Can Quantitative Renography Predict the Outcome of Treatment of Atherosclerotic Renal Artery Stenosis?

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The accuracy of quantitative gamma camera renography in predicting outcome of treatment was assessed in 31 patients with atherosclerotic renal artery stenosis. Glomerular filtration rate, renal perfusion, relative renal function, and mean parenchymal transit time were calculated before and after treatment (renal artery angioplasty or vascular surgery). Patients were also assessed during the follow-up period of up to 6 years. On the pre-treatment study, nine patients did not have prolongation of parenchymal transit time in the kidney on the side of the renal artery stenosis. Despite technically successful angioplasties, none of these patients showed a significant reduction in blood pressure or improvement in renal function. Twenty-two patients had prolongation of parenchymal transit time in the affected kidney. Three suffered complications of treatment, and the remaining 19 showed improvement in blood pressure control, reduction in parenchymal transit time, and improvement in relative renal function. Quantitative renography accurately predicted those patients who improved following intervention for atherosclerotic renal artery stenosis. On progress evaluation, patients with recurrent stenoses were easily identified.

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Percutaneous transluminal angioplasty of renal artery stenosis (RAS) has been available for the past ten years as treatment for renovascular hypertension (*1*). Patients with fibromuscular lesions have a high response rate to such treatment (*2,3*) while notes of caution have appeared in the literature concerning the effectiveness of this procedure in atherosclerotic renal artery stenosis. There is a small percentage of clinically successful results especially in patients with generalized atherosclerosis, reduced renal function, and ostial lesions (*3,4*). These patients also have a higher rate of technical failure and complications (*5,6*). Careful patient selection is therefore important prior to angioplasty to assess the functional nature of the atherosclerotic RAS.

Conventional or digital subtraction angiography provides anatomic information, but is unable to determine whether a stenosis is clinically significant. It has been shown by postmortem (*7*) and angiographic studies (*8*) that renal artery stenosis may be present in normotensive as well as in hypertensive patients. The most common method of evaluating functional significance is to determine the ratio of renin concentration in the venous blood from the "affected" and contralateral kidneys (*9, 10*). This test is invasive and difficult to standardise, but rarely causes morbidity. In some hands, renal vein renin concentrations are good predictors (*11*), but others have shown both false-positive and false-negative results (*12*). This discrepancy probably relates to differences in the sampling procedures.

In the past, nuclear renography was shown to have limited sensitivity and specificity but was used both in a case finding role in severe hypertension and to predict response following surgery of RAS (*13–15*). These studies utilized the instrumentation, radiopharmaceuticals and computer techniques of the 1960s and 1970s.

More recently, the development of quantitative gamma camera renography with measurement of parenchymal transit time (PTT) has greatly increased the specificity of this test for renovascular hypertension (*16, 17*).

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It has been known for over 20 years (*18,19*) that ischemic nephrons could be separated from normal or diseased nephrons by the way the former avidly reabsorbs water and sodium and causes delay in transit of nonreabsorbable substances. Both hippuran and technetium-99m diethylenetriaminepentaacetic acid ([^{99m}Tc]DTPA) are nonreabsorbable solutes and by means of deconvolution analysis, transit time can be measured noninvasively. PTT is also prolonged in patients with obstructive nephropathy (*20*) and acute transplant rejection (*21*) but is not increased in patients with essential hypertension nor patients with a unilateral small kidney due to reflux or previous infection (*16,17,21*).

The purpose of this study was to prospectively assess the value of quantitative renography in predicting outcome of treatment of atherosclerotic RAS and in patient follow-up.

PATIENTS AND METHODS

Over a 6-yr period, 31 hypertensive patients with angiographically demonstrated atherosclerotic renal artery stenosis were investigated by dynamic renal function studies before, and 1 to 2 wk after treatment as well as during the follow-up period. Studies were reported by two experienced nuclear medicine physicians who had no knowledge of the patients' blood pressure control. Treatment consisted of transluminal angioplasty in 27 and bypass vascular surgery in four. Patients with renal artery occlusion and those treated by nephrectomy have been excluded.

There were 16 males and 15 females. Mean patient age was 58 yr ± 10.5 yr (1 s.d.–range 36 to 74 yr). Five patients died during the period of review with causes of death and follow-up interval as follows: (a) bleeding gastric ulcer (postoperative); (b) myocardial infarction (1.6 yr); (c) intracranial hemorrhage (1.6 yr); (d) unknown cause, probably myocardial infarction (2.0 yr); and (e) myocardial infarction (2.2 yr).

Twenty-six patients were alive at the time of review with the follow-up period being a mean of 3.3 yr ± 2.1 yr (1 s.d.) minus the range from 9 mo to 6 yr.

The blood pressure response was classified according to the criteria of the U.S. Cooperative Study of Renovascular Hypertension (*22*).

1. *Cure.* If the supine diastolic blood pressure was <90 mmHg without antihypertensive medication.
2. *Improvement.* If the decrease in diastolic blood pressure was at least 15% but was still >90 mmHg, and <110 mmHg.
3. *No change.* If the diastolic blood pressure decreased by <15% or remained >110 mmHg.

Forty-five normotensive subjects without any history of renal disease, most of whom were potential kidney transplant donors, served as controls for the determination of the normal ranges. In these subjects, mean ± 1 s.d. for GFR was 117.5 ± 18.2 ml/min/1.73 m^2. Right relative renal function was 50.1 ± 3.4%, parenchymal transit time was 2.9 ± 0.5 minutes and the bolus slope ratio was symmetrical between the two kidneys.

Technique

Normal hydration of patients was ensured by not restricting fluid intake, and by giving each patient ~350 ml of fluid at least one-half hour before the study. Existing anti-hypertensive therapy was continued, with the exception of diuretics, which were omitted on the morning of the test. Six patients on Captopril continued with their treatment. In no patient was a Captopril provocation study performed.

The patient was seated in a reclining chair with their back at an angle of ~30° to the vertical. A gamma camera (Siemens LFOV) with a high-resolution collimator was positioned posteriorly to include both kidneys, heart, and, where possible, the bladder in the field of view. Approximately 600 MBq of [^{99m}Tc]DTPA (Australian Radioisotopes) was administered as an i.v. bolus. For the purpose of clearance measurement the net dose administered was accurately measured. Data were collected on-line by a computer (DEC Gamma-11) as 40 × 1-sec followed by 62 × 20-sec frames. Static images were obtained at 2, 5, 10, 15 and 20 min postinjection, pre- and postvoiding, as well as right and left lateral images to assess kidney size and depth. The images, together with a computer playback of all data frames sequentially in a movie format, were viewed by at least two observers to obtain a qualitative impression of the entire study, particularly to assess patient movement.

On the computer images, regions of interest (ROI) were drawn around each kidney, heart, aorta (at a level midway between the kidneys) background, both above and below kidneys, and parenchymal regions of each kidney (Fig. 1). From these regions, activity time curves were produced and the following parameters quantitated: (a) bolus slope ratio, (b) relative renal function, (c) parenchymal tracer transit time (PTT). Total renal function was also measured.

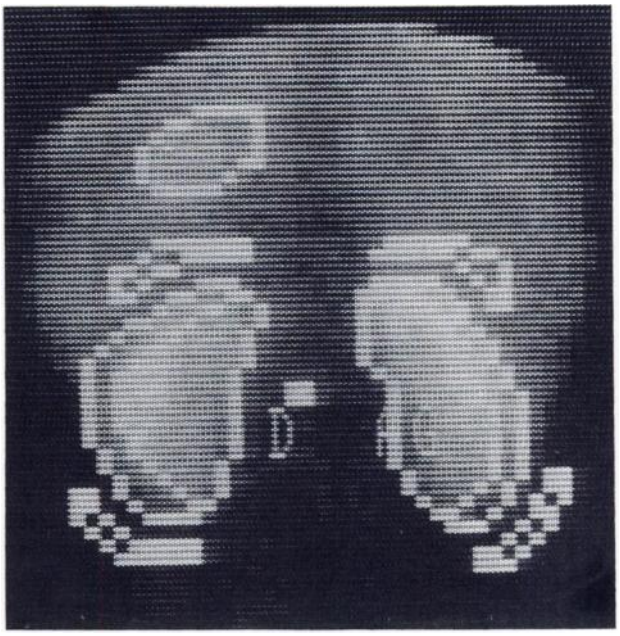

FIGURE 1
Regions of interest used in the analysis.

Bolus slope ratio. The quality of perfusion was measured using a bolus slope ratio (BSR) (*15*). The maximal slope on the rising part of the renal and aorta activity-time curves was calculated. The BSR is defined as the ratio of kidney to aortic slopes. In our experience the precision of this measurement depends on the rapidity of the bolus injection, cardiac output, and the position of the aortic region of interest relative to the kidney. Bolus slope ratios were therefore only used to compare perfusion between right and left kidneys.

Relative renal function. The amount of activity in each kidney before any of the [^{99m}Tc]DTPA has passed into the collecting system is proportional to that kidney's glomerular filtration rate. Following background subtraction and correction for the different depths of the kidneys in the body, the percentage contribution of each kidney to the total uptake was calculated. Renal depth was measured using lead markers on the skin surface during a lateral view. Depth correction of differential function was calculated assuming a uniform attenuation of 0.15 cm^{-1}.

Deconvolution analysis. Deconvolution of renal time-activity curves has been described by a number of authors (*23–25*). This method of analysis simulates the effect of a bolus injection directly into the renal artery and allows calculation of tracer transit time through the kidney. The resulting curve (Fig. 2) is known as the retention function or impulse response function.

Deconvolution was performed using the matrix method which is simple and accurate (*25*), although known to be susceptible to noise (*26*). Noise reduction in the form of a 1:2:1 linear smooth was applied three times to the raw data. The input function for deconvolution was the cardiac time-activity curve. Points in the cardiac curve prior to the peak (i.e., the upslope) were set equal to the peak value, after smoothing had been applied. Renal data was corrected for background activity.

The first point of the retention function was calculated as the ratio of the first point of the renal curve and the first point of the cardiac curve (Diffey BL: personal communication). The end of the retention function was taken as the first zero-crossing point. Although there may be oscillation of the retention function due to the sensitivity of the matrix method to noise in the data, oscillation only becomes a problem in cases of poor renal function, where transit times are quite prolonged.

The total mean transit time is calculated as the area under the retention function from time zero, divided by the plateau value. The mean of the distribution of transit times is calculated similarly, but only from the end of the plateau.

The plateau on the retention function is indicative of the minimum residence time of tracer in the kidney. The end point of the plateau is determined as either the point of inflection in the retention function after the initial fall (Fig. 3A), or (more often) the small peak which may occur due to uptake in the parenchyma (Fig. 3B). From the end of the plateau, renal activity falls as more of the "bolus" is excreted. This minimum transit time is however dependent on the state of hydration of the patient, and will be prolonged if the patient is not well hydrated. A total mean transit time is calculated from time zero to the time when the retention function reaches zero. It is thus quite important in the calculation of mean transit time that all patients are adequately hydrated—dehydration will give prolonged mean transit time.

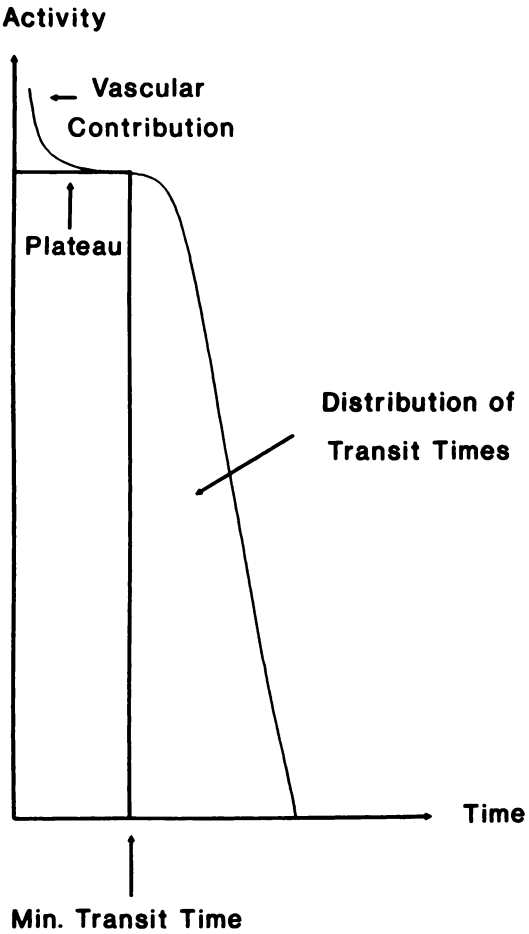

FIGURE 2
Schematic representation of the retention function, or impulse response function.

Retention functions were produced for the whole kidney and the parenchymal regions separately (*27*). It is only the latter which is discussed here as we are concerned with nephron function and wish to exclude any prolongation in transit time due to holdup in the collecting system and renal pelvis. The parenchymal regions were carefully drawn to exclude any areas of pelvicalyceal holdup (verified by checking the later frames of the study) and were ~2 pixels wide, around the lateral aspect of the kidney. Functional imaging in the form of a mean transit time image, was used in most patients to delineate the parenchymal region (*27*).

As a check on deconvolution, the retention functions were reconvolved with the blood time-activity curve to produce a "background subtracted" renogram which was compared with the original data. The study was rejected if the reconvolved renogram was not qualitatively the same as the original data. This however only reveals *failure* of the deconvolution, and not *inaccuracies*. Again, there is only a problem in cases of poor renal function.

Total renal function ([^{99m}Tc]DTPA clearance). The dose of [^{99m}Tc]DTPA administered was measured accurately by a dose calibrator. The net activity injected was determined by assay-

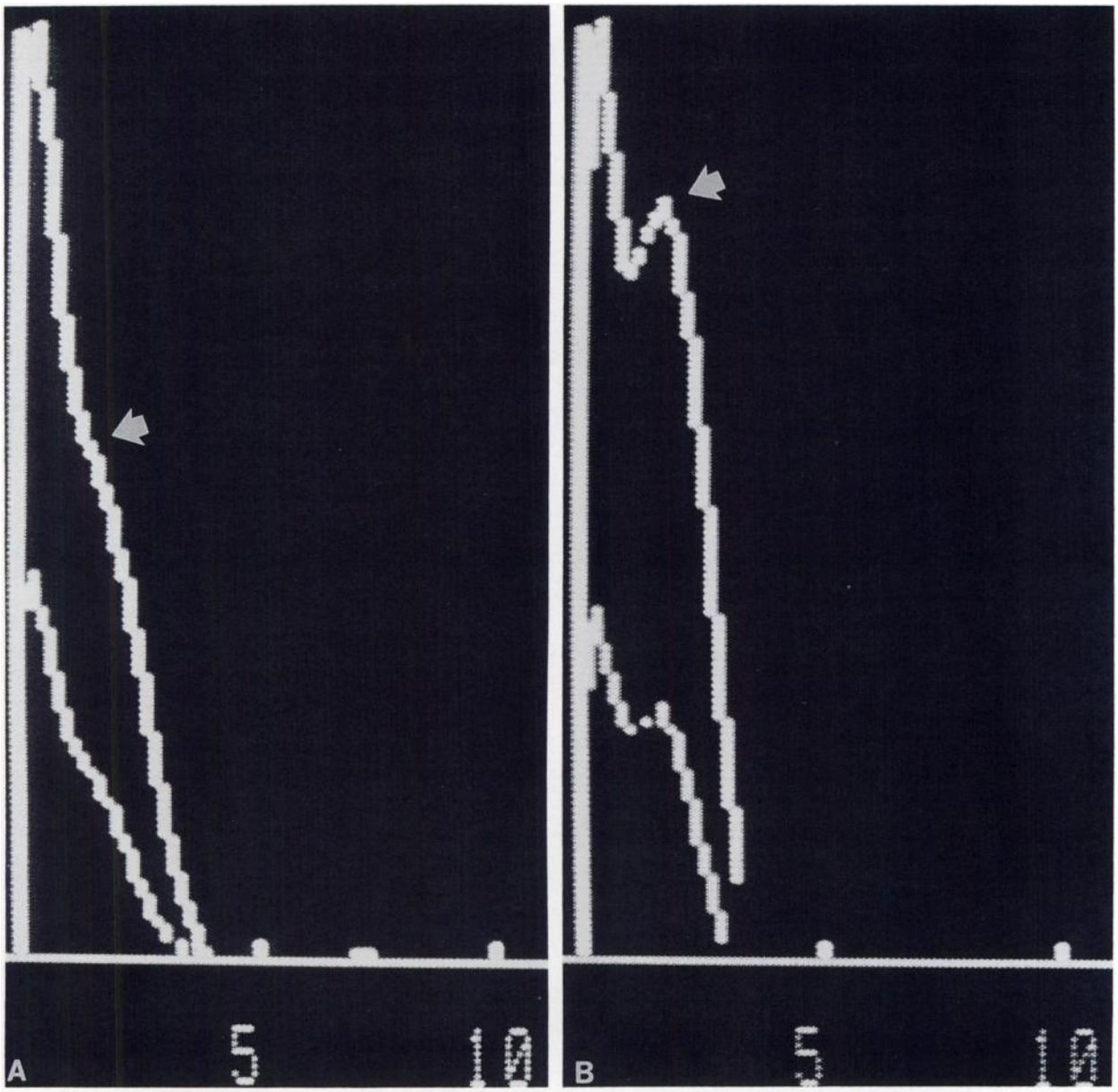

FIGURE 3
Impulse response function before determination of plateau–from (A) point of inflection or (B) peak in IRF.

ing the amount of radioisotope in the syringe before and after injection. The injection site was imaged to check for possible extravasation. The patient then returned at 2 and 3 hr after injection for accurately timed blood sampling to determine plasma clearance (*28*). Technetium-99m DTPA clearance has been shown by inulin and [^{51}Cr]EDTA clearance to correlate well with glomerular filtration rate (*30*).

Statistical analysis. Student's paired t-test was used to assess the statistical significance of all results.

RESULTS

Results outside the 2 s.d. range were considered abnormal, i.e., a GFR below 80 ml/min/1.73 m^2, relative renal function <43% and parenchymal transit time >4.0 min.

All patients had reduced perfusion and function of the kidney on the side of the renal artery stenosis. In patients with bilateral stenoses, results are given for the kidney which had the greater reduction in perfusion and function (Table 1). Patients 1 to 9 did not have prolongation of parenchymal transit time in the affected kidney. Despite technically successful dilatations, none of these patients showed a reduction in blood pressure (Fig. 4). There was no significant change in PTT or percentage function in the affected kidney after treatment (Figs. 5 and 6). Three remained with stable total renal function while six showed a reduction in GFR following the procedure.

On the pre-treatment study, 22 patients had prolongation of parenchymal transit time in the affected kid-

TABLE 1
Results Before and After Treatment of Atherosclerotic Renal Artery Stenosis

			Pre-treatment					Post-treatment			
Patient no.	Age (yr)	Sex	GFR	Side of stenosis % funct	PTT	Angio RAS	Rx	GFR	Side of stenosis % funct	PTT	BP Change
1	70	M	75	40	3.6	Bilat Lt > Rt	A	69	37	3.5	NC
2	57	M	88	28	3.5	Lt	A	86	30	2.9	NC
3	42	M	116	45	2.6	Rt	A	113	45	2.5	NC
4	54	F	9	68	2.7	Bilat Lt > Rt	A	Dialysis			NC
5	54	F	40	Single	2.8	Rt	A	32	Single	3.5	NC
6	50	M	91	45	3.1	Lt	A	65	42	4.1	NC
7	66	F	74	44	3.4	Lt	A	52	45	3.5	NC
8	60	F	68	40	3.9	Rt	A	44	40	3.9	NC
9	64	M	47	44	3.8	Rt	A	26	47	2.9	NC
10	61	F	44	42	9.0	Bilat Lt > Rt	A	Failed Angioplasty			NC
11	72	M	24	18	7.4	Bilat Rt > LT	A	Infarcted Upper Pole			NC
12	46	M	30	36	5.3	Lt	S	Died postop Bleeding Ulcer			NC
13	53	M	48	17	5.7	Lt	A	40	20	2.1	I
14	40	F	25	27	4.3	Bilat Rt > Lt	A	22	45	3.2	I
15	60	M	50	22	*	Rt	A	48	32	4.3	I
16	44	F	77	34	5.0	Rt	A	67	35	3.2	I
17	74	F	53	26	5.5	Bilat Lt > Rt	A	55	29	3.6	I
18	67	M	28	20	8.2	Rt	A	38	42	3.2	I
19	64	M	69	21	5.1	Lt	A	81	30	3.1	I
20	71	M	68	15	7.1	Lt	A	78	25	3.7	I
21	68	M	60	33	5.2	Lt	A	76	40	4.2†	I
22	62	F	84	30	9.3	Rt	A	79	35	3.6	I
23	63	F	23	30	*	Bilat Rt > Lt	S	43	45	4.3†	I
24	43	F	86	20	5.3	Lt	A	106	30	3.4	I
25	72	F	39	20	6.0	Bilat Rt > Lt	S	66	37	5.3†	I
26	65	M	65	25	8.9	Bilat Lt > Rt	S	75	30	4.0	I
27	65	M	35	20	5.2	Bilat Lt > Rt	A	40	30	3.9	I
28	47	F	25	10	*	Lt	A	29	35	2.7	I
29	54	M	56	20	8.7	Lt	A	69	40	2.8	C
30	64	F	57	10	8.6	Lt	A	72	30	5.3†	C
31	36	F	74	30	5.2	Bilat Rt > Lt	A	71	35	2.6	C

* PTT too prolonged to be accurately measured. (Considered 10 min in calculation.)

† PTT Normal on progress study.

PTT = mean parenchymal transit time (minutes); A = angioplasty; S = surgery; NC = no change; I = improved; C = cured; Rx = treatment; BP = blood pressure; GFR = glomerular filtration rate in ml/min/1.73 m^2.

ney. Three patients had complications of therapy. Patient 10 with bilateral stenoses had failed angioplasty. Because of generalized vascular disease and stable renal function and blood pressure on medication, surgery was not performed. Patient 11 suffered an infarcted renal upper pole which, on a subsequent scan, was shown to result in atrophy of the upper pole. Patient 12 died in the postoperative period from a bleeding gastric ulcer.

The remaining 19 patients with prolonged PTT (Fig.

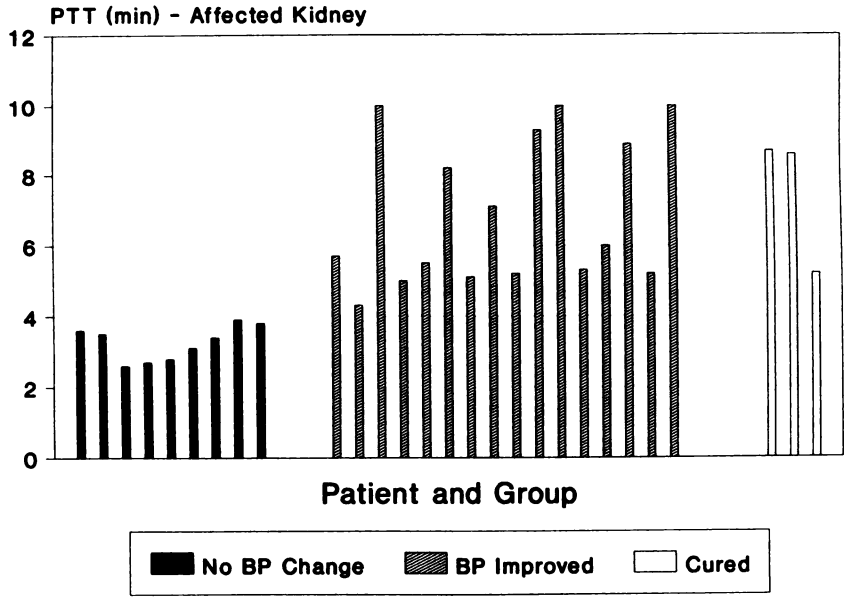

FIGURE 4
Pre-PTA parenchymal transit time. PTT values >10 min could not be accurately measured, and are shown as equal to 10 min.

4), had their hypertension improved (Patients 13 to 28) or cured (Patients 29 to 31) following intervention and this was associated with an increase in relative function ($p < 0.001$) and decrease in PTT ($p < 0.001$) in the affected kidney (Figs. 5 and 6). In five, the PTT following treatment, although improved, was still abnormal (Patients 15, 21, 23, 25, 30). It returned to within the normal range in the four who had progress studies a few months later. Twelve showed improvement in total renal function, while in seven GFR remained stable.

The three patients who became normotensive have remained so for between 5 and 6 yr post-therapy. Follow-up of the remaining 16 with improvement in hypertension has shown that nine have remained with stable hypertension, renal function and scans. One has progressed to chronic renal failure and six have had recurrence of severe hypertension. Progress quantitative renography studies (Table 2) showed that in three of these there was no change in comparison with the improved scan post-therapy. No recurrent functionally significant stenosis was diagnosed and hypertension was controlled following alteration of antihypertensive medication. Patient 13, despite previously successful dilatation, when reinvestigated for recurrence of hypertension, was found to have renal artery occlusion.

On three occasions in two patients who presented with recurrent hypertension, quantitative renography demonstrated a reduction in GFR, relative renal function and prolongation of PTT on the side of the previous stenosis. Recurrent renal artery stenosis was di-

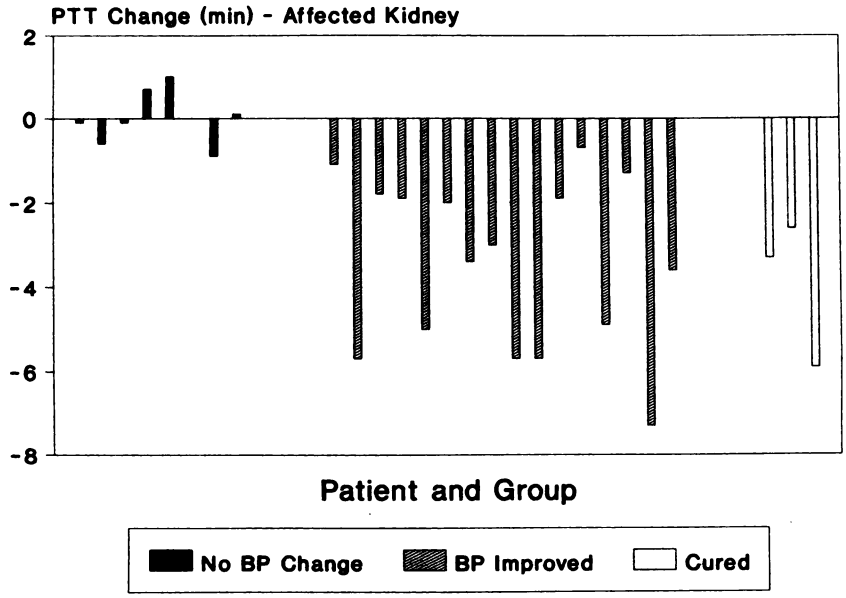

FIGURE 5
Change in parenchymal transit time (PTT) following PTA.

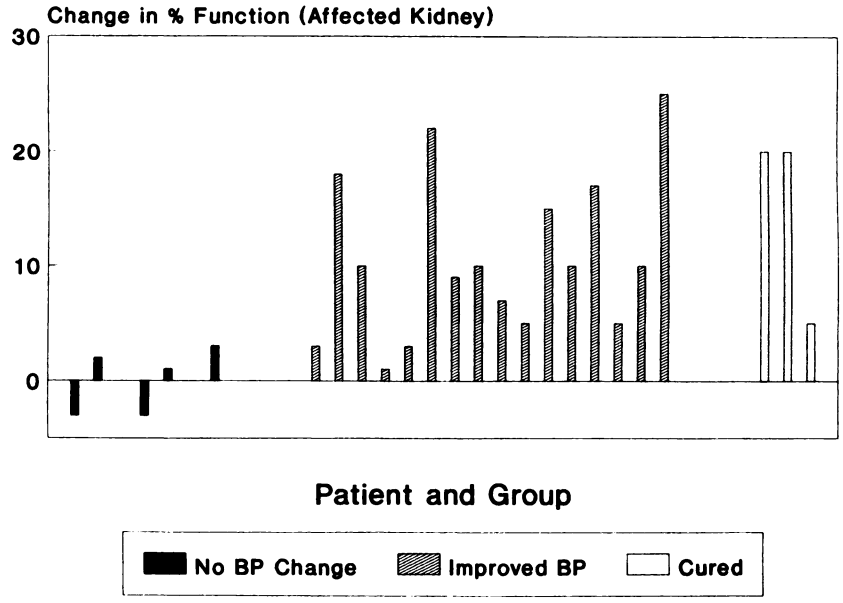

FIGURE 6
Change in relative function in the affected kidney following PTA.

agnosed which was confirmed by angiography and treated successfully by repeat angioplasty (Table 2). On each occasion blood pressure control improved.

DISCUSSION

The relative simplicity of percutaneous transluminal dilatation of stenosed renal arteries initially gave rise to claims that it should be performed without further functional investigation in all patients shown to have hypertension and renal artery stenosis (*30,31*). Time and experience have tempered some of this initial enthusiasm and it is now well accepted that the functional nature of the RAS needs to be assessed (*6,32*).

This study confirms that only patients with functionally significant stenoses as evidenced by prolonged PTT, should have their renal arteries dilated or reconstructed. None of the nine patients without this factor (despite reduced renal perfusion and function) improved in blood pressure control following angioplasty (Fig. 4) and six showed a fall in GFR.

In contrast, 19 patients with prolonged PTT and without complications of treatment, had their hypertension either cured or improved. We have previously shown (*33*) that cure of hypertension can only be expected when in addition to a functionally significant stenosis, the contralateral kidney is normal in regard to perfusion, function and PTT.

Twelve of the 19 patients had an improvement in GFR whilst in the remaining seven, GFR was either stable or reduced due to loss of function by both the affected and contralateral kidneys. This may be due to the effect of the contrast used in angiography.

In the six patients with recurrent severe hypertension following treatment, quantitative renography correctly identified the three episodes of recurrent significant stenoses and the case of renal artery occlusion. Restenosis was evidenced by a reduction in renal function and prolongation of PTT in the affected kidney which returned to normal following repeat angioplasty.

Quantitative renography with deconvolution analysis and assessment of PTT is within the capability of every nuclear medicine department with a dedicated gamma

TABLE 2
Progress Studies for Recurrent Hypertension with Changes in Parameters on the Side of Stenosis

Patient	Post-treatment			Recurrent hypertension			Following repeat angioplasty		
no	GFR	% Funct	PTT	GFR	% Funct	PTT	GFR	% Funct	PTT
16	67	35	3.2	67	38	3.3			
23	43	45	4.3	44	50	2.8			
25	66	37	5.3	60	35	3.6			
13	40	20	2.1	33	<5	—			
20	78	25	3.7	63	15	4.7	71	20	3.3
24	106	30	3.4	79	25	4.7	86	30	3.7
				81	29	4.7	79	31	3.4

camera computer system. One of the factors preventing wider acceptance and utilization of renal transit times is the variation between institutions in the parameters measured from the transit time curve. Some investigators (*21*) calculate the mean transit time through the whole kidney including calyces and pelvis. Others, including ourselves, calculate the mean transit time through the parenchyma alone yielding a shorter mean parenchymal transit time with a smaller standard deviation. To ensure reproducible results, attention to detail is important. Pelvis and calyces must be excluded from the parenchymal region of interest and to facilitate this, patients must be well hydrated to prevent pelvicalyceal tracer retention and functional imaging employed to accurately separate parenchyma from collecting system. In previous publications (*17,33*) we divided the total mean parenchymal transit time into a minimum transit time and a mean of the distribution of transit times (Fig. 2). We showed that the distribution of transit times was also a sensitive indicator of renal ischaemia. However, to enable comparison of our data with other workers in the field, we now also present our data as total mean parenchymal transit time. The normal range at our institution from 45 potential kidney donors is almost identical to the normal range recently presented by another group (*34*).

Recently, Captopril-enhanced scintigraphy has also shown promise in screening of patients with hypertension and in predicting response to angioplasty or surgery (*35–37*). At our institution, Captopril enhanced scintigraphy has not been performed since 1983 when several patients developed transient renal failure following our then protocol of treatment with the drug for a few weeks before scanning. This most likely does not apply to single dose studies, but the sensitivity and specificity of the test is yet unknown especially in cases with preexisting renal impairment (*38*). There has, as yet, been no published study comparing quantitative renography with PTT measurement and Captopril enhanced scintigraphy in the evaluation of renovascular hypertension.

Renal nuclear medicine studies are ideally suited to provide the necessary functional information to complement the anatomic information provided by angiography. We have shown quantitative renography with the calculation of PTT to be an excellent predictor of which patients with atherosclerotic RAS require treatment. In addition the technique readily identifies patients with recurrent functionally significant stenoses.

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