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Baseline and Postcaptopril Renal Blood Flow Measurements in Hypertensives Suspected of Renal Artery Stenosis

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Renal blood flow (RBF) measurements using first-pass radionuclide angiography with DTPA, a glomerularly filtered agent, failed to show significant differences between normal and stenotic kidneys. Since MAG3 is an ideal agent for the study of RBF, this agent might be an attractive alternative tracer to detect differences in RBF. **Methods:** An angiographically controlled prospective study was performed in 48 hypertensive patients, in whom a diagnosis of renovascular hypertension was suspected on clinical grounds. The study was done to determine whether RBF measurements using first-pass radionuclide angiography with ^{99m}Tc-MAG3 could be helpful in the diagnostic work-up of the patients. Additionally, the study was done before and after ACE-inhibition. **Results:** On renal angiography, 29 patients showed to have normal renal arteries (50 patients had normal kidneys and 8 patients had small kidneys). Nineteen patients had renal artery stenosis (13 uni- and 6 bilateral disease). In the patients with normal kidneys, the mean value of RBF measurements ranged from 10.5% to 10.9% of cardiac output. Only small stenotic and small kidneys with normal renal arteries showed a significant reduced baseline RBF as compared with normal kidneys (both $p < 0.05$); this difference disappeared after ACE-inhibition only for the small kidneys with normal renal arteries. In patients with stenosed kidneys, RBF tended to be reduced both at baseline and after captopril, but the differences with normal kidneys were not statistically significant. After ACE-inhibition RBF increased in the majority of kidneys, but postcaptopril RBF data did not differ significantly from those at baseline. **Conclusion:** RBF measurements using first-pass radionuclide angiography with ^{99m}Tc-MAG3, either before or after ACE-inhibition, cannot reliably discriminate between patients with essential hypertension and patients with renal artery stenosis.

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In 1987, Peters et al. (*1*) described a technique for noninvasive measurements of organ blood flow, which was based on the fractional distribution of cardiac output (CO). When applied to the renal circulation, this method yielded values of renal blood flow (RBF) that were similar to accepted normal values (10%–15% of CO per kidney). Using ^{99m}Tc-DTPA as a tracer, investigators estimated RBF in normal subjects to be 10.4% ± 1.2% of CO for the left kidney and 9.0% ± 1.1% of CO for the right kidney. There was a consistent difference of about 1.5% of the CO at the expense of the right kidney, a phenomenon which was attributed to interference with uptake of tracer by the spleen (*1*).

Patients with both essential hypertension and renal artery stenosis (RAS), the RBF may be reduced, although in the latter category of patients, no correlation between the reduction in flow and the angiographic grading of the stenosis is apparent (*2*). In RAS, however, the RBF is usually reduced only on the affected side. Thus, a further decrease may occur after ACE inhibition (*3*). Therefore, the measurement of individual kidney flows may reveal whether a renal artery stenosis is present or not.

Although Peters et al. performed their studies with DTPA, which is excreted by glomerular filtration, MAG3 may be a good alternative tracer. MAG3 is excreted by both glomerular filtration and tubular excretion (*4*) with renal clearance characteristics comparable to those of ortho-iodohippurate, an agent frequently used for the study of RBF (*5*). If studies could be done with MAG3, the theoretical possibility emerges to combine Peters' method with a quantitative estimation of RBF.

Thus, the present study was designed to evaluate prospectively whether in hypertensive patients, in whom a diagnosis of renovascular hypertension is suspected, measurements of RBF from first-pass radionuclide angiography, at baseline and 2 hr after ACE-inhibition, are able to detect RAS.

MATERIALS AND METHODS

Forty-eight consecutive patients in whom a diagnosis of renovascular hypertension was suspected clinically and antihypertensive medication had been discontinued for at least 2 wk were included in this study (*6*). All patients had ^{99m}Tc-MAG3 measurements of RBF by first-pass radionuclide angiography (*1*) performed on two separate days. On one of these days, baseline data were obtained randomly. On the other day, RBF was determined 2 hr after the patients were administered an oral dose of 25 mg captopril. Before RBF measurements, all patients were given 300 ml of fluid to guarantee urine output of at least 1 ml/min. Patients remained supine during all investigations.

A bolus volume of about 1 ml saline solution containing 148 MBq ^{99m}Tc-MAG3 was given followed by rapid flushing with

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TABLE 1
Renal Blood Flow Measurements in 29 Patients with Essential Hypertension and 19 Patients with Renal Artery Stenosis

	Patients with EH (50 normal kidneys)	Patients with EH (8 small kidneys)	Patients with RAS (25 stenotic kidneys)	Patients with RAS (13 contralateral kidneys)
BL RBF/CO-A	10.9% ± 5.2% (10.5–13.4)	6.6% ± 1.7* (5.2–8.0)	9.3% ± 5.4% (7.1–11.6)	10.8% ± 4.2% (8.3–13.4)
CP RBF/CO-A	12.6% ± 5.0% (11.2–14.0)	7.9% ± 3.5% (5.0–10.8)	8.9% ± 4.4% (7.1–10.7)	10.6% ± 3.6% (8.5–12.8)
BL RBF/CO-L	10.7% ± 4.1% (9.5–11.9)	6.6% ± 2.0† (4.9–8.2)	8.2% ± 4.4% (6.4–10.1)	9.3% ± 3.5% (6.9–11.5)
CP RBF/CO-L	11.4% ± 3.9% (10.3–12.5)	6.8% ± 2.9% (4.8–8.8)	8.2% ± 4.3% (6.4–10.0)	9.2% ± 3.8% (7.2–11.4)
BL RBF/CO-LV	10.5% ± 4.2% (9.3–11.7)	6.6% ± 1.3‡ (5.6–7.7)	8.8% ± 4.9% (6.8–10.8)	10.5% ± 3.7% (8.2–12.7)
CP RBF/CO-LV	11.2% ± 4.0% (10.1–12.4)	7.1% ± 2.5% (5.1–9.2)	7.8% ± 4.0% (6.0–9.3)	9.4% ± 3.7% (7.2–12.6)

*$p < 0.01$, †$p < 0.05$, ‡$p < 0.001$.

Mean values ± s.d. and 95% confidence intervals for RBF measurements in 29 patients with essential hypertension (50 normal and 8 small kidneys) and 19 patients with RAS (25 stenotic and 13 contralateral-to-stenotic kidneys). Data are expressed as percentages of CO as computed over aorta (RBF/CO-A), right lung (RBF/CO-L) or left ventricle (RBF/CO-LV) at baseline (BL) and after captopril (CP). RBF = renal blood flow; RAS = renal artery stenosis; EH = essential hypertension; CO = cardiac output.

saline, according to standard procedures (*7*). Regions of interest (ROI) over the relevant organs (left and right kidney, right lung, left ventricle and abdominal aorta) were drawn, and their time activity curves were integrated and calculated according to the Peters method (*1*). During the second RBF measurement, the same ROIs corrected for depth over the kidneys, were used. The RBF was calculated as the percentage of CO as computed over the right lung (RBF/CO-L), left ventricle (RBF/CO-LV) and abdominal aorta (RBF/CO-A) (*1,8*).

All patients had ultrasound examination of the kidneys and renal angiography. Renal angiograms were analyzed according to accepted methods (*6*). In patients with RAS, the degree of luminal narrowing was determined by calculating the ratio of the luminal diameter at the point of greatest stenosis and at the normal part of the artery as seen on angiography. A luminal reduction of more than 50% was considered to denote significant RAS.

Sometimes patients with essential hypertension have small kidneys with normal blood supplies. To account for this phenomenon, the pole-to-pole length of each kidney was measured during ultrasonography. A kidney was classified as small when the contralateral kidney exceeded its size by 10% and no abnormalities were seen on angiography. Renal function was assessed by plasma creatinine levels.

Statistical Analysis

The analysis of RBF measurements was performed per group of kidneys, i.e., normal and small kidneys in patients with essential hypertension and stenotic and contralateral kidneys in patients with RAS. For group comparisons, the two-way t-test and the Mann-Whitney-U test were applied while changes in RBF after captopril were analyzed by the paired t-test. Frequencies in different groups were compared with Fischer's exact test.

A comparison of the number of kidneys in each group, with an increase or decrease in RBF after captopril of more than 2% of CO was performed to determine number of kidneys with a substantial change in RBF. This percentage was similar to the mean increase in RBF induced by ACE inhibition found by Peters et al. (*2*) in stenotic kidneys.

Data are expressed as means ± s.d. and 95% confidence intervals of the mean. A p-value < 0.05 was considered to denote statistical significance. The study's ability to detect a 5% difference in RBF between normal and stenotic kidneys was 85%.

RESULTS

On angiography, 29 patients proved to have normal renal arteries and were diagnosed as having essential hypertension. Ultrasound revealed that eight had a unilateral small kidney with a pole-to-pole length ranging from 7.0 to 10.2 cm; kidneys contralateral to such small kidneys ranged from 10.0 to 12.2 cm in length. Thirteen patients had unilateral and six had bilateral RAS and their kidney length ranged from 6.0 to 12.5 cm; four of these stenotic kidneys differed in length by more than 10% from their counterpart.

The mean serum creatinine and mean age were significantly higher in patients with RAS than in patients with essential hypertension: 111 ± 32 versus 93 ± 26: μmole/liter ($p < 0.01$) and 64 ± 6 versus 51 ± 15 yr ($p < 0.0001$), respectively. All patients with RAS were older than 50 yr. The data of 50 normal kidneys, 8 small kidneys with no RAS, 25 kidneys with RAS and 13 kidneys contralateral to a stenosis were available for RBF analysis.

Although measurements based on the abdominal aorta ROI gave the highest values for RBF, no significant differences were found between the three methods to calculate RBF in the various groups of kidneys, either for the determinations at baseline or for those after captopril.

The majority of kidneys showed an increase in RBF after captopril administration: 64% of the normal kidneys, 63% of the small kidneys, 52% of the stenotic kidneys and 54% of the contralateral kidneys. When comparing stenotic to contralateral kidneys there was no difference in the number of kidneys with an increase in RBF of 2% or more of CO. The number of kidneys with a decrease in RBF of more than 2% of CO after captopril did not differ between the various groups.

Patients with Essential Hypertension

Normal Kidney Group. Average RBF in the 50 normal kidneys ranged from 10.5% to 10.9% of CO at baseline and from 11.2% to 12.6% of CO after captopril for the various methods to calculate RBF (Table 1). Differences between RBF determinations at baseline and after captopril were small and

TABLE 2
Renal Blood Flow Measurements in 25 Normal Left and Right Kidneys and 8 Small Kidneys in 29 Patients with Essential Hypertension

Patients with EH	25 normal left kidneys	25 normal right kidneys
BL RBF/CO-A	13.8% ± 5.3%	10.0% ± 4.5%
CP RBF/CO-A	14.0% ± 5.6%	11.2% ± 4.0%
BL RBF/CO-L	12.1% ± 4.0%	9.2% ± 3.7%
CP RBF/CO-L	12.6% ± 4.5%	10.3% ± 2.9%
BL RBF/CO-LV	12.0% ± 4.2%	9.0% ± 3.6%
CP RBF/CO-LV	12.4% ± 4.4%	10.1% ± 3.1%

Mean values ± s.d. for RBF measurements in 25 normal left and right kidneys and 8 small kidneys of 29 patients with EH. Data are expressed as percentages of CO as computed over aorta (RBF/CO-A), right lung (RBF/CO-L) or left ventricle (RBF/CO-LV) at baseline (BL) and after captopril (CP).
EH = essential hypertension; RBF = renal blood flow; CO = cardiac output.

not statistically significant for any of the methods used to calculate RBF.

The difference in RBF between pairs of normal kidneys ranged from 0.1% to 8.4% of CO for the various RBF measurements at baseline and from 0.4% to 9.7% for measurements after captopril. Although RBF data tended to be lower in right kidneys, differences between left and right kidneys were not significant (Table 2).

Small Kidney Group. On average, RBF for all eight small kidneys was similar at 6.6% of CO at baseline and ranged from 6.6% to 7.9% of CO after captopril for the various methods to calculate RBF (Table 1). Again, changes in RBF after captopril administration were not statistically significant. The average difference between RBF determinations at baseline and after captopril ranged from 0.2% to 1.3% of CO in the small kidneys and 0.2% to 0.9% in the contralateral ones.

The difference in RBF measurements between the normal and small kidneys for the eight individual patients ranged from -1.6% to +15% (mean value 6.4%) at baseline and -1.0% to +15.2% (mean value 7.8%) after captopril administration.

In all patients with essential hypertension, there was a statistically significant difference ($p < 0.05$) for the RBF measurements in small kidneys ($n = 8$) and in normal kidneys ($n = 50$) at baseline, but this difference disappeared after captopril.

Patients with Renal Artery Stenosis

The mean baseline and mean postcaptopril RBF of all affected kidneys ($n = 25$) and of the contralateral ones ($n = 13$) in patients with RAS are given in Table 1. Although there was a trend in kidneys with stenosis to have reduced RBF, there were no significant differences between stenotic kidneys and contralateral ones for RBF measurements at baseline or after captopril. Additionally, no significant changes were induced by captopril in either group of kidneys.

Both mean baseline and mean postcaptopril RBF of the affected kidneys or of the contralateral ones in patients with RAS were not significantly different from those of normal kidneys of patients with essential hypertension.

Small Kidney Group. Average RBF for all four small kidneys ranged from 4.4% to 5.3% of CO at baseline for the various methods to calculate RBF, with no significant change in RBF after captopril. The mean RBF of the four small kidneys with RAS was significantly lower than that of normal sized kidneys with RAS ($n = 21$) and that of normal kidneys in patients with essential hypertension (both $p < 0.05$).

DISCUSSION

In their studies Peters et al. (*2*) failed to find significant differences in RBF between normal, stenotic and contralateral-to-stenotic kidneys. They used DTPA, however, as the marker substance. Since MAG3 renal clearance has a linear relationship with effective renal plasma flow (*4*), it could be an attractive alternative tracer to detect differences in renal flow.

Split renal function renography has shown that in patients with renovascular hypertension ACE inhibitors reduce both the glomerular filtration rate and the effective renal plasma flow on the affected side, while the glomerular filtration rate and the effective renal plasma flow remain intact or slightly increase on the contralateral side. In patients with essential hypertension the renal hemodynamic changes are similar as those in the contralateral kidney of patients with unilateral renal artery stenosis (*9,10*). The effect of ACE inhibitors on tracer uptake eliminated by tubular excretion may vary in experimental renovascular hypertension. Some authors (*11-13*) found no effect on the uptake of such agents by stenosed kidneys after ACE inhibitors, while others found a reduced uptake (*5*). According to Jonker et al. (*14*), variations in uptake or effective renal plasma flow may be related to the degree of stenosis.

Thus, theoretically, measurements of split RBF before and after ACE inhibition in patients suspected of renovascular hypertension could be helpful in the diagnostic work-up of such patients. For this reason, we conducted a prospective angiographically controlled study of RBF measurements from first-pass radionuclide angiography (*1*), at baseline and 2 hr after ACE inhibition.

Our data show that measurements based on the abdominal aorta ROI give the highest values for RBF, although these do not differ significantly from those derived from the other methods to calculate RBF. Thus, our results are in agreement with those of Bell and Peters (*7*) who also found that organ blood flow measurements based on the aorta ROI yielded higher values than when the left ventricle or lung was used as ROI.

In patients with essential hypertension, we found the average values of RBF determinations to range from 10.5% to 10.9% of CO, which is close to the values found by Peters et al. in such patients (*1,2*). As in normal subjects (*1*), RBF tended to be lower in right than in left kidneys. Although the explanation for this finding is not readily apparent, it is thought to be due to greater interference with tracer uptake by the spleen (*1*).

We further found that ACE inhibition stimulated RBF in the majority of kidneys, both in essential hypertension and RAS patients, although differences between RBF measurements at baseline and after captopril never became statistically significant.

Our RBF data obtained with ^{99m}Tc-MAG3 are comparable to those obtained by Peters et al. with ^{99m}Tc-DTPA, except for the fact that the latter investigators found a statistically significant RBF increase after ACE-inhibition in both normal and stenotic kidneys (*1,2*). Since DTPA is primarily a marker for glomerular filtration, while MAG3 uptake more reflects tubular blood flow, the discrepant results between Peters' group and ours with respect to the effect of ACE-inhibition may be due to a greater role of angiotensin II in maintaining glomerular filtration than in regulating renal perfusion. On the other hand, changes in CO may have influenced the results of our measurements. Further studies, using CO measurements are needed to clarify this issue.

Our results also suggest that RBF measurements before and after ACE inhibition in patients in whom a diagnosis of renovascular hypertension is suspected cannot discriminate between patients with essential hypertension and those with RAS, at least when MAG3 is used as the tracer. Moreover, in patients with essential hypertension and small kidneys significantly

reduced values of RBF may be found that are even lower than those in patients with RAS.

CONCLUSION

Our data demonstrates that measurements of RBF from first-pass radionuclide angiography using ^{99m}Tc-MAG3 are of little help as a diagnostic test in patients in whom a diagnosis of renovascular hypertension is suspected on clinical grounds.

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Imaging Osteomyelitis with Streptavidin and Indium-111-Labeled Biotin

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Animal studies of infection imaging by a two-step protocol have shown that important improvements in target to nontarget ratios are possible. In this protocol, unlabeled streptavidin is administered and allowed sufficient time to accumulate in the lesion, probably by nonspecific processes, and to clear elsewhere. Thereafter, ^{111}In-biotin is administered. A fraction of the labeled biotin may be retained in the lesion because of biotin's high affinity for streptavidin while most of the activity is cleared through the kidneys. **Methods:** Radioscintigraphy with unlabeled streptavidin followed with ^{111}In-labeled biotin was performed in 15 patients with chronic osteomyelitis. As controls, each patients received either ^{111}In-labeled biotin without the preadministration of streptavidin or ^{111}In-labeled nonspecific IgG. **Results:** Regions of focal uptake were identified in all patients receiving streptavidin followed by radiolabeled biotin as early as 10 min postadministration of radioactivity, and retention of label was evident through 24 hr. Coincident regions of abnormal accumulation were apparent with ^{111}In-IgG, but only in delayed images. Moreover, with ^{111}In-biotin alone, without the preadministration of streptavidin, focal accumulations were detected in areas similar to that identified with the two-step protocol. Although, these observations were only in the earliest images. **Conclusion:** The results of this preliminary clinical investigation suggest that a two-step protocol with unlabeled streptavidin and radiolabeled biotin may be an alternative for the detection of infection.

Key Words: streptavidin; radiolabeled biotin; pretargeting; infection imaging; osteomyelitis

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Recently, radiolabeled nonspecific polyclonal IgG has been shown to be useful in the diagnosis of infection and inflammation (*1*). The accumulation of this protein is thought to be due to nonspecific diffusion resulting from increased vascular permeability and edema at these sites (*1–3*). Despite the obvious success of this method, a major disadvantage to the use of ^{111}In-IgG is its slow rate of accumulation into a lesion and its slow clearance from normal tissues and circulation. As a result, diagnosis is often delayed 24 to 48 hr postadministration of radioactivity. We have previously considered in an animal model whether streptavidin may be a more useful agent to detect infection (*4*). Unlabeled streptavidin was administered and allowed to accumulate nonspecifically into the lesion, probably in a manner similar to polyclonal IgG. Some time later, the radiolabel was delivered bound to biotin, a low mole weight vitamin. Biotin has an extremely high affinity for streptavidin (*5*). Therefore the labeled biotin may diffuse rapidly into the lesion, and bind irreversibly to streptavidin therein, while the unbound biotin clears from the circulation and normal tissues. Thus, one advantage with this approach is the low accumulation of label in normal tissues, mainly the result of biotin's rapid whole-body clearance. As such, target-to-nontarget tissue ratios on the order of 10 have been reported in a mouse model within hours of postadministration of labeled biotin (*4*). We report the results of the use of this two-step approach to detect infection in patients.

MATERIALS AND METHODS

Reagents

Streptavidin was obtained as a sterile, pyrogen-free lyophilized powder in single use vials. Each vial contained 10 mg of streptavidin that was solubilized in 2 ml sterile saline before administra-