Enalaprilat-Enhanced Renography in a Rat Model of Renovascular Hypertension

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The effect of rapid converting enzyme inhibition (CEI) with intravenous enalaprilat on technetium-99m- (^{99m}Tc) diethylenetriaminepentaacetic acid (DTPA) and ^{99m}Tc-dimercaptosuccinic acid (DMSA) renograms was evaluated in rats with two-kidney, one-clip renovascular hypertension. Rapid sequential DTPA renograms, performed immediately before and five minutes after enalaprilat injection (30 μg/kg), demonstrated a selective decrease in clipped kidney DTPA plasma clearance following CEI and no significant effect on unclipped kidney function. Pre- and post-CEI data were obtained with a single injection of DMSA by administering enalaprilat five minutes after the radiopharmaceutical. Enalaprilat slowed the rate of DMSA accumulation in clipped relative to unclipped kidneys, and reduced the clipped/unclipped kidney ratio of absolute DMSA uptake at 10 and 30 min. DTPA and DMSA were equally effective in demonstrating the CEI effect. Enalaprilat was also compared with captopril (3 mg/kg, intraperitoneally), using sequential DTPA renograms. Clipped kidney DTPA plasma clearance was reduced to an identical degree (40%) by both converting enzyme inhibitors. Clinical renographic protocols can probably be devised to take advantage of the rapid, reliable CEI of enalaprilat, thereby shortening total procedure time.

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Converting enzyme inhibition (CEI) with captopril improves the sensitivity and specificity of radionuclide renography in the diagnosis of renovascular hypertension (RVH) (*1-6*). In affected kidneys, captopril typically reduces early uptake of technetium-99m- (^{99m}Tc) diethylenetriamine pentaacetic acid (DTPA) (*1-6*) and increases the late accumulation of sodium iodine-131 (^{131}I) orthoiodohippurate (Hippuran) (*1,2,4,5*). Since intrinsic renal disease can sometimes produce similar changes, accurate diagnosis of RVH by this technique requires comparison of pre- and post-CEI renograms (*1-6*).

Enalaprilat is the pharmacologically active de-esterified metabolite of the prodrug enalapril (*7*). It has a potential advantage over oral converting enzyme inhibitors for the renographic detection of RVH because of its rapid induction of CEI after intravenous administration (*8*). This property could make it possible to collect pre- and post-CEI data from a single renogram, or reduce the time necessary between sequential renograms. Either would result in improved efficiency, and make CEI-enhanced renography a more practical procedure for detection of RVH. We evaluated enalaprilat for CEI-enhanced renography in a rat model of unilateral RVH, using ^{99m}Tc-DTPA and ^{99m}Tc-dimercaptosuccinic acid (DMSA).

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MATERIALS AND METHODS

Animal Preparation

Male Sprague-Dawley rats weighing 170-190 g (Taconic Farms, Germantown, NY) anesthetized with ether underwent surgical placement of a solid silver clip (slit width, 0.22 mm) on the left renal artery (two-kidney, one-clip [2K1C] rats). Three weeks after operation, systolic blood pressure was determined as reported previously (*9*). Only 2K1C rats with systolic blood pressure over 150 mmHg were included. Separate groups of 2K1C rats were prepared for each series of experiments. All rats were housed together with free access to standard chow (Purina Formulab 5008, 0.35% sodium; St. Louis, MO) and water throughout the study. Experiments were performed from 3 to 6 wk after renal artery clipping.

Experimental Protocols

In preliminary studies without CEI in normotensive rats (n = 4), single-kidney DMSA uptake averaged ~25% of the injected dose at 30 min, half of which (~12% per kidney) was achieved at 5 min. In order to equalize the anticipated DMSA uptake before and after CEI during all subsequent DMSA studies, enalaprilat was administered 5 min after the radiopharmaceutical.

For preliminary dose response experiments, 2K1C rats (n = 5) received saline vehicle (week 1), or enalaprilat (10, 30 or 50 μg/kg i.v., weeks 2-4) 5 min after injection of DMSA. Pretreatment with furosemide (25 mg/kg, i.p., 4 hr prior to the radionuclide study) was given to augment the effect of CEI on clipped kidney function (*9*). No furosemide was given prior to the control vehicle study. The effect of furosemide itself (25 mg/kg) on DMSA uptake was determined in a separate group of 2K1C rats (n = 12).

Subsequent studies with enalaprilat were carried out on another group of 2K1C rats (n = 15) over a three-week period according to the following protocol:

Week 1: baseline DMSA study without drug treatment; 4 days later, baseline DTPA study without drug treatment for determination of individual kidney DTPA plasma clearance (C_{DTPA}).

Week 2: DMSA study following furosemide (25 mg/kg) pretreatment, with enalaprilat (30 μg/kg) given at 5 min.

Week 3: DTPA studies before and 5 min after enalaprilat (30 μg/kg) for determination of individual kidney C_{DTPA}.

Analysis of data from week 3 of this study excluded two rats which failed to complete the entire protocol.

Sequential DTPA renal studies were performed on still another group of 2K1C rats (n = 15) over a two-week period. On Week 1, 5 min after completion of a baseline DTPA study, rats randomly received either enalaprilat (30 μg/kg, i.v., followed by a second DTPA study 5 min later) or captopril (3 mg/kg, i.p., followed by a second DTPA study 1 hr later). On Week 2, an identical series of studies was carried out but each rat received the alternate drug. Only rats with acceptable clipped kidney function on the first baseline DTPA scan ($C_{DTPA} \geq 0.20$ ml/min/100 g body weight) were used in this study. In similarly prepared 2K1C rats, we have shown previously that captopril, at this dosage and timing of administration, decreased clipped kidney C_{DTPA} significantly without reducing systolic blood pressure at the time of scanning (*9*). Because of the time difference required to perform sequential DTPA studies with enalaprilat (total 45 min) and captopril (total 95 min), furosemide pretreatment was not given to this group.

Direct blood pressures were measured in a separate group of 2K1C rats (n = 5) with acceptable clipped kidney function. Under pentobarbital anesthesia (50 mg/kg, i.p.), a 25-gauge teflon catheter was placed in a tail vein for drug infusion and a PE-50 catheter was placed in a femoral artery and connected to a Statham P23DC pressure transducer for blood pressure display on a Grass physiograph. After an equilibration period for blood pressure stabilization, systolic, diastolic and mean arterial pressure were recorded continuously for 15 min following i.v. injection of vehicle and enalaprilat (30μg/kg).

Renal Radionuclide Studies

Radiopharmaceuticals were administered by tail-vein injection with the rats under pentobarbital anesthesia. Technetium-99m-DMSA (200 μCi) (Medi-Physics, Inc., Paramus, NJ) injection was followed by scintillation camera imaging for 30 min (one frame every 30 sec). Renal uptake curves were computer generated as cumulative percent injected dose per kidney over time as described previously (*10*). For purposes of analysis, the rate of DMSA uptake for each kidney (expressed as percent injected dose per minute) was estimated by linear regression analysis of data points acquired over the interval before (0–5 min) and over two time intervals after the 5-min point of each study (5–10, 10–30 min). Comparison of left clipped with right unclipped kidney function before and after CEI was made by calculating the ratio of these regression slopes (L/R slope ratio). In several animals, clipped kidney regression slopes with slightly negative values during the 10–30-min interval were treated as zero slopes. Average linear regression coefficients of 0.95, 0.84 and 0.82 were obtained for DMSA uptake slopes calculated during the 0–5, 5–10, and 10–30-min intervals, respectively.

For the sequential DTPA studies, baseline scans were performed with 100 μCi of ^{99m}Tc-DTPA (in-house preparation) and post-CEI scans with 1 mCi of ^{99m}Tc-DTPA. The interval between scans was 15 min and 65 min for the enalaprilat and captopril studies, respectively. To correct for residual activity after the baseline scan, background frames were obtained prior to each post-CEI study and subtracted from each subsequent frame. Following each DTPA injection, scintillation camera imaging was carried out using 15-sec interval images computer-digitized for 15 min. The 0.5- to 1.5-min interval image was quantitated as the percentage of the injected dose in each kidney, as reported previously (*10*). Estimation of DTPA plasma clearance (C_{DTPA}) was obtained from regression equations relating plasma clearance to renal uptake. Regression equations were developed from previous rat plasma clearance studies of DTPA (n = 60) done concurrently with renal uptake studies (see Appendix). Plasma clearances were quantitated using the two-exponential model of Sapirstein et al. (*11*). The same technique (using DTPA) was used to quantitate individual kidney function of 2K1C rats undergoing DMSA studies. DMSA clearances were not calculated, because the coefficient of correlation between the renal uptake and plasma clearance of this agent was poor (*10*).

Comparisons between baseline renographic studies and studies carried out after treatment on the same group of 2K1C rats were made using the two-tailed paired Student's t-test. Where more than one comparison was made, the Bonferroni adjustment was applied. In the group of rats studied with both DMSA and DTPA, 30 different measured parameters (in the form of left/right renal ratios) were evaluated by the same subjects repeated measures analysis of variance (*12*), and Tukey's procedure to isolate differences in the means (*13*). Comparison between 2K1C rats with good and poor clipped kidney function undergoing the same treatment were made using the unpaired Student's t-test. Statistical significance was defined as a p value < 0.05.

RESULTS

In preliminary studies, the effect of various enalaprilat doses on renal DMSA uptake in furosemide pretreated 2K1C rats was determined. Compared to saline, enalaprilat at doses of 10, 30 and 50 μg/kg had no effect on the shape of the DMSA uptake curve after 5 minutes in unclipped kidneys (Fig. 1A). In clipped kidneys, 30 μg/kg of enalaprilat at 5 min produced maximum flattening of the DMSA uptake curve (Fig. 1B). Systemic blood pressure was reduced only transiently by this dose and returned to baseline levels within 6 min of injection, suggesting that the observed changes in clipped kidney radiopharmaceutical handling were the result of intrarenal rather than systemic hemodynamic effects of CEI (*9,14*). Hence, a 30-μg/kg enalaprilat dose was used in all subsequent studies.

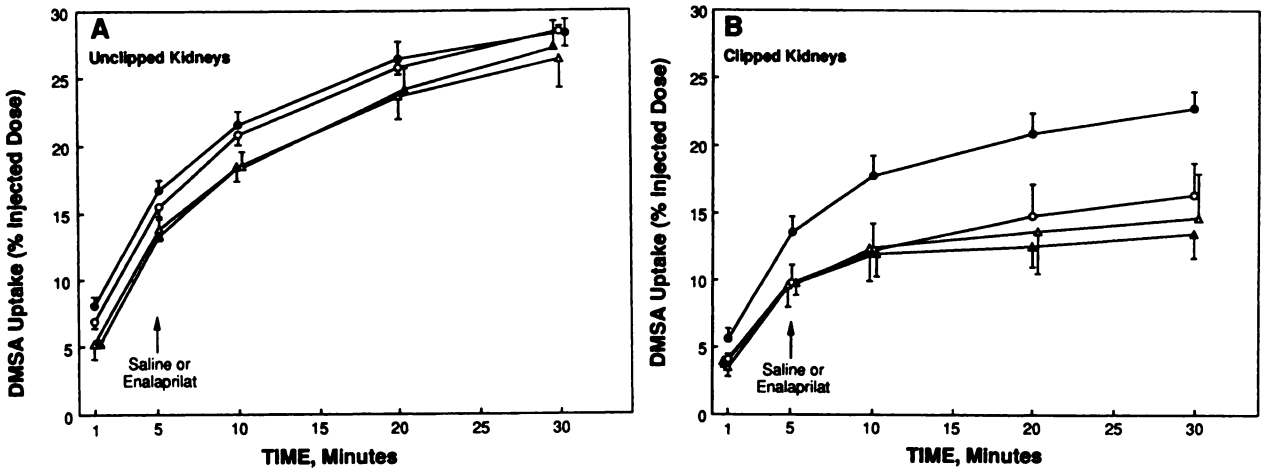

FIGURE 1
DMSA uptake at 1, 5, 10, 20 and 30 min by right unclipped (A) and left clipped (B) kidneys of 2K1C rats. Treatment protocols: No pretreatment and saline (closed circles); furosemide pretreatment and enalaprilat 10 μg/kg (open circles), 30 μg/kg (closed triangles), and 50 μg/kg (open triangles). Saline or enalaprilat (arrows) were injected into a tail vein 5 min postinjection of ^{99m}Tc-DMSA (200 μCi). The same group of five 2K1C rats was used for all four experiments over a three-week period. Values are mean ± s.e.m.

Furosemide pretreatment appeared to reduce absolute DMSA uptake in both clipped and unclipped kidneys prior to enalaprilat treatment (Fig. 1A and B, 1- and 5-min time points). In order to determine if furosemide influenced clipped relative to unclipped kidney DMSA uptake additional studies were performed on 2K1C rats without enalaprilat treatment (Fig. 2). Although furosemide pretreatment produced a modest (5%–9%) decrease in mean DMSA uptake at all time points in both unclipped and clipped kidneys, there was no statistically significant difference between the pre- and post-furosemide values in either kidney (Fig. 2). Clipped kidney function, as estimated by the rate of DMSA uptake relative to unclipped kidneys, was not changed by furosemide pretreatment either before or after the 5 minute point of the DMSA study (Table 1).

Figure 3 shows the results of enalaprilat treatment on DMSA uptake in a group of 15 furosemide pretreated 2K1C rats. An initial DMSA study, performed on the same animals without drug treatment, showed no significant difference between the mean L/R slope ratio before (0–5 min, 0.73 ± 0.08) and after (5–10 min, 0.87 ± 0.09; 10–30 min, 0.68 ± 0.10) the 5-min point in the scans.

Clipped kidney function was reduced after enalaprilat administration at 5 min in the DMSA studies (Fig. 3). The mean L/R slope ratio of 0.75 ± 0.08 during the 0–

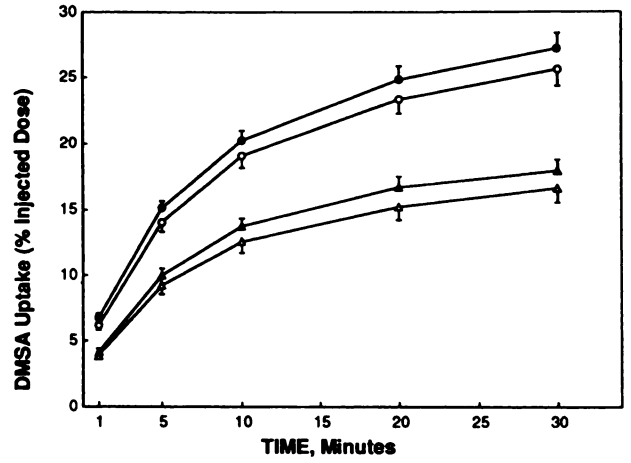

FIGURE 2
DMSA uptake a 1, 5, 10, 20 and 30 min determined with and without prior diuretic-induced volume depletion. Data shown are for unclipped (circles) and clipped (triangles) kidneys in studies performed without pretreatment on a normal sodium intake (closed symbols) and 4 hr after furosemide (25 mg/kg i.p.) pretreatment (open symbols). The same group of twelve 2K1C rats was used for both studies over a one-week period. Values are mean ± s.e.m. At all time points, $p > 0.05$ for no treatment versus furosemide pretreatment in both clipped and unclipped kidneys.

TABLE 1
Left/Right Kidney DMSA Uptake Ratios Before and After Furosemide Pretreatment

Time interval post-DMSA injection	L/R slope ratio* No pretreatment	Furosemide pretreatment	p value
0– 5 min	0.72 ± 0.06	0.71 ± 0.08	NS
5–10 min	0.73 ± 0.05	0.65 ± 0.04	NS
10–30 min	0.65 ± 0.08	0.66 ± 0.07	NS

* Using the same twelve 2K1C rats shown in Figure 2, rates of DMSA uptake (% injected dose/min) into left clipped and right unclipped kidneys over various time intervals were estimated by linear regression analysis. The dimensionless ratio of these uptake slopes (L/R Slope Ratio) was calculated to estimate clipped relative to unclipped kidney function during each of these intervals.
NS = not statistically significant.

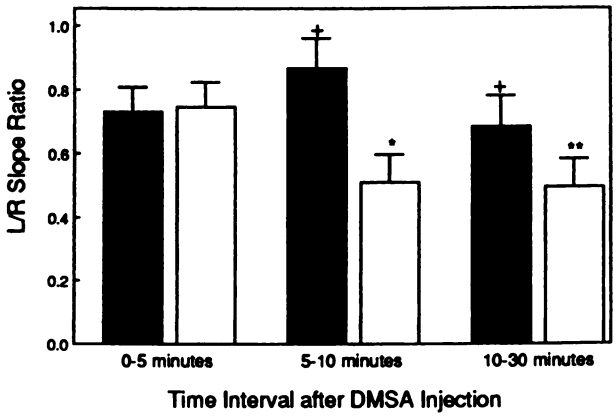

FIGURE 3
Relative DMSA uptake rate of left clipped to right unclipped kidneys represented as L/R slope ratios during intervals from 0–5, 5–10, and 10–30 min after DMSA injection in fifteen 2K1C rats. Initial study without drug treatment (shaded bars), and repeat study performed 1 wk later on the same rats with furosemide pretreatment and enalaprilat (30 μg/kg) given at 5 min (open bars). ★ = $p < 0.02$ and ★★ = $p < 0.001$ versus respective 0–5 min interval. + = no significant difference versus respective 0–5 min interval.

TABLE 2
Effect of Enalaprilat on Early Renal DTPA Plasma Clearance in 2K1C Rats*

Kidney	C_{DTPA} Baseline	C_{DTPA} Enalaprilat	p value†
Clipped	0.22 ± 0.02	0.11 ± 0.02	$p < 0.001$
Unclipped	0.37 ± 0.03	0.33 ± 0.03	NS

* Data from thirteen of the fifteen 2K1C rats shown in Fig. 3. Two rats failed to complete this part of the protocol and were excluded from analysis. C_{DTPA} expressed in ml/min/100 g.
† p-values versus corresponding baseline study.
NS = not statistically significant.

5-min interval fell significantly after enalaprilat to 0.51 ± 0.08 and 0.50 ± 0.09 during the 5–10- and 10–30-min intervals, respectively. The L/R slope ratio decreased during at least one of the post-enalaprilat intervals (5–10 or 10–30 min) in 14 of the 15 animals. Results from a representative animal (Fig. 4), show the abrupt slowing of DMSA uptake by the clipped kidney immediately following enalaprilat administration. Thus, a decrement in clipped kidney function relative to unclipped kidney function can be detected following CEI with enalaprilat during a single DMSA renal scan.

The response of clipped and unclipped kidney C_{DTPA} to enalaprilat in the same group of 2K1C rats is shown in Table 2. Clipped kidney C_{DTPA} decreased significantly following enalaprilat treatment, whereas unclipped kidney C_{DTPA} was unaffected by enalaprilat. The ratio of clipped to unclipped kidney C_{DTPA} was also reduced significantly by enalaprilat, from 0.62 ± 0.05 to 0.36 ± 0.07 ($p < 0.02$).

Since poor baseline stenotic kidney function can produce negative results with CEI-enhanced renography (*4*), the DMSA uptake response to enalaprilat was evaluated with respect to initial clipped kidney function. The group of fifteen 2K1C rats was divided into two subgroups, based on clipped kidney C_{DTPA} (Table 3). Rats with poor clipped kidney function tended to have lower L/R slope ratios, but these differences did not reach statistical significance during any interval in the untreated or treated experiments. Baseline clipped kidney function had no effect in the absence of CEI, since L/R slope ratios during the 5–10- and 10–30-min intervals did not differ statistically from the 0–5-min interval in either group. Rats with good clipped kidney function showed a significant decline in the L/R slope ratio after enalaprilat treatment. However, rats with poor clipped kidney function failed to respond in the immediate post-CEI interval (5–10 min), although the mean L/R slope ratio subsequently dropped significantly during the 10–30-min interval.

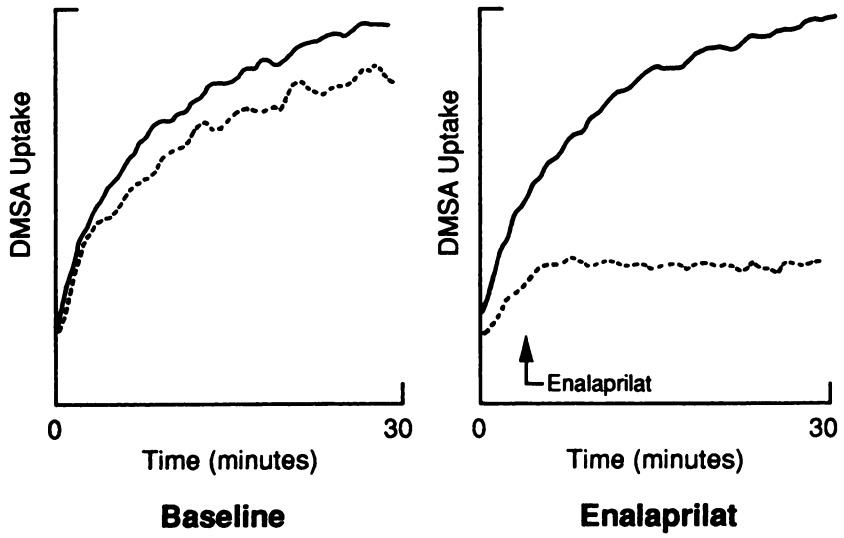

FIGURE 4
Baseline and enalaprilat-enhanced ^{99m}Tc-DMSA renograms performed on the same 2K1C rat on different days. Cumulative uptakes (as % injected dose) in the unclipped kidney (solid lines) and the clipped kidney (broken lines) over 30 min following injection of ^{99m}Tc-DMSA are shown. Enalaprilat (30 μg/kg) was injected 5 min after DMSA during the second renogram (arrow). Absolute scale of the uptake axis is computer determined for each study, with a maximum value of 17.9% for the baseline study and 25.9% for the enalaprilat study.

TABLE 3
Effect of Baseline Clipped Kidney Function on DMSA Uptake Response to Enalaprilat

Treatment	Baseline-Clipped Kidney C_{DTPA}*	L/R slope ratio				
		0–5 min	5–10 min	p value†	10–30 min	p value†
None	Good	0.80 ± 0.09	0.96 ± 0.05	NS	0.77 ± 0.08	NS
	Poor	0.63 ± 0.14	0.74 ± 0.22	NS	0.56 ± 0.21	NS
Enalaprilat	Good	0.83 ± 0.07	0.52 ± 0.11	$p < 0.025$	0.56 ± 0.10	$p < 0.01$
	Poor	0.62 ± 0.15	0.50 ± 0.16	NS	0.39 ± 0.15	$p < 0.01$

* Data from the same fifteen 2K1C rats shown in Figure 3 was subgrouped according to baseline clipped kidney function, as determined by DTPA renography performed on a different day (see Methods). Arbitrarily, good function was defined as clipped kidney C_{DTPA} >0.20 ml/mm/100 g (n = 9, C_{DTPA} = 0.29 ± 0.09) and poor function as clipped kidney C_{DTPA} <0.20 ml/min/100 g (n = 6, C_{DTPA} = 0.17 ± 0.03). L/R slope ratios for each time interval of the DMSA scan were calculated as previously described.

† = p value versus corresponding 0–5 min interval.

NS = not statistically significant.

In twelve of the group of fifteen 2K1C rats without markedly abnormal baseline clipped kidney function, DMSA and DTPA were compared directly by analysis of variance, using 30 different parameters of renal function. For DMSA, the best indicators of a response to CEI, judged by the enalaprilat-induced decrease in left/right kidney ratios were the 10-min and 30-min DMSA uptakes, and the 5–10-min and the 10–30-min uptake slopes. By Tukey's procedure for assessing differences between means, the change in early renal uptake of DTPA following enalaprilat was equally effective in demonstrating the response to CEI on clipped kidney function in 2K1C rats.

The effect of enalaprilat on clipped and unclipped kidney function was compared directly with captopril in another group of 2K1C rats, using two sequential ^{99m}Tc-DTPA renograms (Fig. 5). Captopril decreased clipped kidney C_{DTPA} significantly from baseline (0.33 ± 0.02 to 0.20 ± 0.03 ml/min/100 g, $p < 0.001$) and had no effect on unclipped kidney function. Enalaprilat had a similar effect on clipped kidney C_{DTPA} (0.32 ± 0.02 to 0.19 ± 0.03 ml/min/100 g, $p < 0.005$). Although enalaprilat did not reduce unclipped kidney C_{DTPA} significantly, the percentage change in unclipped kidney function (−16.4%) was larger than that induced by captopril (−2.2%). The ratio of clipped to unclipped kidney C_{DTPA} was significantly reduced by captopril (0.85 ± 0.07 to 0.51 ± 0.08, $p < 0.001$) and enalaprilat (0.80 ± 0.07 to 0.55 ± 0.08, $p < 0.05$).

DISCUSSION

Radiopharmaceuticals which enter the urine primarily via glomerular filtration are well suited for CEI-enhanced renography since renal uptake of these agents is directly (if not exclusively) related to glomerular filtration rate (GFR). Early renal uptake of DTPA correlates well with GFR over wide ranges of renal function in experimental animals (*10*) and humans (*15*), and has been used to detect CEI-induced GFR changes in stenotic kidneys (*6,9*). DTPA has the advantage of a rapid uptake phase, such that early renal accumulation is relatively independent of urine flow rate or excretion (*16*). We previously showed that several other radiopharmaceuticals which undergo glomerular filtration yield results comparable to DTPA chelates in CEI-enhanced renography in 2K1C rats (*17*). One of those agents, DMSA, was chosen for the current study in comparison with DTPA for several reasons. Due to protein binding in the plasma (*18*) DMSA is taken up slowly by glomerular filtration, allowing accurate acquisition of pre- and post-CEI data. DMSA also accumulates progressively in proximal tubular cells

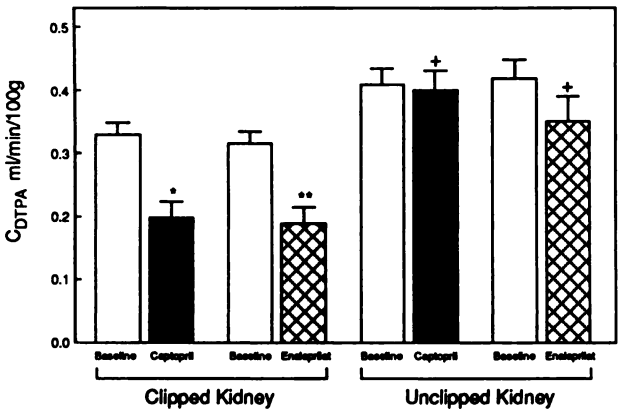

FIGURE 5
Comparison of the effects of captopril and enalaprilat on kidney function in 2K1C rats. Fifteen 2K1C rats with preserved clipped kidney function (initial clipped kidney C_{DTPA} > 0.20 ml/min/100 g body weight) underwent sequential DTPA renal scans on two successive weeks. Baseline studies using 100 μCi of ^{99m}Tc-DTPA (open bars) were followed immediately by CEI with captopril (3 mg/kg, i.p.) or enalaprilat (30 μg/kg, i.v.). Post-CEI scans with 1 mCi ^{99m}Tc-DTPA were performed 60 min after captopril (shaded bars) and 5 min after enalaprilat (hatched bars). All rats underwent studies with both drugs. Individual kidney DTPA plasma clearances (C_{DTPA}) determined before and after each treatment are shown (see Methods for details). ★ = $p < 0.001$, ★★ = $p < 0.005$, + = not statistically significant, versus corresponding baseline study.

following filtration (*18*), limiting early excretion from the kidney. Clinical use of DMSA for conventional sequential CEI-enhanced renography has been reported (*19–20*).

In this study, the two-injection DTPA and the single-injection DMSA procedures were of equal value in demonstrating the response to enalaprilat in 2K1C rats via changes in clipped/unclipped renal ratios. DTPA is a particularly useful agent for CEI-enhanced renography because renal uptake measurements are readily converted by linear regression into plasma clearance values (*10*). This approach allows independent measurement of individual kidney function in bilateral renal diseases. Since our previous experience indicated that the early renal uptake of DMSA correlates poorly with its plasma clearance (*10*), we devised an alternative method for analysis of CEI-enhanced DMSA renograms based on the relative rates of single kidney DMSA uptake. A CEI effect on clipped kidney DMSA uptake data was consistently demonstrated by comparing clipped and unclipped kidney function (L/R slope ratios) before and after CEI with enalaprilat. It was not possible to quantitate absolute changes in clipped and unclipped kidney GFR produced by enalaprilat from our DMSA data. The observation that unclipped kidney GFR sometimes increases after captopril treatment in unilateral RVH (*21*) while clipped kidney GFR falls could be advantageous to a relative kidney analysis technique. However, we did not detect an increase in unclipped kidney GFR with captopril or enalaprilat using DTPA (Fig. 5). Relative kidney analysis, of course, is not applicable in bilateral renal artery stenosis, or with solitary kidneys.

The effect of enalaprilat on L/R slope ratios was less marked in rats with poorly functioning stenotic kidneys (Table 3). Similar results have been noted in patients with poor stenotic kidney function using DTPA (*4*). Decrements in kidney function are necessarily more difficult to detect when initial kidney function is poor and measurements of very low renal uptake of DMSA or DTPA are less accurate. Nevertheless, a lack of response to CEI clinically is proving to be a predictor of poor relief of hypertension after correction of renal artery stenosis (*3*).

In adapting these techniques for CEI-enhanced renography to the clinical setting, differences from the experimental conditions must be considered. DMSA accumulates in the renal cortex more quickly and to a higher level in the rat than in man. Typically, a normal rat kidney concentrates 25%–28% of the administered activity in 30 min, whereas in normal man it takes 3 hr to reach 18%. Moreover, early uptake of DMSA has not been a reliable indicator of renal function, in contrast to its later uptake. Hence, it is possible that the early slope assessment may not differentiate RVH from other unilateral renal lesions. For eventual clinical applications, it may be more practical to use the dual-injection DTPA technique to shorten the time of computer acquisition and total procedure time.

The renography protocols used in this study were designed to take advantage of the rapid CEI which can be achieved with enalaprilat. Intravenous enalaprilat produces virtually complete inhibition of rat renal angiotensin converting enzyme (ACE) activity within 3 min (*8*). When compared directly with captopril in a group of 2K1C rats using DTPA renography, enalaprilat (30 μg/kg, intravenously) had essentially the same effect as captopril (3 mg/kg, intraperitoneally) on clipped kidney C_{DTPA} (Fig. 5), suggesting that both drugs produced a similar degree of CEI. These results are consistent with a previous report which found the ACE inhibiting capacity of enalaprilat to be approximately 100 times that of captopril (*22*). Recently, enalaprilat was also used to successfully perform sequential Hippuran renography in a dog model of RVH (*23*).

Overall, the effects of enalaprilat and captopril on kidney function in 2K1C hypertension appear comparable, suggesting that either drug could be used successfully in a CEI-enhanced renography protocol. Enalaprilat does offer some practical advantages over oral CEI. The possibility of incomplete or erratic drug absorption is eliminated, and the rapid onset of CEI allows two DTPA renographic studies to be performed in quick succession. This factor increases the convenience of CEI-enhanced renography as a screening test, and minimizes variations in volume status and blood pressure (particularly in patients receiving diuretic or antihypertensive drugs), which may occur when pre- and post-CEI studies are separated by several hours or days.

APPENDIX

The regression equations (Table A-1) for estimating plasma clearance from in vivo renal uptake measurements of ^{99m}Tc-DTPA were derived from data generated for a previous publication (*14*). Plasma clearances obtained from multiple plasma samples were correlated with the summed uptake of right and left kidneys quantitated by gamma camera computer techniques in a series of rats including controls (n = 24) and rats with glomerular damage induced by graded dose of puramycin aminonucleoside (n = 60). For the purpose of the present study, the plasma clearances of the right and left kidneys of these animals were assumed to be equal. Hence, the renal DTPA uptake of the individual kidneys were regressed against half the plasma clearance values.

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TABLE A-1
Linear Regression Equations for Calculating Clearances of Individual Rat Kidneys from In Vivo Early Renal Uptake

	Kidney	
	Left	Right
DTPA clearance (Y) (ml/min/100 g body wt)	$y = 0.0677x - 0.116$	$y = 0.0623x - 0.0698$

x = in vivo early renal uptake.
Values expressed as percentage of administered activity per kidney.

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