentage of positive or negative results in the two patient groups with or without renovascular hypertension respectively is shown in Table 2 under the heading "captopril-induced change." Table 2 also presents the percentage of positive or negative results of the renograms with and without captopril pretreatment. For this analysis the following criteria were used for a positive test result: DTPA uptake affected/total, less than 45%; difference in time to peak of the hippurate curve, 1 minute or longer; and a hippurate relative activity at 15 minutes of the affected/contralateral kidneys of 2.0 or more.

Table 2 shows that captopril did increase the sensitivity of some criteria (DTPA uptake from 64 to 80%, difference in time to peak from 87 to 93%) but did not improve the specificity, which is rather low for all criteria. This low specificity could not be improved by combining criteria. The results are better when captopril-induced change is considered, which yields an acceptable percentage sensitivity and specificity of the DTPA uptake (86 and 89%) and of the difference in time to peak of the hippurate curve (87 and 89). A
lower sensitivity but a higher specificity was obtained by combination testing: the captopril-induced changes in the renographic studies are called positive when at least two of the three criteria are positive. This lowers the sensitivity to 80% but increases specificity to 100%. The sensitivity of 80% is caused by three of the 15 patients with a functional renal artery stenosis who did not have at least two positive criteria. The first had a stenosis in one of two segmental renal arteries, supplying blood to the dorsal half of the kidney. Eventual renographic alterations in that part were overshadowed by the central part with a normal blood supply. The second patient had a small kidney with a strongly abnormal initial renogram in which no further deterioration could be detected after captopril. The third patient had only one of the three positive criteria: after captopril a decrease of the relative DTPA uptake from 34 to 26% (−8%) but no increase of asymmetry in the excretion phase of hippurate. This result appeared to be due to a slow excretion of the normal contralateral kidney caused by low diuresis during that investigation. Operating characteristics of captopril renography using this combination of criteria are shown in Figure 5.

Discussion

Our data show that captopril-induced renal insufficiency, as reported in patients with a single kidney with artery stenosis or with bilateral renal artery steno-

<table>
<thead>
<tr>
<th>Treatment</th>
<th>$^{99m}$Tc-DTPA (affected/total)</th>
<th>Difference in time to peak</th>
<th>Ratio at 15 minutes</th>
<th>Two of three criteria positive*</th>
</tr>
</thead>
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<tr>
<td>Control (%)</td>
<td>64</td>
<td>87</td>
<td>73</td>
<td>80</td>
</tr>
<tr>
<td>Captopril, 25 mg (%)</td>
<td>80</td>
<td>93</td>
<td>73</td>
<td>87</td>
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<tr>
<td>Captopril-induced change (%)</td>
<td>86</td>
<td>87</td>
<td>47</td>
<td>80</td>
</tr>
<tr>
<td>Control (%)</td>
<td>50</td>
<td>74</td>
<td>84</td>
<td>68</td>
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<tr>
<td>Captopril, 25 mg (%)</td>
<td>47</td>
<td>79</td>
<td>79</td>
<td>74</td>
</tr>
<tr>
<td>Captopril-induced change (%)</td>
<td>89</td>
<td>89</td>
<td>100</td>
<td>100</td>
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</tbody>
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DTPA = diethylenetriamine pentaacetic acid.
*See text for criteria used to decide whether a test is positive or negative.
†Percentage positive in 15 patients with renovascular hypertension = sensitivity.
†Percentage negative in 19 patients without renovascular hypertension = specificity.
sis, also occurs in the affected kidney of patients with unilateral renal artery stenosis. This unilateral renal insufficiency has not yet been revealed because renal function tests, such as serum urea or creatinine concentration, and diuresis are well maintained by the intact contralateral kidney, which is untouched by the effects of captopril. In an overview of captopril therapy in 269 patients with renovascular hypertension, Hollenberg, using blood urea nitrogen and diuresis as criteria, found rapidly progressive renal insufficiency only in patients with bilateral renal artery stenosis or a single kidney. However, with split renal function studies using radioactive labeled compounds, it would be possible to unmask this unilateral deterioration of renal function. Thus, we chose the combination of the renographic time-activity curves of $^{99m}$Tc-DTPA and $^{131}$I-hippurate because they measure different renal functions. The uptake of DTPA is an estimate of GFR, while the uptake of hippurate parallels the effective renal plasma flow. The excretion phase of both isotope curves represents the diuresis.

Our observations that the uptake of DTPA was decreased while hippurate uptake was not affected and hippuric acid excretion was delayed are compatible with a decrease of the GFR and diuresis with unchanged renal plasma flow. These findings confirm previous reports that captopril’s main effect in a kidney with a stenosed renal artery is a decrease of the GFR while the renal perfusion is maintained. Wenting et al., using renal artery and vein catheterization in patients with renal artery stenosis, found a reduction in the extraction ratio of $^{131}$Iodothalamate in the affected kidney after administration of captopril, reflecting a lower filtration fraction. Fommei et al. recently reported a patient with unilateral renal artery stenosis in whom captopril induced a marked reduction of $^{99m}$Tc-DTPA accumulation in the affected kidney, together with an unchanged uptake of $^{99m}$Tc-albumin microspheres, suggesting a decreased GFR while the blood flow remained unaffected.

The results of these radioisotope studies fit the hypothesis that captopril induces a dilatation of the postglomerular arterioles. This, in combination with the very low pressure in the renal artery, causes a fall in filtration pressure and, hence, in GFR, whereas the effective renal plasma flow remains constant. In dogs it has been shown that circulating as well as intrarenally formed angiotensin II has an important role in the autoregulation of the GFR. In these experiments, reduction of the blood pressure during CEI decreased GFR while the renal blood flow remained well above control values.

The decrease of GFR after CEI is not a specific effect of a further decrease of the already low blood pressure distal of the artery stenosis. In humans as well as in dogs with all kidney tissue situated distal to an artery stenosis, an equivalent decrease of the blood pressure by other antihypertensive medication did not (whereas CEI did) cause renal failure. Although the low pressure certainly plays a role, these observations give additional evidence of a specific action of CEI on GFR.

More important than the theoretical interest is the fact that our findings show that gamma camera renography before and after CEI can be used to detect deterioration of renal function in a kidney with artery stenosis in the presence of an unaffected contralateral kidney. The results of the present study confirm suggestions in a previous report of our group with a smaller number of patients that unilateral change in a renogram after captopril premedication can be used as a test for true renovascular hypertension. The test reveals an unilateral dependency of the GFR on its autoregulation by angiotensin II, due to a low perfusion pressure and an increased angiotensin II concentration, a prerequisite for a renin-dependent Goldblatt-like hypertension. Although the salt state of the patients may modify this dependency of the GFR on angiotensin II, it does not play a major role in a kidney with a functioning renal artery stenosis. As shown in Table 1, seven of the 15 patients with renovascular hypertension (and a positive test) did not receive pretreatment with a diuretic.

In the present study a positive test (unilateral changes in the renograms after captopril) was seen in 12 of the 15 patients with renovascular hypertension, as judged by the decline of their blood pressure after PTA. On the other hand, a negative test (no unilateral changes after captopril) was obtained not only in the 13 patients with normal renal arteries but also in all six patients with anatomical renal artery stenosis, which apparently was not causing the hypertension as the blood pressure remained elevated after adequate PTA. This testing procedure yielded a specificity of 100%. To obtain these results, limits were set and prerequisites chosen to decide when a test was positive or negative. In general, the sensitivity of a diagnostic test can be increased by lowering the criteria set for a positive test, but this will automatically decrease the specificity, and more false-positive tests are obtained. The reverse is also true: higher limits will decrease sensitivity but increase specificity and will number of false-negative results. The ultimate choice of criteria is therefore dependent on the goal for which the test is used, which in our case was the exclusion of renovascular hypertension in a small group with a high probability of disease. Increasing the number of patients tested in a prospective study using the same criteria would help to define the sensitivity and specificity more precisely.

Arteriography is generally considered to be the standard method for verifying renal artery stenosis. It has an additional advantage in that PTA can be performed immediately when a stenosis is found. However, most patients remain hypertensive after PTA. Thus, the physician frequently must decide to what extent these patients should be reinvestigated to establish whether they still have a renovascular component in their hypertension because of insufficient dilatation or recurrence of the stenosis. Whenever a pre-PTA abnormal captopril renogram becomes normal after PTA, the renovascular component has been removed and a residual hypertension can be treated with antihypertensive medication. A converting enzyme inhibitor may be used without risking renal function. An initial
ly normal captopril renogram predicts a poor effect of PTA on blood pressure. Knowing this beforehand can prevent disappointment and troublesome repetition of arteriography.

References


Renovascular hypertension identified by captopril-induced changes in the renogram.
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