Stenosis and Renographic Characteristics in Renovascular Disease

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This study was designed to determine the degree of renal artery stenosis (RAS) which produces changes in renographic parameters. **Methods:** The angiographic severity of luminal narrowing in RAS was compared to ^{131}I-hippuran renographic characteristics in 72 patients who had been selected for renal angiography because of suspected renovascular hypertension. **Results:** Significant differences in T_{max}, $T\frac{1}{2}$ and counts under the curve to T_{max} were apparent at 30% of arterial luminal narrowing when stenotic and nonstenotic kidneys were compared. In patients with unilateral RAS, the difference in counts under the T_{max} curve between pairs of kidneys was also significantly different at 30% of stenosis. Patients with bilateral stenosis, on the other hand, could not be differentiated well from patients with essential hypertension because the T_{max} value on either side or the difference of T_{max} between the two kidneys and the values of the other parameters were similar, except for the difference in counts to T_{max}. Based on these findings it seems that bilateral RAS does not "mimic" unilateral stenosis in renographic terms, but rather, resembles a normal situation. **Conclusion:** Significant renographic changes can occur at 30% of arterial luminal narrowing in renal artery disease.

Key Words: renal artery stenosis; renography; minimal degree

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Renovascular hypertension is a retrospective diagnosis that can be made with certainty only when correction of the stenosis leads to blood pressure normalization or improvement. In the work-up of patients suspected of having renovascular hypertension, renography screening is often performed. Accordingly, changes in certain renographic parameters are used to predict the presence of renal artery stenosis (RAS). In a meta-analysis, however, Havey (1) found the sensitivity and specificity of ^{131}I-hippuran renography screening (without ACE-inhibition) to be only around 75%. This disappointing result may stem from our inability to establish reliably whether a certain degree of stenosis is important hemodynamically.

There is no consensus about what percentage of renal arterial narrowing should be considered hemodynamically significant in the literature. Although some authors argue that only stenoses of 75% or more are significant (2–4), others favor a percentage of more than 50% (5,6). There are even reports indicating that correction of a stenosis with a luminal narrowing of less than 50% may cure renovascular hypertension (7).

Iodine-123-hippuran renography studies in animals reveal that even a slight degree of stenosis (25% reduction in renal blood flow) causes changes in renographic parameters (8). Moreover, in hypertensive humans, a renal perfusion pressure diminution of 10%–30% activates the renin-angiotensin system (9). In the present study, we sought to determine the smallest degree of RAS that may cause changes in renographic parameters. To do so, we analyzed the data of 72 patients for whom

an angiogram was available and compared the renographic and angiographic characteristics.

MATERIALS AND METHODS

Patients

Seventy-five patients who had been referred to the hypertension clinic for evaluation were included in the study. All had a diastolic blood pressure above 100 mm Hg on at least three occasions and had been selected for renal angiography because a renovascular hypertension was suspected either on clinical grounds, such as those formulated by the Working Group on Renovascular Hypertension (10), or based on ^{131}I-hippuran renography. All patients underwent angiography via the femoral approach. They were given 40 ml of contrast material for the aortic films and, if necessary, an additional 10 ml for the selective ones. Abdominal aortic and renal angiograms were taken in the anterior-posterior projection. When deemed necessary, oblique projections were performed to better visualize stenoses or vasculature parts obscured by organ superposition (7). Prior to angiographic evaluation, patients had undergone renography with 9.3 MBq ^{131}I-hippuran according to accepted standard procedures. Images were obtained using a gamma camera with the patient in recumbent position. The appropriate region of interest was chosen over both kidneys using a small tracer amount. Immediately after intravenous administration of ^{131}I-hippuran counts were recorded every 20 sec over a 20-min period and computed (11). Before renography, all patients were given 300 ml of fluids to guarantee urine output of at least 1 ml/min during the investigations. Renal angiograms were assessed together with the ^{131}I-hippuran renograms. Renographic data of patients whose kidneys had less than 10% tracer uptake (less than the blood background activity) were excluded from analysis. This occurred in three patients who had otherwise showed normal renal blood supply on their angiogram.

Evaluation of Angiograms

Two radiologists evaluated the angiograms and determined the percentage of renal artery narrowing. On the films the pre- and poststenotic renal arterial lumen diameters were measured in millimeters by marking the luminal contours seen with a magnifying glass. Stenosis percentage was measured at the narrowest point by calculating the ratio of normal minus stenotic lumen to normal lumen diameter.

Evaluation of Iodine-131-Hippuran Renography

The following renographic parameters were used to analyze the renogram (Fig. 1).

1. Perfusion phase (PP) and secretion phase (SP) angles. The tangents of the respective angles were calculated as a quantitative parameter for the steepness of the initial upstroke (perfusion phase) and that of the second part of this curve (inclination of the initial curve towards the early part of the secretion phase, which is just before the maximum count rate).
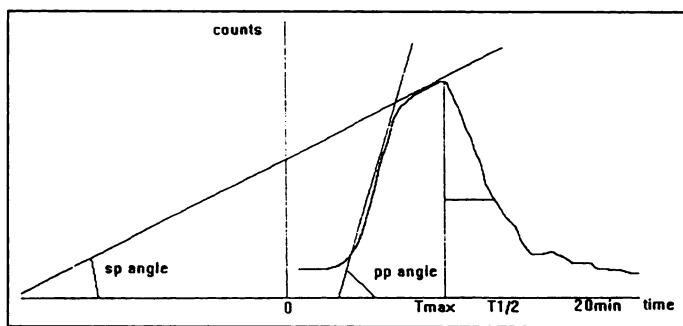
FIGURE 1. Parameters used in renogram analysis.

2. Fractional uptake of tracer by each kidney calculated from total renal counts during the first 1–3 min of recording.
3. Time to maximum count rate (T_{max}), defined as time from injection to time of maximum count rate for each of the two kidneys.
4. Half time ($T_{1/2}$), was defined as the time from maximum activity above the kidney to time of half maximal count rate.
5. T_{max} and total counts were measured as the area under the curve to T_{max} (CT_{max}) or during the 20-min of recording (CT_{20}).
6. Differences in T_{max}, $T_{1/2}$, CT_{max} and CT_{20} between the two kidneys, were calculated as follows: for normal kidneys, right kidney value minus left kidney value; for unilateral RAS, for the value of T_{max} and $T_{1/2}$ the affected side minus the value of the contralateral side, and the opposite for CT_{max} and CT_{20}; for bilateral RAS, the same as for unilateral RAS, with the side with greater stenosis considered the affected one.
7. Ratio for CT_{max} and CT_{20} ratios was defined as CT_{max} or CT_{20} right kidney/left kidney as follows: for unilateral RAS, affected side/contralateral side; for bilateral RAS, the same as for unilateral RAS, with the side with greater stenosis considered the affected one.

Analysis of Renographic and Angiographic Parameters of Stenosis

Since the aim of our study was to evaluate, taking the angiogram as starting point, what percentage of RAS renogram alterations would occur at, we did not include the visual interpretation of scintigraphic curves and sequential renographic images by nuclear medicine physicians in our analysis. Rather, the renographic parameters were analyzed and compared to the degree of stenosis found on the renal angiogram. This was done for three different arterial luminal narrowing (ALN) cutoff points; i.e., at an ALN greater than either 20%, 30% or 50%, respectively. Each cutoff point represents an ALN degree below which stenosis is considered absent. For instance, an ALN of 38% is considered to be stenotic in the analysis with cutoff points of 20% and 30% but nonstenotic with a cutoff point of 50%. We refrained from analyzing the data at cutoff points greater than 50%, because this would leave too few patients for a meaningful evaluation. According to the various cutoff points for each analysis, kidneys and their corresponding renographic parameters were categorized into three groups: no stenosis, unilateral stenosis and bilateral stenosis.

Statistical Analysis

The age difference between patients with or without renal artery disease was compared with the two-way t-test. The various renographic parameters at the different ALN cutoff points were compared with a Mann-Whitney U-test or a Kruskal-Wallis test. To determine at what ALN degree significant renographic changes occurred, discriminant analysis was performed, with the ALN degree taken as the independent variable and the different reno-

TABLE 1
Patient Characteristics (Median and Ranges)

	Essential hypertension (n = 45)	Renal artery stenosis (n = 27)
M/F	26/19	14/13
Age (yr)	42 (28–69)	47 (22–73)
Body surface area (m²)	1.8	1.8
Systolic BP	184 (140–220)	185 (140–290)
Diastolic BP	114 (84–140)	111 (80–130)
Creatinine clearance (ml/min)	105 (73–141)	83 (26–140)*

*Significantly different from essential hypertension (p < 0.05).
BP = blood pressure.

graphic parameters as dependent variables. Significance was determined with the Wilks' lambda test. Results are expressed as medians and ranges. A p value < 0.05 was considered statistically significant.

RESULTS

Patient Characteristics

Of the 75 patients included in the study, three were excluded because the fractional tracer uptake in one of their kidneys was less than 10%. Forty-five patients with no renal artery disease were considered to have essential hypertension (EH), as other causes of hypertension had already been excluded, and their kidneys were classified as normal. The final angiographic diagnoses of the 27 patients who had RAS was unilateral RAS ranging from 14%–99% in 18 patients and bilateral RAS with a luminal narrowing ranging from 17%–90% in 9.

Of the 36 stenosed arteries, 31 were found to be due to atherosclerosis and the others to fibromuscular dysplasia. In cases of bilateral disease, all but one was due to atherosclerosis.

The clinical characteristics of patients with EH and RAS are given in Table 1. Ages ranged from 22 to 73 yr. The median age of renal artery disease patients did not differ from that of EH patients. Systolic and diastolic blood pressures were similar in both groups. RAS was associated with a lower creatinine clearance (p < 0.05), which correlated inversely with ALN percentage (r = −0.43, p < 0.05).

The number of patients with no stenosis, unilateral stenosis or bilateral stenosis at the different ALN cutoff points is shown in Table 2.

Renogram Analysis

PP and SP Angles. For patients with EH (normal kidneys), PP and SP angles ranged from 70°–89° and 35°–84°, respectively. The median PP angle was 82° for both the left and right kidneys, with an average difference between the two kidneys of less than one degree. The median SP angle values were 69° on the left side and 68° on the right, with a median difference of less than two degrees between the two kidneys.

TABLE 2
Number of Patients with no Stenosis, Unilateral Stenosis or Bilateral Stenosis at Different ALN Cutoff Points

ALN Cutoff point (%)	No stenosis	Unilateral stenosis	Bilateral stenosis	Total
20	49	16	7	72
30	52	16	4	72
50	58	11	3	72

TABLE 3
Median Values and Ranges for T_{max} and $T_{1/2}$ (sec) at Different ALN Cutoff Points

ALN cutoff point (%)	Nonstenotic kidneys		Stenotic kidneys		Contralateral kidneys	
	T_{max}	$T_{1/2}$	T_{max}	$T_{1/2}$	T_{max}	$T_{1/2}$
20	204	279	222*	474	195	366
	72–1074	6–1038	72–1038	72–1128	72–822	60–960
30	204	273	237*	474*	180†	402
	72–1074	6–1038	72–1038	72–1128	72–822	60–960
50	210	282	222*	603*	159	300
	72–1074	6–1038	72–1038	72–1128	72–342	60–960

*$p < 0.05$ as compared to nonstenotic kidneys.
†$p < 0.05$ as compared to stenotic kidneys.

For patients with RAS, the PP and SP angles ranged from 50°–89° and from 28°–87°, respectively. At the different ALN cutoff points (20%, 30%, 50%), the median PP angles of stenotic kidneys were 82°, 83° and 82°, while the median values for SP angles, were 63°, 64° and 67°.

There were no significant differences between normal and stenotic kidneys with respect to their PP or SP angles. Moreover, PP and SP angles were not related to the degree of stenosis.

Fractional Uptake of Tracer by Each Individual Kidney

Fractional tracer uptake by normal kidneys (EH patients), expressed as a percentage of total renal uptake, ranged from 33%–67%. When patients with abnormal creatinine clearance were excluded from analysis (i.e., below 100 ml/min, normalized for 1.73 m^2 body surface area), the fractional uptake ranged from 43% to 58% (median 50%), with no significant difference between left and right kidney values.

In patients with RAS, the fractional uptake ranged from 13% to 87% (median in unilateral RAS 48%, in bilateral RAS 50%). A significant uptake difference was found at an ALN cutoff point of 50% between the various groups of kidneys: 50% (range 33%–87%) for nonstenotic kidneys, 44% (range 14%–65%) for stenotic kidneys and 53% (range 13%–80%) for kidneys contralateral to a stenotic one. Compared to normal kidneys (either normal or contralateral), fractional uptake was significantly reduced in stenotic kidneys ($p < 0.01$). It should be stressed, however, that there were several kidneys with normal fractional uptake.

Time Intervals

T_{max}. In EH patients, no statistical difference was found in T_{max} values between the left and the right kidney (medians 192 and 216 sec; range: left side 90–528 sec, right side 72–480 sec). In RAS patients, median T_{max} of the affected kidneys was 228 sec (median in unilateral RAS 228, range 72–1038 sec; median in bilateral RAS 198 sec, range 72–378 sec) and, on the contralateral side, 210 sec (range 102–1038 sec).

Median values and ranges of T_{max} and $T_{1/2}$ for different ALN cutoff points are presented in Table 3. Significant T_{max} differences were observed at various ALN cutoff points: 20% ($p < 0.05$), 30% ($p < 0.05$) and 50% ($p < 0.05$). When comparing contralateral with stenotic kidneys, T_{max} differences were observed only at 30% ($p < 0.05$).

In EH patients, the median T_{max} difference between the two kidneys was 12 sec (range -240–348 sec), which was not significantly different from both RAS patient groups and was true at all ALN cutoff points.

$T_{1/2}$. No statistical difference was found in $T_{1/2}$ values between the left and the right side (medians 272 and 276 sec; range left side 20–498 sec, right side 20–482 sec in all normal kidneys). At a 50% stenosis cutoff point, there was a significant difference in $T_{1/2}$ values between kidney groups: for nonstenotic, versus stenotic and versus contralateral kidneys: 282, 603 and 300 sec, respectively ($p < 0.05$). Comparing the $T_{1/2}$ of nonstenotic kidneys with all stenotic ones, a significant difference occurred at ALN cutoff points of 30% ($p < 0.05$) and 50% ($p < 0.01$) (Table 3).

The median $T_{1/2}$ difference between the two kidneys in EH patients was 48 sec (range 6–708 sec) and 120 sec in RAS patients (range 160–346 sec). Right minus left $T_{1/2}$ differences were similar in the various patient groups at the different ALN cutoff points.

Taking the ALN seen on angiogram as a starting point, the renographic data revealed the following:

1. In unilateral stenosis patients, the absolute T_{max} on the stenotic side indicates RAS better when it is compared to the T_{max} of normal kidneys than when compared to that of the same patient's contralateral kidney.
2. In bilateral stenosis patients, the T_{max} value on either side or the T_{max} difference between the two kidneys differs not at all from that in EH patients.

T_{max} and Total Counts

CT_{max}. The median CT_{max} in normal kidneys was 235×10^6 counts (range 61×10^6–952×10^6) and in stenotic ones 153×10^6 (range 41×10^6–1877×10^6). The median in unilateral RAS was 164×10^6 and in bilateral RAS 135×10^6.

At an ALN cutoff point of 50%, a significant difference was found between kidney groups: nonstenotic, stenotic and contralateral kidney groups: 236×10^6 versus 130×10^6 versus 211×10^6, respectively ($p < 0.05$). When comparing the CT_{max} of nonstenotic kidneys with all stenotic ones, a significant difference was found at an ALN cutoff point of 30% (234×10^6 versus 143×10^6, $p < 0.05$), and the difference was even more apparent at an ALN cutoff point of 50% ($p < 0.01$).

In EH patients, the median of the CT_{max} difference between both kidneys was -27×10^6 (range -245×10^6–120×10^6). In RAS patients this was 6×10^6 (range -332×10^6–351×10^6; median 4×10^6 in unilateral RAS and 14×10^6 in bilateral RAS). At a 30% ALN cutoff point the difference in CT_{max} between kidney pairs was significantly different between patient groups: in patients with EH, unilateral RAS and bilateral RAS, the differences were -25×10^6, 6×10^6 and 57×10^6, respectively ($p < 0.05$). This difference became more significant at 50% ALN.

CT_{20}. The median of the total counts in normal kidneys was 259×10^6 (range: 59×10^6–1930×10^6) and 235×10^6 in stenotic kidneys (range: 26×10^6–2799×10^6), with a median

of 324×10^6 in unilateral RAS and 201×10^6 in bilateral RAS. There were no significant differences between normal and stenotic kidneys with respect to their CT_{20} or between patient groups at the different ALN cutoff points.

CT_{max} and CT_{20} ratios. For EH patients the median CT_{max} and CT_{20} ratios were 0.96 (range: 0.72–1.46) and 0.90 (range: 0.77–1.49), respectively. In RAS patients, the median CT_{max} and CT_{20} ratios were 1.07 (range: 0.18–3.74) and 1.11 (range: 0.16–4.00), respectively. There were no significant differences between patients with EH and RAS with respect to CT_{max} and CT_{20} ratios at the different ALN cutoff points.

DISCUSSION

In the visual interpretation of renographic studies, the angle and steepness of the first part of the renographic curve are often considered important parameters for RAS diagnosis, particularly after ACE-inhibition ([12]). These two angles, however, have hardly been studied as a quantitative parameter of RAS. Our data demonstrate that these parameters are insensitive in diagnosing uni- or bilateral RAS. Conversely, although fractional uptake of ^{131}I-hippuran varies considerably in EH patients ([13]), it is a sensitive criterion for the diagnosis of RAS ([14,15]), as our study confirms at 50% ALN.

Our analysis of renographic data in relation to the degree of arterial luminal reduction indicates that changes in renographic parameters tend to occur at an ALN of 30%. At this degree of stenosis, significant differences in time intervals (T_{max} and $T_{1/2}$) and total counts under the T_{max} curve (CT_{max}) between nonstenotic and stenotic kidneys were seen. Fractional tracer uptake was significantly different between kidney groups (nonstenotic, stenotic and contralateral) at 50% ALN.

These results suggest that renographic changes occur relatively early in RAS. A prospective study, however, will be necessary to evaluate whether such renographic changes can be used to screen patients for RAS.

T_{max} and $T_{1/2}$ are sensitive renographic parameters, and with CT_{max} and the difference in CT_{max} between the two kidneys, they provide maximum differentiation between EH and RAS patients. Prolonged T_{max} seems to be a highly specific predictor of blood pressure response after interventional therapy ([16]).

CONCLUSION

In our analysis, bilateral stenosis patients could not be differentiated from EH patients well, except for the difference in T_{max} counts. Based on the present findings, we believe that renographically bilateral RAS does not "mimic" unilateral stenosis ([17,18]), but rather, contrary to the literature resembles a normal situation. Our finding that renographic changes occur at 30% of arterial narrowing indicates the need to explore whether early intervention in patients with renovascular disease is necessary.

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