Noninvasive Measurement of Renal Blood Flow with Technetium-99m-DTPA in the Evaluation of Patients with Suspected Renovascular Hypertension

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If a hypertensive patient with renal artery stenosis (RAS) is to benefit from percutaneous transluminal renal angioplasty (PTRA) in terms of a sustained improvement in blood pressure control, one may postulate a demonstrable reduction in renal blood flow (RBF) to that kidney, reversible by PTRA. In a population of 32 hypertensive patients, RAS was present in 23 of 62 kidneys. Eleven of the 32 patients underwent renal revascularization, of whom 6 showed improvement in blood pressure control at 6 mo, i.e., had renovascular hypertension (RVH). There was no correlation between RBF and angiographic appearances of the renal artery. Furthermore, there was no significant difference between RBF in the stenosed kidneys of the patients with RVH compared with the stenosed kidneys of patients without RVH. Individual kidney RBF was 22% (s.d. 11) higher 1-3 wk after PTRA but the increase did not correlate with clinical outcome. Angiotensin converting enzyme (ACE) inhibition increased RBF by 25% (s.d. 25) of baseline flow before PTRA but the increase did not correlate with clinical outcome. Measurement of RBF is of limited value for the prediction of the long-term blood pressure response following PTRA.

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Renal artery stenosis (RAS) is common both in hypertensive and normotensive patients, with incidences (including minor disease) approaching 60% and 30%, respectively, and increases with advancing age (*1*, *2*). The incidence of renovascular hypertension (RVH) is not clearly known and estimates have ranged from 0.5% to 5% of all hypertensive patients (*3*,*4*). This apparent disparity between RAS and RVH underlines the need for a screening test for selection of those patients who have functionally significant RAS and who might benefit from percutaneous transluminal renal angioplasty (PTRA) with respect to blood pressure control.

It may be postulated that if RAS is functionally significant, renal blood flow (RBF) to the stenosed kidney would be reduced both as a result of the stenosis itself and any resulting increased efferent arteriolar tone. Furthermore, if the patient with RAS is to gain benefit from PTRA, an increase in RBF to the revascularized kidney should be demonstrable.

In the study reported here we have measured individual kidney RBF before and after angiotensin converting enzyme (ACE) inhibition, using a recently described noninvasive technique (*5*,*6*), in patients with suspected RVH and correlated it with renal angiography. We have also measured RBF before and after a revascularization procedure—PTRA or surgical—in order to examine the effect of revascularization on RBF.

METHODS

Patients

A total of 32 patients were studied. They were recruited from a larger trial taking place in the Hammersmith Hospital Hypertension Clinic, which was investigating the prevalence of RVH in a group of patients with severe hypertension (defined as requiring three or more drugs) or hypertension with renal impairment (defined as a serum creatinine of > 125 μmole/l). Ten patients fell into the latter group with a mean serum creatinine of 179 μmole/l (range 136–274). Nine of the 32 patients had ischemic heart disease, 7 were diabetic, and 2 were hypothyroid.

All patients underwent intraarterial (IA) digital subtraction angiography (DSA) of the renal arteries, with no intention to perform PTRA if a treatable stenosis was found. Stenoses considered unsuitable for PTRA were those where bilateral severe stenoses (>80% of the luminal diameter) were present or where a severe stenosis was seen in a patient with a solitary kidney (*7*).

Eleven of the 32 patients underwent revascularization (8 unilateral, 3 bilateral). Follow-up renography was not performed on two of them. Amongst the 9 with follow-up renography, 3 had bilateral PTRA, giving a total of 12 individual kidneys that were revascularized and for which renographic

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follow-up data are available. Six of the 11 patients who were revascularized showed evidence of clinical improvement in blood pressure control 6 mo following the procedure, and on these grounds were diagnosed as having RVH. Thus, RVH is defined as hypertension which disappeared or was easier to control as a result of revascularization of a stenotic kidney (*8*).

Patient and kidney categorization is summarized in Table 1.

Angiography

All patients were studied using IA DSA, performed as an in-patient examination. A 5F or 7F pigtail catheter was introduced into the abdominal aorta via the left or right femoral artery and 30–40 ml of one-third strength contrast (Iohexol [Nycomed], containing 100 mg/ml iodine) injected at 12–15 ml/sec. If necessary, selective renal arteriograms were performed. No angiographic complications occurred in these patients.

The patients' renal arteries were graded, as showing no evidence of stenosis (13 patients) or as minor, moderate, or severe stenosis. The grading was performed by a radiologist (MER), who was blinded to the RBF value according to the following criteria: minor, 30%–50% of the luminal diameter; moderate, 50%–80%; severe, >80%, measured directly from the angiogram by ruler (*9*).

Revascularization

Of the 11 patients who were revascularized, PTRA was unsuccessful in 3 and these were promptly treated surgically by renal arterial grafts. In the other 8, the PTRA was judged to be technically successful in that the postangioplasty arteriogram demonstrated a residual stenosis of <30% of the luminal diameter. Follow-up renography was performed between 7 and 21 days after successful PTRA or reconstructive surgery in nine patients. Two further patients who had PTRA did not have follow-up renography. The remaining eight patients with RAS were not considered suitable for PTRA. Six of these had minor stenoses (<50% of the luminal diameter) of uncertain clinical significance and two had bilateral severe stenoses.

Hemodynamic Measurements

RBF was calculated, as a fraction of cardiac output, from analysis of first-pass time-activity curves recorded after i.v. bolus injection of technetium-99m-DTPA (diethylenetriaminepentaacetic acid). The technique has been described previously (*5*) and validated in a canine model (*6*). In principle, it uses a region of interest (ROI) placed over arterial blood to forward extrapolate the renal first-pass time-activity curve to a plateau count rate which represents the count rate that would have been obtained if the ^{99m}Tc-DTPA behaved like a microsphere and was completely trapped in the kidney on first-pass. This plateau count rate, after correction for photon attenuation and camera sensitivity, is then expressed as a fraction of the injected dose, thereby giving RBF as a fraction of cardiac output.

Technetium-99m-DTPA (~ 300 MBq) was injected rapidly as a compact bolus, having first been accommodated in a short i.v. line (angiocath connected to a 19-g butterfly needle of total internal volume 2 ml) and then flushed into the patient with 20 ml normal saline. The patient was supine with the gamma camera (IGE 400A or 400T) positioned below to record activity posteriorly from the chest and upper abdomen. It was interfaced to a computer (MDS A^2), which recorded data in dynamic mode on a 64 × 64 matrix at a frame rate of 1 per sec for 40 sec (the remainder of the renogram [20 min] being recorded at a frame rate of 10 or 20 sec). ROIs were placed over the right lung, left ventricle, and upper abdominal aorta, in order to record the time course of arterial activity and over both kidneys. Since most of the bolus spreading that takes place between the antecubital vein and renal arteries occurs within the pulmonary vascular bed, the right lung was taken as an arterial signal. The time-activity curve recorded over the right lung was also used to correct for lung activity "seen" within the left ventricular ROI as previously described (*5,6*). Great care was taken to draw the renal ROIs exactly around the outline of the kidney, viewed on an image which was the summation of all images between ~10 and 60 sec.

Each arterial curve (i.e., lung, left ventricle, and aorta) was corrected for recirculation using a gamma variate fit, integrated and scaled by a factor (f) such that the upslope of the integrated curve was parallel to that of the renal curve (*5,6*). Then

$$\frac{RBF}{CO} = \frac{f \times A \times d}{D \times \delta}, \qquad \text{(Eq.1)}$$

where CO is cardiac output, A is the area (in counts) of the unscaled, recirculation corrected (i.e., fitted) arterial curve, δ, is the sensitivity of the camera (in counts MBq-1 sec-1), d is an attenuation correction factor based on kidney depth, and D the injected dose (MBq). By scaling the integrated, fitted arterial curve, it then effectively represents the renal curve that would have been obtained if the ^{99m}Tc-DTPA had an infinite transit time through the renal vascular bed. A, the area under the fitted arterial curve, is also the plateau height of the integrated curve, and, following multiplication by f, represents the dose delivered to the kidney on first-pass (Fig. 1). Note that since the curves are acquired at a frame rate of 1 per sec, f has units of sec-1.

Depth correction was achieved by assuming an attenuation constant of 0.12 cm-1 and by measuring the distance between the skin surface and the center of activity of the kidneys on lateral views.

Estimates of RBF/CO were obtained from each of the three arterial curves from which the median was selected. No at-

TABLE 1
Patient and Kidney Data

	Kidneys	Patients
Controls (no evidence of RAS in either kidney)	26	13 (0)
Unilateral RAS (no evidence of RAS in contralateral kidney)	13	13 (3)
Contralateral normal kidney in unilateral RAS	13	
Solitary kidney RAS	2	2 (1)
Bilateral RAS	8	4 (2)
Total	62	32 (6)

Figure in parentheses indicates number of patients ultimately diagnosed as having RVH.

tempt was made to subtract background, which is probably the reason why the mean value in normals was significantly higher for the left kidney (resulting from splenic overlap) (11.4 [s.d.1.3]%CO) than for the right (on which side hepatic activity arrives later) (9.9[1.1]%CO). The lower limits of normality were 8.8 and 7.7% CO, respectively, for left and right kidneys.

As an index of renal function, global glomerular filtration rate (GFR) was estimated from the subsequent plasma disappearance rate of ^{99m}Tc-DTPA as previously described (*10,11*).

Angiotensin converting enzyme (ACE) inhibition was achieved by an oral dose of 25 mg captopril (Squibb, Princeton, NJ) given 1 hr before the study. The patient was then maintained in a supine position for 4 hr with regular monitoring of blood pressure. Renographic data under ACE inhibition was not available prior to revascularization in two patients (one of whom had bilateral stenosis and bilateral PTRA). Five patients (one with bilateral RAS) had baseline and captopril renograms at follow-up after technically successful PTRA.

RESULTS

Baseline Evaluation of RBF

Of the 32 patients, 13 had bilateral normal angiograms (controls), 13 had unilateral RAS, 2 had RAS in a solitary kidney, and 4 had bilateral RAS, giving a total of 62 kidneys of which 23 had RAS.

Individual kidney RBF was highly variable within this hypertensive population, and showed no correlation with the angiographic grading of the renal artery (Fig. 2). Considering the entire population of 62 kidneys, 22 had normal RBF, of which 5 were stenosed. Thus, 17 of 39 non-stenosed kidneys had normal RBF while 5 of 23 with RAS had normal RBF ($p > 0.05$) (Table 2A). Individual kidney RBF in the stenosed kidneys of patients with RVH was not significantly different compared with RBF in the stenosed kidneys

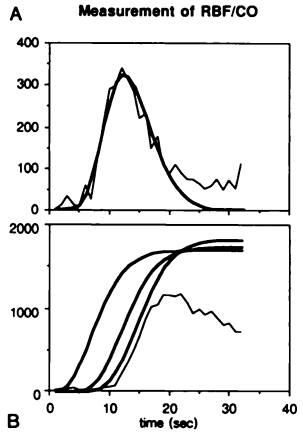

FIGURE 1
Measurement of individual kidney RBF, as a fraction of cardiac output (CO), from first-pass time-activity curves. (A) Left ventricular curve (following correction for lung activity) with gamma variate fit (bold); (B) integrated fitted curves (bold) for right lung, left ventricle (from A, above) and aorta, scaled to be parallel to the upslope of the renal curve. Each has a plateau height f.A (see Equation 1) and each represents an estimate of the renal curve that would have been obtained for infinite tracer transit time. In this case, as the median, the left ventricular estimate was chosen. Upper ordinate: counts per second; lower ordinate: counts (arterial curves), counts per second (renal curve); abscissa: time from injection (seconds).

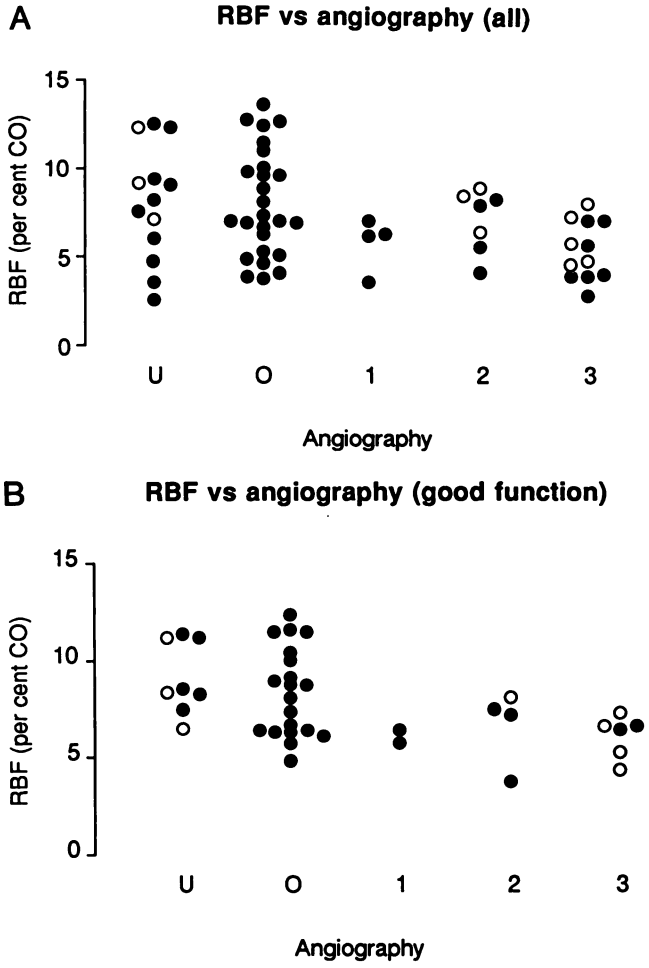

FIGURE 2
Correlation between individual kidney RBF, as a fraction of cardiac output (CO), and angiography. U: non-stenosed kidneys in unilateral RAS; O: bilaterally normal angiograms (controls); 1,2,3: minor, moderate, and severe stenosis respectively. (A): All kidneys; (B): following exclusion of patients with poor renal function. Kidneys in patients with RVH are shown as open symbols.

TABLE 2
Incidences of Normal RBF in (A) Kidneys with and without RAS* and (B) After Exclusion of Patients with Less than Half Normal Total GFR*

(A)	RAS	no RAS
Reduced RBF	18	22
Normal RBF	5	17
(B)	**RAS**	**no RAS**
Reduced RBF	8	11
Normal RBF	4	17

*n = 62.

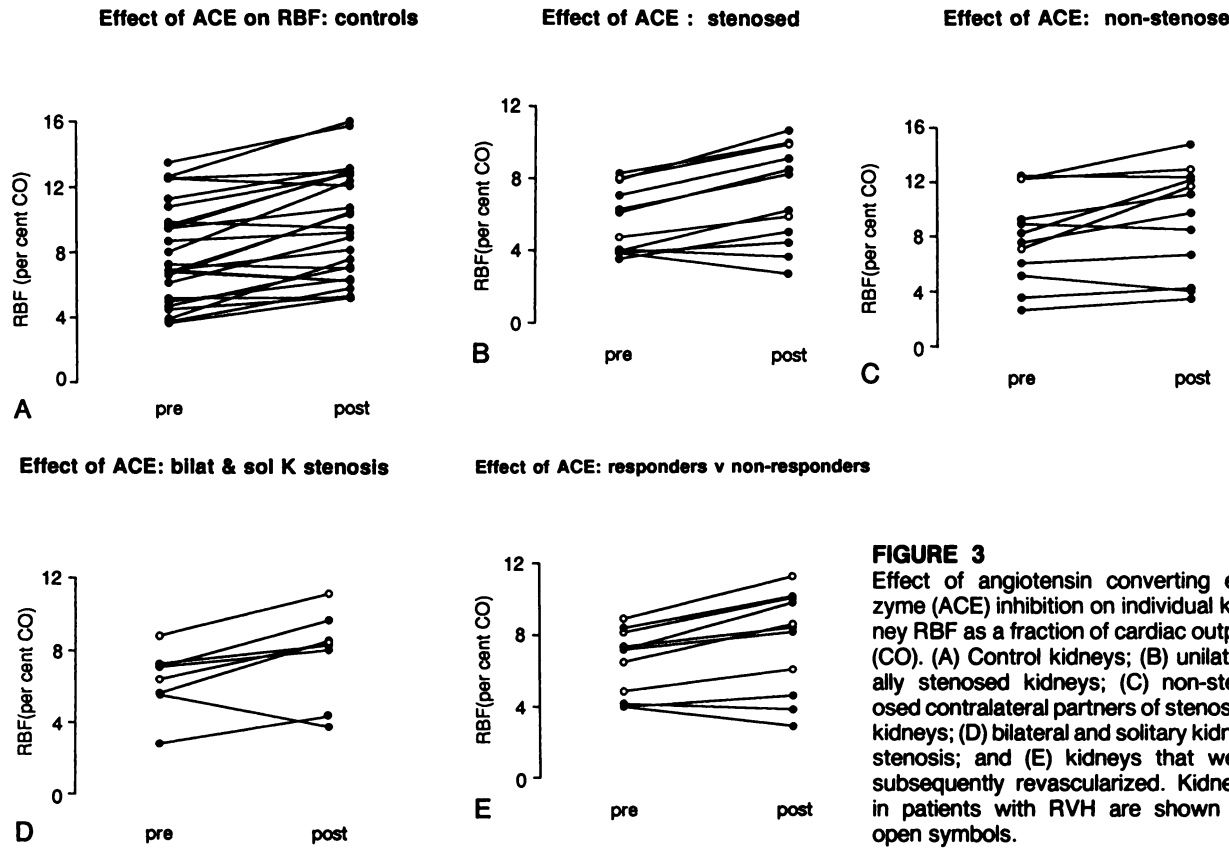

FIGURE 3
Effect of angiotensin converting enzyme (ACE) inhibition on individual kidney RBF as a fraction of cardiac output (CO). (A) Control kidneys; (B) unilaterally stenosed kidneys; (C) non-stenosed contralateral partners of stenosed kidneys; (D) bilateral and solitary kidney stenosis; and (E) kidneys that were subsequently revascularized. Kidneys in patients with RVH are shown as open symbols.

of patients who did not ultimately have a diagnosis of RVH (Fig. 2). The correlation between RBF and angiography improved when those patients with poor renal function (GFR reduced to 50% or less of normal [i.e., 120 ml/min/1.73 m^2]) were excluded, but there were still large overlaps between controls and all angiographic groups. Similarly, following exclusion of patients with poor renal function (which left 40 kidneys), 17 of 28 non-stenosed kidneys had normal RBF, while 4 of 12 with RAS had normal RBF ($p > 0.05$) (Table 2B).

ACE inhibition increased RBF in the great majority of kidneys, but the change in RBF did not correlate with angiographic grading, functional status or outcome after PTRA. Nor was any consistent asymmetry observed in the blood flow response between the two kidneys in patients with unilateral RAS. RBF in control kidneys increased significantly following ACE inhibition by 25% (s.d. 25) of baseline flow ($p < 0.001$, Student's paired t-test). RBF increased following ACE inhibition in unilaterally stenosed kidneys (24% [s.d. 23] of baseline, $p < 0.01$), increased in the kidneys of patients with bilateral stenosis or with a stenosed solitary kidney (24% [s.d. 27] of baseline, $p < 0.05$) and increased in the non-stenosed kidneys of patients with unilateral stenosis (18% [s.d. 23] of baseline, $p < 0.05$). RBF values, either baseline or the change in response to ACE inhibition, were unremarkable in patients with RVH compared with the remainder of the study population (Fig. 4).

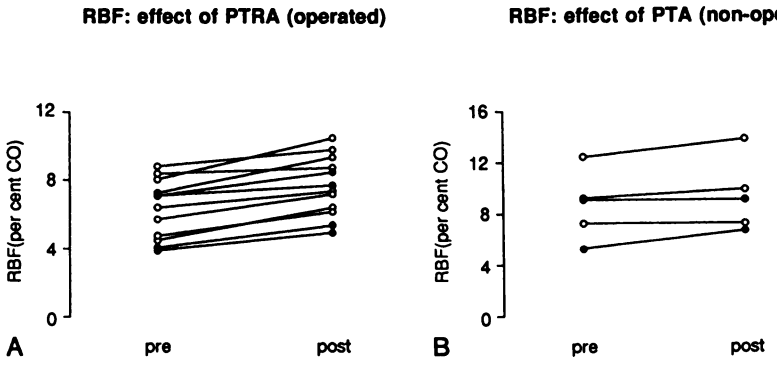

FIGURE 4
Effect of revascularization on RBF as a fraction of cardiac output (CO). (A) Revascularized kidneys; (B) nonoperated partners. Kidneys in patients with RVH are shown as open symbols.

Effect of Renal Revascularization

Blood Pressure. All 11 patients who underwent revascularization had normal or significantly improved blood pressure at the time of follow-up renography. In the six classified as having RVH, it either remained normal at 6 mo or was improved in spite of a reduction in the number of drugs required to control it, as defined by standard criteria (*8*).

Renal Blood Flow. Individual kidney RBF increased in all 12 kidneys that were studied following revascularization (Fig. 5). The mean increase was 1.3% (s.d. 0.6) of cardiac output ($p < 0.001$; Student's paired t-test) or 22% (s.d. 11) of baseline (overall range 4%–41%). RBF also increased in three of the five contralateral kidneys that were negative on angiography and not revascularized and remained the same in the other two (range 0%–28% of baseline). The increase in RBF was, in all five nonoperated kidneys, less than that seen in the corresponding contralateral revascularized kidney.

At the time of follow-up renography, RBF again increased in response to ACE inhibition in all of the six kidneys of five patients who underwent Captopril renography studies after PTRA (which was technically successful in all six kidneys). The increase, 20% (s.d. 20) of the post revascularization baseline value, was very similar to the increases induced by ACE inhibition before PTRA and by PTRA itself.

DISCUSSION

With this renographic technique, RBF is derived as a fraction of cardiac output rather than in absolute units. There is an advantage in expressing it in this form since RBF is known to vary in response to primary changes in cardiac output such that the fraction is held constant (*12*). RBF as a fraction of cardiac output should, therefore, be less sensitive than RBF in absolute units to the systemic effects of PTRA and other variables, such as the level of hydration.

The technique has some advantages, particularly within this population of patients, over the most commonly used method for measuring RBF, hippuran clearance, which, more precisely, measures effective renal plasma flow (ERPF). Thus, although ERPF may be a more appropriate physiologic parameter on which to base the effects of RAS (on the grounds that it potentially measures actual flow to nephrons), there is evidence that hippuran extraction fraction is reduced in RAS (*13–15*), and, furthermore, may be reduced further by ACE inhibition (*13,14*).

It is generally accepted that RVH is caused by renal hypoperfusion, and the success of PTRA assumed to be due to restoration of RBF. It should be useful, therefore, to be able to measure RBF, noninvasively, at the time of renography. Using a recently described technique for measuring RBF, our data show that there was no correlation between RBF and angiography, at least in this group of severe hypertensives. Although the angiographic grading of the RAS was subjective, it is difficult to see how any other grading system would change these results, given the wide range of RBF values. Even when the patients are divided into angiographically positive and negative, or patients with poor renal function excluded, the two ranges are still wide. Two explanations for this observation are possible. First, renal hypoperfusion per se is not the cause of RVH. This seems unlikely. Second, and more probably, the secondary effects of hypertension on the kidney are variable and result in a wide range of RBF values, independent of the angiographic appearances. Exclusion of patients with poor renal function had little effect on this poor correlation.

These data suggest that blood flow measurement, with or without ACE inhibition, has limited value in terms of diagnosing RVH (unless RBF is normal so tending to exclude it), or predicting the long-term response of the blood pressure to PTRA, and are consistent with the findings of Carmichael et al. (*16*) who concluded that no test (including renography and even renal venous renin sampling) has useful predictive value. The predictive value of newer tests, such as captopril renography, in which the effect of ACE inhibition on individual kidney GFR is quantified (*17, 18*), are under investigation. The therapeutic role of PTRA in patients with hypertension is controversial. Sherwood (*19*), for example, has pointed out that, because only 8% of patients with atherosclerotic RAS benefit from PTRA, it is not a cost-effective procedure. This low incidence of benefit fits in with earlier studies showing a suprisingly high incidence of RAS, which is clearly not functionally significant in terms of blood pressure (*1,2*). Nonetheless, the absence of any benefit from PTRA in patients with RAS does not mean that these patients did not have an underlying renovascular cause at the outset of their hypertension. The hypertension may have caused further renal damage, or become irreversible (*7*), blunting the effects of revascularization. The finding of normal RBF in a greater proportion of kidneys without RAS compared to those with RAS would be consistent with the notion of RVH becoming irreversible.

If PTRA is used to cure a patient's hypertension, then it would be expected to do so by improving RBF. Measurement of RBF before and after PTRA has potential value in documenting that any subsequent fall in the blood pressure is the result of renal revascularization, or conversely, that in the absence of any improvement in RBF, no therapeutic response can be anticipated.

The finding of an increased RBF at about 2 wk after PTRA in all patients, irrespective of blood pressure outcome at 6 mo, suggests an early nonspecific response to PTRA, possibly resulting from the immediate fall in

blood pressure which was observed in all patients regardless of outcome.

It is of interest that Gruenewald and Collins (*20*), using a ^{99m}Tc-DTPA renographic index of RBF, reported early follow-up increases in RBF in five hypertensive patients with RAS. What they and ourselves have not done, however, is repeat the hemodynamic measurements some months later in order to identify those patients in whom the increases in RBF are sustained and to correlate late changes with the clinical response to PTRA. It would be particularly interesting, for example, to examine the RBF increments at this time in relation to the response categories, such as described by Brawn and Ramsay (*21*) as cured, improved, and failed. It is hoped that the technique described here will prove useful in such an evaluation.

CONCLUSION

We have described a new noninvasive technique for measurement of RBF, enabling a critical examination of the relationship between RBF and RAS, as determined angiographically, in hypertensive patients. Many hypertensive patients without RAS have reduced RBF, while a few patients with RAS have normal or almost normal RBF. In view of the poor correlation between angiography and RBF, measurement of RBF as a means of detecting functionally significant RAS is unlikely to be of much clinical benefit, unless RBF is normal, whereupon RAS, and therefore RVH, become unlikely. The use of ACE inhibition shows no promise as a means of increasing the sensitivity of detecting RVH when using RBF as the end point. Finally, RBF improves following revascularization over the short term, but the extent of this improvement is unable to predict the later outcome in terms of blood pressure control. The technique described here for measuring RBF has potential value in the investigation of renovascular disease at a clinical research level.

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