Comparison of Different Radioactive Agents for the Detection of Renovascular Hypertension with Captopril in a Rat Model

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In Goldblatt hypertension in rats produced by implanting a silver clip on the left renal artery, captopril induces a greater difference in the 1-min uptake of diethylenetriaminepentaacetic acid (DTPA) between the two kidneys than in baseline uptakes, similar to the experiences in unilateral renovascular hypertension in man. The combination of captopril and furosemide induces an even greater difference in renal uptakes than with captopril alone in this rat model. In paired experiments, DTPA complexes were used as a standard to compare the differences in renal uptake between the two kidneys after captopril-furosemide with other existing and potential renal radiodiagnostic agents. No statistically significant difference was found between DTPA, glucoheptonate, dimercaptosuccinic acid, aminated dextran, or lysozyme. However, the differences in renal uptake were significantly less with hippuran than with DTPA. Furosemide and captopril caused delayed renal retention of hippuran after one minute. This response appeared to be due to non-specific volume depletion because it occurred in both clipped and unclipped kidneys.

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In unilateral renovascular hypertension, angiotensin II-mediated efferent arteriolar vasoconstriction acts to maintain the glomerular filtration rate (GFR) of the "stenotic" kidney (*1,2*). Interference with angiotensin II production or action in this setting causes predominantly efferent arteriolar vasodilatation, thereby lowering the GFR of the affected kidney with little or no change in effective renal plasma flow (ERPF). Concurrently, the GFR and ERPF in the contralateral kidney do not change or increase slightly (*3,4*). Wenting et al. (*5*) first used captopril, an angiotensin I converting enzyme inhibitor, to exaggerate the differences in GFR and renal uptake between the "stenotic" and contralateral kidneys in order to increase the sensitivity of detection of renovascular disease by scintigraphy with technetmium-99m diethylenetriaminepentaacetic acid ([^{99m}Tc]DTPA). By performing this procedure before and after captopril, other workers (*6,7,8*) have confirmed the specificity of this response for renovascular disease. In other conditions, such as essential hypertension, chronic pyelonephritis, hydronephrosis and renal hypoplasia (*9*), GFR and ERPF either do not change, or may increase somewhat due to nonspecific vasodilatation from captopril. Some patients with renovascular disease also do not respond; this behavior has been viewed as an unfavorable prognostic indicator for alleviation of hypertension after correction or bypass of the renal arterial stenosis (*10*).

Gates (*11*) found that the renal uptake of [^{99m}Tc] DTPA 2 to 3 min after injection expressed as a percent of the administered activity, corrected for tissue attenuation, was related linearly to the creatinine clearance. From a regression equation, therefore, the GFR of each kidney could be estimated from the renal uptake. With several renal agents, we observed a similar correlation between plasma clearance and the renal uptake 0.5 to 1.5 min after injection in rats with and without glomerular disease (*12,13*). In a preliminary study, we used this approach for estimating the clearance of [^{99m}Tc]DTPA and hippuran in two-kidney, one-clip Goldblatt hypertensive rats and controls (*14*). Captopril decreased the clearance of [^{99m}Tc]DTPA in clipped

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kidney by 39% from baseline values. Prior volume depletion with furosemide in addition to captopril produced a more profound decrease, to a level 68% below baseline. Hence, in renovascular disease, we concluded that the diagnostic sensitivity of captopril enhanced renal scintigraphy in detecting differences in renal uptake could be improved further by furosemide-induced volume depletion.

Other renal radiodiagnostic agents besides DTPA have been advocated to demonstrate the response from captopril, particularly [^{99m}Tc]dimercaptosuccinic acid (DMS) (*7,15*) and iodine-131 (^{131}I) hippuran (*7,16*). However, no systematic comparison of these various agents has been published. In this paper, we have compared [^{99m}Tc]DTPA with [^{131}I]hippuran in one group of rats with two-kidney, one-clip Goldblatt hypertension; some aspects of this work were reported previously (*17*). In another group of rats, we have compared four other agents administered in succession with Tc- or In-DTPA. The goal of this study was to determine if any agent available to us was superior to labeled DTPA for this diagnostic application.

Material and Methods

Male Sprague-Dawley rats weighing 182 to 237 g were anesthetized with ether and a solid silver clip with a slit width of 0.20 mm was surgically implanted on the left renal artery. Three weeks after surgery, systolic blood pressure was monitored by tail plethysmography under light ether anesthesia, as described previously (*17*). Only rats with a systolic blood pressure >150 mmHg and an estimated baseline DTPA clearance >0.18 ml/min/100 g b.w. in the clipped kidney were accepted to the study. All experiments were carried out under ether anesthesia within eight weeks of renal artery clipping. Systolic blood pressure and body weight were determined immediately prior to each radionuclide study.

In the first group of 12 rats, baseline studies were performed after tail-vein injections of 1 mCi of [^{99m}Tc]DTPA, followed in 20–30 min by 200 μCi [^{131}I]hippuran. Fifteen-second interval images were obtained using a small field scintillation camera. The images were computer-digitized at 15-sec intervals for 3 min, followed by 1-min images for an additional 12 min. The 0.5–1.5 min. interval image was quantitated as percent injected dose in each kidney, as reported previously (*12*). For subsequent studies, furosemide (25 mg/kg intraperitoneally 6 hr prestudy) and captopril (3 mg/kg intraperitoneally 1 hr pre-study) were administered either in combination or individually. These experiments were performed on the day following the baseline study or at weekly intervals for each animal. The imaging sequences using [^{99m}Tc]DTPA and [^{131}I]hippuran were repeated in each experiment as described above.

In a second group of ten rats, the same protocol was followed, except that baseline studies were performed only with [^{99m}Tc]DTPA, furosemide was given four hours before the radionuclide experiments, and studies with furosemide and captopril administered individually were not performed. The following agents were compared with either [^{99m}Tc]DTPA or indium-111 (^{111}In)DTPA (Medi-Physics, Inc., Richmond, CA) administered in tandem—[^{99m}Tc]glucoheptonate (GHA), [^{99m}Tc]dimercaptosuccinic acid (Medi-Physics, Inc., Richmond, CA), [^{111}In]aminated dextran (T5 amdex) prepared as reported previously (*13*), and [^{111}In]human milk lysozyme. The last agent was selected as a representative low molecular weight protein (mol wt 14,000 D), coupled with the cyclic dianhydride of DTPA and labeled with ^{111}In as described previously for amdex (*13*). Technetium-99m DTPA and GHA also were "in-house" preparations. These agents were administered through a tail vein in the following sequences:

(1) 100 μCi [^{99m}Tc]DTPA followed by 100 μCi [^{111}In] amdex;

(2) 100 μCi [^{111}In]DTPA followed by 500 μCi [^{99m}Tc]GHA;

(3) 100 μCi [^{111}In]DTPA followed by 500 μCi [^{99m}Tc]DMS;

(4) 100 μCi [^{99m}Tc]DTPA followed by 100 μCi [^{111}In] lysozyme.

The imaging and computer processing were the same as for the first group of rats, except that the frames were obtained every 15 sec for 5 min. For sequences (2) and (3), the second injection was delayed 45 min after the first injection, at which time the residual ^{111}In counts in the ^{99m}Tc window of the spectrometer were negligible. The results of the renal uptake studies of all agents from 0.5–1.5 min after injection were expressed as a percent of the administered activity per kidney. These values were corrected for tissue attenuation from a linear equation predicting renal depth from body weight

$$y = 6.61 + 0.0238x,$$

where x is the body weight in grams and y is the depth of the centroid of the kidney from the posterior skin surface in millimeters. This equation was obtained by direct measurement of kidney depth and animal weight in another series of 60 male Sprague-Dawley rats ranging in weight from 200–450 g. The corrected values proved to be a maximum of 5% greater than corresponding uncorrected values—i.e., the errors due to tissue attenuation from variations in renal depth in the rat were less than in man. The uptake of [^{99m}Tc]DMS was measured between 2 and 3 min after injection, because earlier values were very low. Uptakes of [^{99m}Tc]DMS and [^{111}In]lysozyme were measured also at 2 hr, because these agents progressively accumulate in the renal parenchyma. Such delayed measurements were invalid for [^{99m}Tc]GHA, because of the excessive late biliary and intestinal excretion of this agent in the rat.

The differences in corrected uptake values for all agents were recorded also as $\frac{R - L}{R} \times 100\%$ and L/R ratios, where R and L are right and left corrected renal uptakes. Intercomparison of the agents was performed by analysis of variance. The clearances of individual kidneys were estimated from the renal uptake values using linear regression equations developed from previous work (*12,13*) (listed in the Appendix). This was not done for [^{99m}Tc]DMS, because the coefficient of correlation between the renal uptake and clearance of this agent is poor (*12*).

RESULTS

In the first group of rats, the comparisons between DTPA and [^{131}I]hippuran are shown in Figure 1 and Table 1. The baseline study shows a somewhat greater

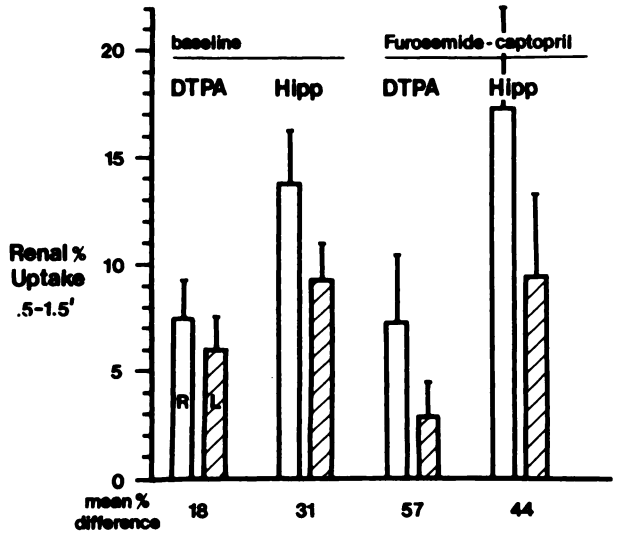

FIGURE 1
In vivo uptake measurements of right unclipped and left clipped kidneys comparing DTPA and hippuran at baseline and following combined treatment with furosemide and captopril in 12 rats with two-kidney one-clip hypertension.

difference in uptake with hippuran than with DTPA. However, in response to the captopril-furosemide challenge, the early uptake of DTPA in the clipped left kidney was markedly and significantly depressed ($p < 0.001$), while the hippuran uptake was virtually unchanged from the baseline values. Even though the hippuran uptake increased in the contralateral right kidney after captopril-furosemide, the percent difference between the two kidneys was significantly greater with DTPA than with hippuran. Likewise, the left/right renal uptake ratios were significantly lower with DTPA than hippuran ($p < 0.05$ by paired t-test).

Frequently, renal retention of hippuran was observed in the 15 minute computer-generated time-activity curves. Therefore, the uptakes at 5, 10, and 15 min were expressed as % dose/kidney and studied quantitatively along with the one minute values. The mean values are plotted in Figure 2. Captopril alone produced only a slight increase in renal retention beyond the baseline values. With furosemide alone, the retention was greater, and the curve almost horizontal. The greatest retention occurred with the combination of captopril and furosemide, so their effects appeared additive. A similar sequence of alterations in renal retention occurred in the contralateral kidney (Fig. 2A) as in the clipped kidney (Fig. 2B). The uptake values in the clipped kidney for each treatment were not significantly different at one minute. Although the drug response mean values became widely separated from baseline values at later times, the variability from animal to animal was very large. Consequently, the large standard deviations (not shown) in these four experiments overlapped considerably. No criterion was identified from these late uptake data which could reliably distinguish differences in response between the clipped and contralateral kidneys.

TABLE 1
First Series of Hypertensive Rats with Left Renal Artery Stenosis*

	Early renal uptake % dose/kidney				Predicted clearance ml/min/100 g b.w.	
Agent	R	L	% Difference	Ratio	R	L
Baseline						
DTPA	7.49	6.00	17.6	0.823	0.397	0.290
	(1.76)	(1.57)	(19.0)	(0.189)	(0.110)	(0.106)
Hippuran	13.7	9.23	30.6	0.693	1.37	1.18
	(2.51)	(1.64)	(15.0)	(0.150)	(0.197)	(0.120)
Furosemide and captopril						
DTPA	7.23	2.89	56.9	0.439	0.385	0.0986
	(3.22)	(1.48)	(18.6)	(0.190)	(0.183)	(0.0773)
Hippuran	17.33	9.31	44.1	0.543	1.66	1.18
	(4.71)	(3.81)	(20.1)	(0.191)	(0.375)	(0.279)

* Mean values; s.d. in parentheses; N = 12.

The mean (±1 s.d.) renal uptakes of right and clipped left kidneys for the 10 rats of the second group are compared in Figure 3. Part of the data required to evaluate the different agents by analysis of variance are listed in Table 2. For all agents, the percent difference in uptake between the clipped kidney and the right kidney following captopril and furosemide was greater than that of the initial baseline study with DTPA. The ten different "treatments" including amdex, GHA, four with DTPA, and early and 2-hr uptakes of dimercaptosuccinic acid (DMS) and lysozyme were compared by random block analysis of variance (*18*) and by the same subjects repeated measure analysis of variance (*19*). The values used for these tests were the L/R renal ratios. Neither test showed evidence of significance ($p > 0.05$) between any of the "treatments". The lack of change between the four experiments with DTPA suggested that the response to captopril and furosemide did not change detectably over 4 wk and that the early uptakes of [^{99m}Tc]DTPA and [^{111}In]DTPA were similar. None of the other agents were detectably better or worse than DTPA. The 2-hr uptake of DMS was much higher than the early uptake and therefore easier to measure. The mean values suggested the 2-hr measurement was better, but this was not statistically significant.

The percent differences in uptake between the two kidneys and clearances predicted by regression equations from the renal uptakes also are listed in Table 2.

DISCUSSION

Throughout this study, blood pressure was monitored continually. Substantial changes in blood pressure were relatively small using furosemide and a relatively low dose of captopril. Otherwise, a sizable reduction in

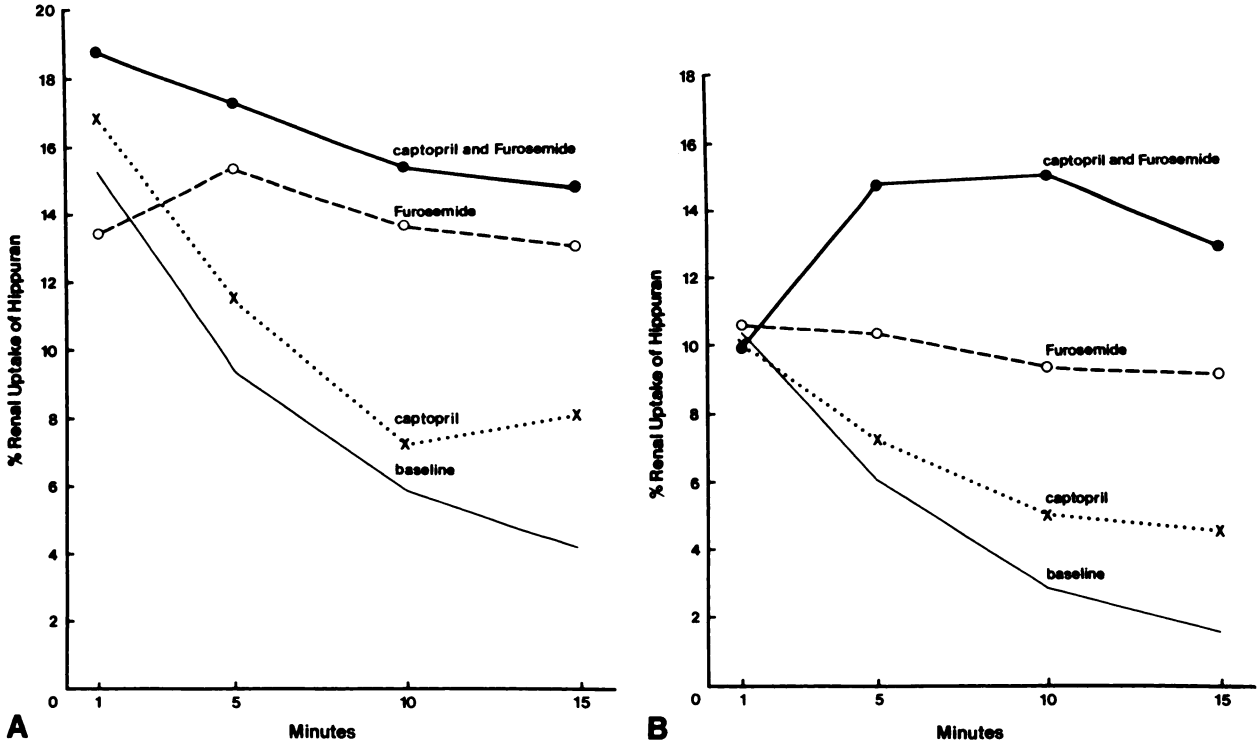

FIGURE 2
In vivo renal uptake measurements of hippuran up to 15 min after injection. Data from baseline studies, and following administration of furosemide and captopril in combination and individually are shown. Increased renal retention after drug challenge is evident in both the right kidney (A) and clipped left kidney (B).

systemic pressure could result in a nonspecific decrease in GFR or ERPF. Similarly, in the clinical setting, it would appear desirable to monitor blood pressure before and after administration of captopril with or without furosemide.

The poor performance of hippuran in response to captopril challenge in renal artery stenosis shown in the present study agrees with previous work. Its high renal extraction efficiency reflects primarily ERPF. In two-kidney one-clip hypertension in dogs (*20*), captopril

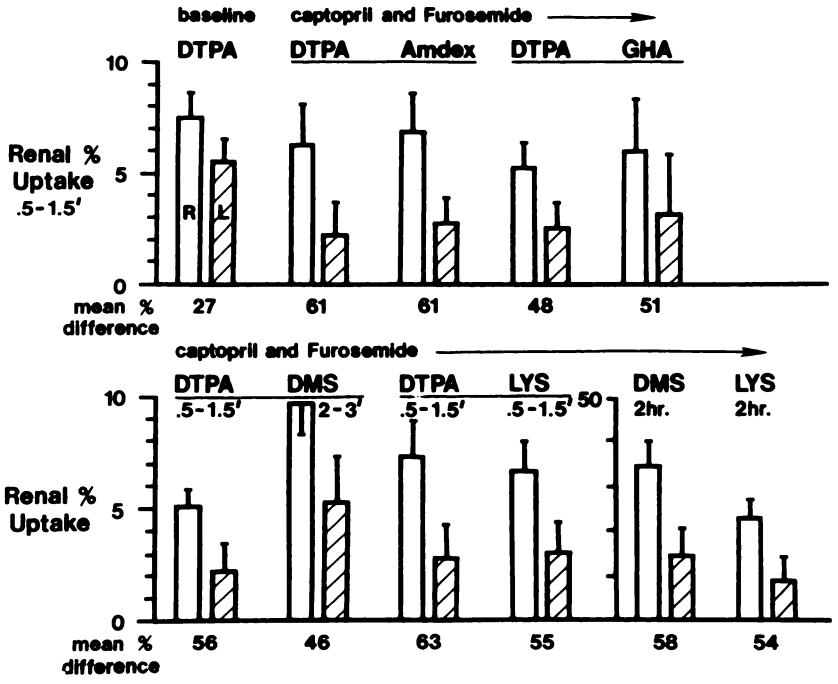

FIGURE 3
In vivo uptake measurements of right and clipped left kidneys in a second group of ten rats. A DTPA complex was paired with one of the other agents in each experiment.

TABLE 2
Second Series of Hypertensive Rats with Left Renal Artery Stenosis*

Agent	Early renal uptake % dose/kidney R	L	% Difference	L/R Ratio	Predicted clearance ml/min/100g b.w. R	L	2-h renal uptake % dose/kidney R	L	% Difference	L/R Ratio
Baseline										
DTPA	7.54	5.50	27.1	0.736	0.435	0.288				
	(1.08)	(1.11)	(10.5)	(0.114)	(0.0830)	(0.0841)				
Furosemide and captopril										
DTPA	6.24	2.34	60.7	0.394	0.324	0.0622				
	(1.85)	(1.34)	(21.0)	(0.210)	(0.150)	(0.0774)				
Amdex	6.91	2.59	61.0	0.389	0.368	0.115				
	(1.65)	(1.19)	(17.1)	(0.173)	(0.134)	(0.0813)				
DTPA	5.11	2.50	48.1	0.519	0.234	0.0890				
	(1.19)	(1.13)	(29.4)	(0.293)	(0.0961)	(0.0793)				
GHA	6.00	3.15	50.8	0.491	0.282	0.165				
	(2.30)	(2.79)	(26.5)	(0.263)	(0.106)	(0.109)				
DTPA	5.05	2.22	56.0	0.441	0.229	0.0520				
	(0.765)	(1.09)	(20.3)	(0.204)	(0.0619)	(0.0585)				
DMS	9.78	5.33	45.7	0.542	—	—	34.3	13.8	58.3	0.412
	(1.39)	(2.00)	(20.7)	(0.206)	—	—	(5.17)	(6.62)	(21.5)	(0.199)
DTPA	7.35	2.76	63.3	0.366	0.415	0.0821				
	(1.54)	(1.31)	(14.4)	(0.144)	(0.125)	(0.0898)				
LYS	6.70	3.03	55.3	0.448	0.310	0.106	22.8	9.22	54.2	0.453
	(1.32)	(1.32)	(15.9)	(0.159)	(0.0675)	(0.0737)	(4.42)	(4.92)	(31.9)	(0.317)

* Mean values; s.d. in parentheses, N = 10.

markedly lowers GFR measured by inulin clearance, whereas ERPF by PAH clearance is not altered significantly in either kidney. In patients with renal artery stenosis (*5*), the clearance of hippuran does not change after captopril. Apparently an increase in true renal plasma flow related to nonspecific dilatation of the renal vasculature is offset by decreased renal extraction efficiency from shortening of the renal transit time (*5*).

In our rat model, the hippuran uptake in the right unclipped kidney increased after captopril and furosemide compared to baseline levels. We attributed this to nonspecific vasodilatation from the captopril, because it occurred when captopril was administered alone (*17*). On the contrary, furosemide alone resulted in a slight decrease from baseline levels. The delayed renal retention of hippuran after 1 min was probably a nonspecific phenomenon because it was more pronounced with furosemide alone than with captopril alone. It occurred in the contralateral as well as the clipped kidney and was probably due to volume depletion and reduced urine flow rate. Alteration in hippuran transport from the furosemide is a more remote possibility because the two injections were 6 hr apart. Volume depletion from furosemide causes additional stimulation of the renin-angiotensin system in the stenotic kidney at reduced perfusion pressures, thereby potentiating the effects of captopril in lowering the GFR (*17*).

The same rats were used to evaluate the other renal agents (except hippuran) in the second group of experiments to minimize the wide variations in response to both renal arterial clipping, captopril and furosemide from one group to another. DTPA chelates were used as a "standard" agent in all experiments. There was no evidence of consistent decline in renal function and only minimal changes in blood pressure throughout the four week study.

The different agents were evaluated because their mechanisms of renal accumulation and excretion are dissimilar. The renal uptake and clearance of the DTPA chelates reflect the glomerular filtration rate. Amdex, like all dextrans, is cleared only by glomerular filtration, but its clearance and early renal uptake normally exceed those of DTPA (*13*) because its cationic charge facilitates transglomerular passage. It demonstrates the loss of the normal anionic charge in primary glomerular diseases well. Its similar efficacy to DTPA in the present study suggests that loss of electrostatic charge barriers does not occur in this model of "early" renovascular disease.

The renal mechanisms for handling GHA are still not totally settled. Its early renal uptake and plasma clearance correlate well with DTPA clearance in normal rats and those with glomerular disease (*12*), but its later renal retention does not. Probenecid blockade and PAH infusion significantly decrease its plasma clearance and greatly depress its later renal retention, indicating that transport from peritubular capillaries to proximal tubular cells plays a major role (*21*). The early uptake of

GHA was similar to DTPA uptake in the present experiments. It is suspected that the late retention of GHA would not reflect changes in GFR from captopril in renovascular disease, but this could not be evaluated. Delayed camera images showed considerable intestinal activity overlapping particularly the left kidney.

The early and 2-hr uptakes of DMS both mirrored the changes in GFR demonstrated with DTPA. This is in keeping with the concept that DMS undergoes glomerular filtration and progressively accumulates in the proximal tubular cells from the tubular lumen (*7*). Its slow clearance is attributed to marked plasma protein binding. Probenecid blockade does not affect the renal uptake of DMS (*22*), but it is influenced by changes in urinary pH more than GHA uptake (*21*).

Lysozyme (14,000 daltons) is probably handled like other small molecular weight proteins which are catabolized primarily by the kidney rather than the liver; i.e., accumulation in the proximal tubules predominantly by glomerular filtration and absorption from the tubular lumen (*23*), but also by some absorption from peritubular capillaries (*24*). It adequately reflects the changes in GFR in the present study. Indeed, it appears that any renal agent which reflects changes in GFR similar to DTPA chelates may be useful in this challenge test with captopril and furosemide.

APPENDIX

Linear regression equations for estimating clearances (y) of individual rat kidneys from in vivo renal uptake (x) expressed as % dose/kidney.

These were derived from data generated for previous publications (*12,13*). Plasma clearances obtained from multiple plasma samples were correlated with the summed uptake of right and left kidneys quantitated in vivo by gamma camera computer techniques in two series of rats. Both of these included controls and rats with glomerular damage induced by puromycin aminonucleoside. The [^{99m}Tc]DTPA series of 60 rats and the [^{131}I]hippuran series of 48 rats each contained 24 controls. The remaining series consisted of 12 controls and 12 with glomerular damage. For the purposes of the present study, it was assumed that the plasma clearances of the right and left kidneys in these previous studies were equal. Hence, the renal uptakes of the individual kidneys were regressed against half the plasma clearance values.

Clearances (y) ml/min/100 g body weight

Agent	No. of rats	Right kidney	Left kidney
Series I rats			
DTPA	60	0.0623x − 0.0698	0.0677x − 0.116
Hippuran	48	0.0796x − 0.284	0.0732x − 0.499
Series II rats			
DTPA	24	0.0809x − 0.180	0.077x − 0.142
Amdex	24	0.080x − 0.190	0.0692x − 0.065
GHA	24	0.046x + 0.0043	0.0389x + 0.0426
LYS	24	0.0510x − 0.0322	0.0557x − 0.0630

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REFERENCES

1. Hall JE, Guyton AC, Cowley Jr. AW. Dissociation of renal blood flow and filtration rate autoregulation by renin depletion. *Am J Physiol* 1977; 232:F215–F221.
2. Hall JE, Guyton AC, Jackson TE, et al. Control of glomerular filtration rate by renin-angiotensin system. *Am J Physiol* 1977; 233:F366–F372.
3. Huang WC, Ploth DW, Navar LG. Effects of saralasin infusion on bilateral renal function in two-kidney, one-clip Goldblatt hypertensive rats. *Clin Sci* 1982; 62:573–579.
4. Textor SC, Tarazi RC, Novick AC, et al. Regulation of renal hymodynamics and glomerular filtration rate in patients with renovascular hypertension during converting enzyme inhibition with captopril. *Am J Med* 1984; 76:29–37.
5. Wenting GJ, Tan-Tjiong HL, Derkx FHM, et al. Split renal function after captopril in unilateral renal artery stenosis. *Br Med J* 1984; 288:886–890.
6. Geyskes GG, Oei HY, Puylaert CBAJ, et al. Renography with captopril. Changes in a patient with hypertension and unilateral renal artery stenosis. *Arch Intern Med* 1986; 146:1705–1708.
7. Hovinga KTJ, Beukbot JR, van Luyk WHJ, et al. Reversible diminished renal ^{99m}Tc-DMSA uptake during converting-enzyme inhibition in a patient with renal artery stenosis. *Eur J Nucl Med* 1984; 9:144–146.
8. Fommei E, Ghione S, Palla L, et al. Captopril suppresses glomerular filtration rate but not blood flow in the affected kidney in renovascular hypertension: Report and comments on one case. *J Nucl Med Allied Sci* 1985; 29:175–177.
9. Fommei E, Ghione S, Palla L, et al. Acute effect of captopril on single kidney glomerular filtration rate in arterial hypertension. *J Hypertension* 1985; 3(suppl 2):S137–138.
10. Oei HY, Geykes EJ, Dorhout EJ, et al. The significance of captopril renography in renovascular hypertension [Abstract]. *J Nucl Med* 1986; 27:575–576.
11. Gates GF. Glomerular filtration rate: estimation from fractional renal accumulation of ^{99m}Tc-DTPA (Stannous). *Am J Roentgenol* 1982; 138:565–570.
12. McAfee JG, Thomas FD, Subramanian G, et al. Detection of diffuse glomerular lesions in rats. I. Comparison of conventional radioactive agents. *J Nucl Med* 1986; 27:502–512.
13. McAfee JG, Thomas FD, Subramanian G, et al. Detection of diffuse glomerular lesions in rats: II. Comparison of indium-111 cationic small macromolecules with technetium-99m DTPA. *J Nucl Med* 1986; 27:513–520.
14. Thomas FD, Kopecky RT, McAfee JG, et al. Evaluation of captopril challenge in a rat model of renovascular hypertension [Abstract]. *J Nucl Med* 1986; 27:962.
15. van der Woude FJ, van Son WJ, Tegzess AM, et al. Effect of captopril on blood pressure and renal function in patients with transplant renal artery stenosis. *Nephron* 1985; 39:184–188.

16. Sfakianakis G, Kyriakides G, Jaffe D, et al. Single visit captopril renography for the diagnosis of curable renovascular hypertension (RVH) [Abstract]. *J Nucl Med* 1985; 26:P133.
17. Kopecky RT, Thomas FD, McAfee JG. Furosemide augments captopril effects on nuclear studies in renovascular stenosis. *Hypertension* 1987; 10:181–188.
18. Steel RGD, Torrie JH. *Principles and procedures of statistics. A biometrical approach.* New York: McGraw-Hill Book Co., 1980:197–203.
19. Glantz SA. *Primer of biostatistics.* New York: McGraw-Hill Book Co., 1981:249–261.
20. Nally JV, Clarke HS, Grecos GP, et al. Effect of captopril on ^{99m}Tc-diethylenetriaminepentaacetic acid renograms in two-kidney, one-clip hypertension. *Hypertension* 1986; 8:685–693.
21. Lee H-B, Blaufox MD. Mechanism of renal concentration of Technetium-99m glucoheptonate. *J Nucl Med* 1985; 26:1308–1313.
22. Yee CA, Lee H-B, Blaufox MD. Tc-99m-DMSA renal uptake; influence of biochemical and physiologic factors. *J Nucl Med* 1981; 22:1054–1058.
23. Maack T, Sigulem D. Renal handling of lysozyme. In: Osserman EF, Canfield RE, Beychok S., eds. *Lysozyme.* New York: Academic Press, 1974:321–333.
24. Strober W, Waldmann TA. The role of the kidney in the metabolism of plasma proteins. *Nephron* 1974; 13:35–66.